Safety Assessment of Caprylhydroxamic Acid as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	May 15, 2020
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The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Monice M. Fiume, Senior Director, CIR.

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Monice M. Fiume MMF
Senior Director, CIR
Date: May 15, 2020
Subject: Safety Assessment of Caprylhydroxamic Acid as Used in Cosmetics

Enclosed is the Draft Tentative Report of the Safety Assessment of Caprylhydroxamic Acid as Used in Cosmetics. (It is identified in this report package as *caphyd062020rep*.) At the June 2019 meeting, the Expert Panel for Cosmetic Ingredient Safety (Panel) found that the data were insufficient to determine safety. Although the results for a number of human repeated insult patch tests (HRIPTs) were largely negative, there were some alerts for sensitization in HRIPTs on formulations containing Caprylhydroxamic Acid at less than the maximum reported use concentration. Because 1) the potential for sensitization could not be ruled out completely based on the reactions observed in the HRIPTs; 2) there were reported reactions to Caprylhydroxamic Acid in a reformulated moisturizer in Finland; and 3) there was an absence of a local lymph node assay or guinea pig maximization test to demonstrate a lack of sensitization potential, the following were requested:

- Human repeated insult patch test at maximum use concentrations
  - the Panel requested that the study include a minimum of 100 subjects, preferably with Fitzpatrick skin types 1-4
- a quantitative risk assessment (QRA) using an appropriate no-expected-sensitization-induction-level (NESIL)

At the December 2019 meeting, the Panel was made aware that the requested studies were being conducted, but the results were not available in time for that meeting. Thus, the report was tabled awaiting the data. Those data have now been received, and incorporated in the report (as indicated by yellow highlighting). The data submissions include:

- Gerberick FG, Sminkey CS, Fevola MJ. 2020. Quantitative risk assessment for allergic contact dermatitis: Caprylhydroxamic Acid as used in cosmetics. (*caphyd062020data_1*)
- SGS. (2020) Repeated insult patch test study - Caprylhydroxamic Acid tested at 1.9%. (*caphyd062020data_1*)
- SGS. (2020) Repeated insult patch test study - Caprylhydroxamic Acid tested at 3.8%. (*caphyd062020data_1*)
- Anonymous. (2020). Summary of an HRIPT of an aqueous formulation containing 0.76% Caprylhydroxamic Acid. (*caphyd062020data_2*).

Updated VCRP (2020) data have been received, and are also included (*caphyd062020FDA*). Frequency of use of Caprylhydroxamic Acid increased slightly, from 227 uses in 2019 to 269 uses in 2020.

Comments that were received from the Council prior to the June meeting (on the Draft Report) and prior to the December meeting (on the Draft Tentative Report) were addressed, and are included (*caphyd062020pcpc_1* and *caphyd062020pcpc_2*, respectively). The following are also included as a part of this report package:

caphyd062020flow: report flowchart
caphyd062020hist: report history
caphyd062020prof: data profile
caphyd062020strat: search strategy
caphyd062020min: transcripts

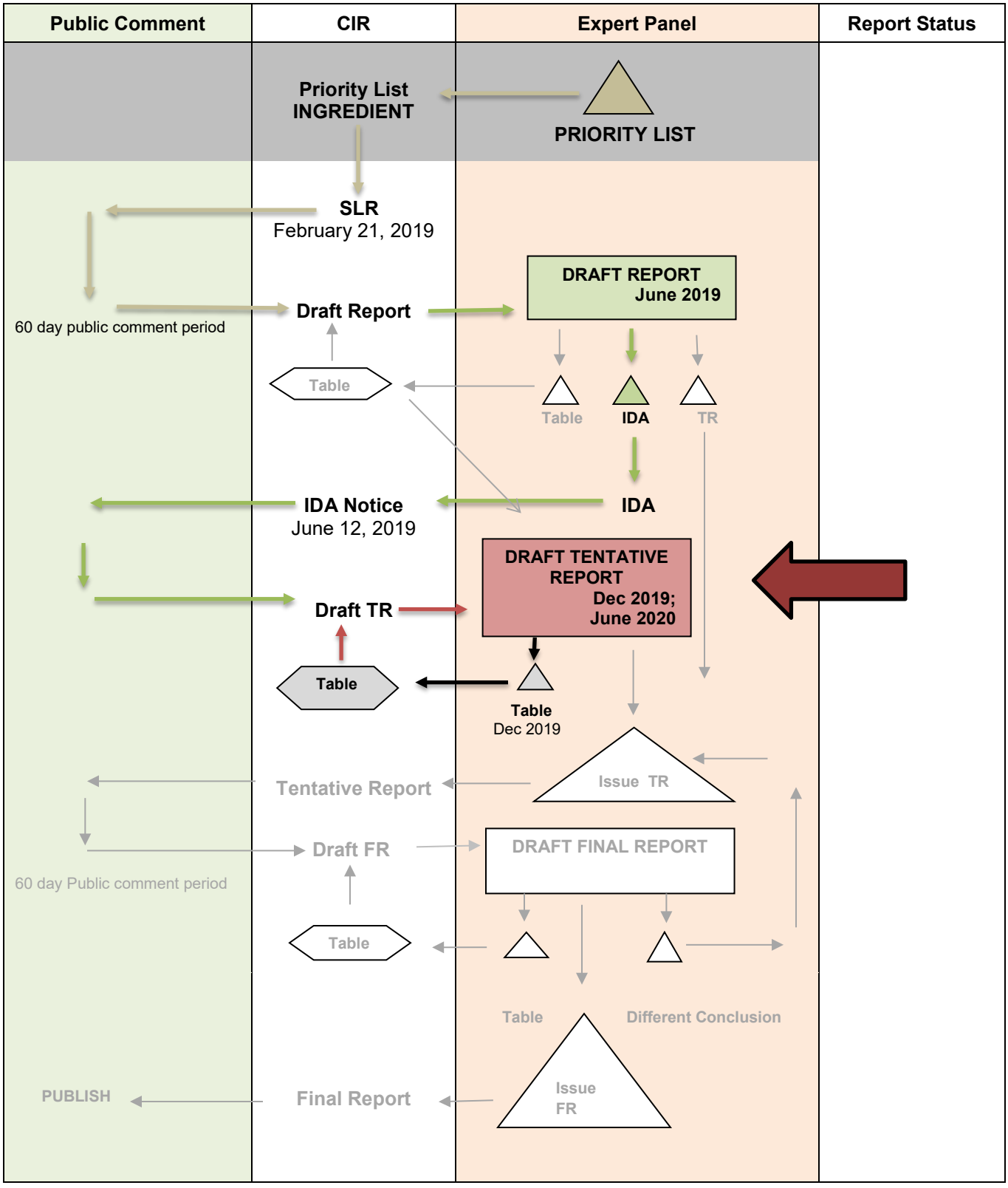
The Panel should carefully consider the data, and issue a Tentative Report with a safe, safe with qualifications, insufficient data, or unsafe conclusion. The draft Discussion should also be reviewed, and additional discussion items identified.

Distributed for Comment Only -- Do Not Cite or Quote

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Caprylhydroxamic Acid

MEETING June 2020



CIR Report History: Caprylhydroxamic Acid

SLR: February 21, 2019
The following data were received prior to announcing the SLR:"

1. PCPC. 2018. Council concentration of use survey: Caprylhydroxamic Acid.

Draft Report: June 6-7, 2019
The following unpublished data were received either from the Council or as a direct submission to CIR prior to review of the Draft Report:

1. Inolex. 2019. Method of manufacture for Caprylhydroxamic Acid.
2. Nelson Laboratories Inc. 2007. The *Salmonella typhimurium* reverse mutation assay (Ames test), liquids or soluble chemicals, with caprylohydroxamic acid.
3. BioReliance. 2013. *In vitro* mammalian cell micronucleus assay in human peripheral blood lymphocytes (HPBL) with Caprylhydroxamic Acid.
4. MatTek Corporation. 2018. Evaluation of the skin irritation potential of diheptyl succinate and Caprylhydroxamic Acid using the EpiDerm skin irritation test OECD TG 439.
5. Consumer Product Testing Company. 2014. Repeated insult patch test of an eyeliner containing 0.105% Caprylhydroxamic Acid.
6. Consumer Product Testing Company. 2018. Repeated insult patch test of a lotion containing 0.15% Caprylhydroxamic Acid, tested undiluted.
7. Consumer Product Testing Company. 2018. Repeated insult patch test of W/O thick balm containing 0.15% Caprylhydroxamic Acid, tested undiluted.
8. Consumer Product Testing Company. 2018. Repeated insult patch test of a wipe juice containing 0.15% Caprylhydroxamic Acid, tested undiluted.
9. Anonymous. 2019. Summary of an HRIPT of a facial cream containing 0.15% Caprylhydroxamic Acid
10. Anonymous. 2019. Summary of an HRIPT on a brow thickening powder containing 0.195% Caprylhydroxamic Acid.*)*
11. Consumer Product Testing Company. 2018. Repeated insult patch test of CHA blend #3 containing 5% Caprylhydroxamic Acid, tested as a 6% dilution.
12. Consumer Product Testing Company. 2018. Repeated insult patch test of CHA blend #5 containing 7.5% Caprylhydroxamic Acid, tested as a 4% dilution.
13. Consumer Product Testing Company. 2018. Repeated insult patch test of CHA blend #2 containing 10% Caprylhydroxamic Acid, tested as a 3% dilution.
14. Consumer Product Testing Company. 2018. Repeated insult patch test of CHA blend #1 containing 15% Caprylhydroxamic Acid, tested as a 2% dilution.
15. Consumer Product Testing Company. 2018. Repeated insult patch test of CHA blend #4 containing 15% Caprylhydroxamic Acid, tested as a 2% dilution.
16. Clinical Research Laboratories Inc. 2008. Repeated insult patch test of undiluted caprylohydroxamic acid.
17. MB Research Laboratories. 2011. Bovine Corneal Opacity and Permeability Test (BCOP) with a 20% solution of Caprylhydroxamic Acid.
18. MB Research Laboratories. 2010. MatTek EpiOcular™ MTT Viability Assay with CHA (Caprylhydroxamic Acid).

The Panel issued an IDA, and the following was requested:

- Human repeated insult patch test at maximum use concentrations
    - the Panel has requested that the study includes a minimum of 100 subjects, preferably with Fitzpatrick skin types 1-4
    - a quantitative risk assessment (QRA) should be performed, and a no-expected-sensitization-induction-level (NESIL) should be determined

Draft Tentative Report: December 9-10, 2019

Prior to the meeting, CIR was made aware that an HRIPT had been commissioned. However, a study report (and therefore, a NESIL) had not yet been received.

The Panel tabled this report until the HRIPT and QRA are received.

Draft Tentative Report: June 8-9, 2020

The following unpublished data were received and incorporated:

1. Gerberick FG, Sminkey CS, Fevola MJ. 2020. Quantitative risk assessment for allergic contact dermatitis: Caprylhydroxamic Acid as used in cosmetics.
2. Anonymous. 2019. Summary of an HRIPT of a brow thickening powder containing 0.195% Caprylhydroxamic Acid.
3. SGS. 2020. Repeated insult patch test study - Caprylhydroxamic Acid tested at 1.9%.
4. SGS. 2020. Repeated insult patch test study - Caprylhydroxamic Acid tested at 3.8%.

Updated (2020) VCRP data were also received and incorporated.

Caprylhydroxamic Acid* – June 8-9, 2020 – Writer, Monice Fiume																														
				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization					Ocular Irritation		Clinical Studies		
	Reported Use	Method of Mfg	Impurities	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro/In Chemico /In Silico	Animal	Human	QRA/NESIL	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Provocative Testing	Case Reports
Caprylhydroxamic Acid	yes	X	X	X	X	X		X			X			X	X				X		X	X		X	X		X			X	X

* "X" indicates that data were available in a category for the ingredient

Caprylhydroxamic Acid – 2/7/19

Ingredient	CAS #	SciFin	PubMed	FDA	EU	ECHA	ECETOC	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Caprylhydroxamic Acid	7377-03-9	5/160	2/7	no	X	X	no	X	no	no	no	no	no	no	no

Search Strategy

PubMed (2/7/19; updates received weekly): ((((Caprylhydroxamic Acid) OR 7377-03-9[EC/RN Number]) OR Octanamide, N-Hydroxy-) OR N-hydroxyoctanamide) OR Octanohydroxamic Acid – 7 hits/2 useful
SciFinder: searched by CAS No; refined by document type – 160 hits/5 useful

online searches

Caprylhydroxamic Acid sensitization
Adverse event reporting caprylhydroxamic acid
Adverse event reporting phenostat
Sensitization to Phenostat
Allergic contact dermatitis caused by cosmetic products.
Allergic contact dermatitis caused by preservatives in cosmetic products.
Contact dermatitis caused by preservatives.
Chemistry of hydroxamic acids
hydroxamic acids and the effect of straight versus cyclic chains

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Scifinder (https://scifinder.cas.org/scifinder)

appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org
- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- EAFUS: http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- OTC ingredient list: https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- ChemPortal: https://www.echemportal.org/echemportal/index.action
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/

- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org

- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://www.oecd.org/env/ehs/risk-assessment/publishedassessments.htm
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/

- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/

- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

CAPRYLHYDROXAMIC ACID

JUNE 2019 MEETING – INITIAL MEETING/DRAFT REPORT

Belsito Team – June 6, 2019

DR. BELSITO: Okay. Then we have the Caprylhydroxamic Acid. This is an initial report of one ingredient, and we received the Wave 2 data on that with the dermal absorption. I think it was 45 percent, was the max. So, this is our first look. I thought we needed data on sensitization and irritation. And I didn't like that comment on page 3 that sensitization is possible.

It says it has been shown to have protein reactivity, an important factor in skin sensitization potential. And then it says the sensitization potential cannot be ruled out. Of course it can't be ruled out. It can never -- I don't know who -- it's in quotation marks, so I'm presuming it's coming from the NICNAS dossier, but I would not keep that sentence in.

MS. FIUME: So that sentence isn't currently in the report, so my question was whether or not it should be included. So, great. Thank you.

DR. BELSITO: Okay, yeah. That was at the beginning. Right.

DR. LIEBLER: Yeah. Just to clarify this, hydroxamates, as a class, are metal chelators. And this is part of that class. But a lot of the activity depends on what else is in the molecule. This fatty acyl component is probably going to reduce its ability to do that.

The other thing is that, if you broadly ascribe removing a metal that might be part of an enzyme prosthetic group or a cofactor from a protein as being protein reactive, I guess it's okay to say that. But it's not reactive in the sense that we think of being concerned about it in sensitization where you covalently modify the protein structure. This molecule will not do that.

DR. BELSITO: Okay. Now, what about the effects on enzymes metalloproteinases, particularly given the absorption of this material? Dan, were you concerned about that?

DR. LIEBLER: No, I actually looked in a little bit on hydroxamates and their abilities to do this. There was, I guess, a couple of references. I looked at those. But these are inhibitors that often work in the low to mid micromolar range, depending on the enzyme and the structure of the enzyme and the structure of the hydroxamate. And none of the effective inhibitors have straight alkyl chain structures like this one does.

I think this would be -- like I said, it falls chemically into a class, some of which can do this. I think that this is unlikely to be a significant activity at the amounts that would likely be present after any skin absorption. I think it's not an issue.

DR. BELSITO: Okay. You had a comment?

MS. FIUME: So, again, should that information stay in the report or come out?

DR. LIEBLER: It's okay to have it there, because I'm looking at PDF page 10, right under the structures where you describe the hydroxamic acid functional group makes it, you say, an excellent chelating agent. I would say a chelating agent, because excellent really doesn't have a meaning without an effective concentration.

DR. BELSITO: But then we'll have to say something about it in the discussion?

DR. LIEBLER: Correct.

DR. BELSITO: And your approach would be that this differs from the other similar chemicals? Or they're not similar because of the difference in the hydroxamate structure?

DR. LIEBLER: I didn't write anything, but I could write a sentence to put into the discussion.

DR. BELSITO: Okay. And then is any --

DR. LIEBLER: But yeah, that's basically what I would say, is that there are lots of different hydroxamates. And the ones that are described as being effective chelators have different structures than this.

DR. BELSITO: Okay. And the ones that inhibit the metalloproteinases, you mean, have different structures?

DR. LIEBLER: That's right. Exactly. Yeah.

DR. BELSITO: Okay. What about the impurities? Is that something we'd put in the discussion? The nitrosamides?

DR. LIEBLER: Oh. Yeah, I have a note to myself here. Hang on a second. Nitrosamide formation, theoretically possible but not observed with this class of molecules; may not even need discussion, although we can put it in.

DR. BELSITO: So, you would put it, but say that it's unlikely but manufacturers should monitor, or something to that effect.

DR. LIEBLER: Correct. I mean, it says right under Nitrosation on PDF page 11, the last short paragraph under Nitrosation: However, while indirect test methods have supported the likelihood of formation, N-nitrosated hydroxamic acid derivatives have yet to be isolated.

DR. BELSITO: Okay. So, then, we have a margin of exposure and calculation on this that comes off of a 13-week oral study. Is a 13-week oral study adequate for use when you're calculating a margin of exposure?

DR. SNYDER: Yes.

DR. LIEBLER: Yeah.

DR. BELSITO: Okay. And I guess, to everyone, do you think the DART and genotox studies are adequate? Is there enough information in them?

DR. SNYDER: Yeah, I thought they were fine.

DR. LIEBLER: Yeah, there's the one positive in the *E. coli* test, but I was inclined to accept the OECD Ames data and micronucleus data over this weak *E. coli* result. So, I think that the genotox is largely consistent and supportable.

DR. BELSITO: Okay.

DR. LIEBLER: Again, this molecule does not have structure alerts that would raise concerns about carcinogenicity or mutagenicity.

DR. BELSITO: Okay. So you may have partially answered this then, but I was a little concerned with the sensitization data, primarily with the -- I mean, there were several HRIPTs that were clear, but then there was one where you had 104 subjects. They were tested with varying concentrations. And mild or moderate erythema with occasional edema were noted throughout the test.

The conclusion was that it wasn't an issue, but I'm just a bit worried about this, particularly because it's used in baby products, right? We need to go back and look. Yeah, six baby products. It's used in mucous membranes. There are no reported use in underarm deodorants, which would be another area of concern for sensitization. But I'm not sure that we have the data since I was under the assumption that it was protein reactive. But you're saying that it's not.

DR. LIEBLER: No, it's not; not in the way that we normally think of protein reactive chemicals. It doesn't have a structure that would covalently modify proteins. I think we kind of consider that an almost universally obligatory initial step in skin sensitization.

So, I don't know how you interpret the result that's described here on that HRIPT with 104 subjects with erythema and edema. I can't provide anything more on that because that's not my area.

DR. BELSITO: Well, normally, slight erythema, you discount. But edema, you don't. So, I'm just still a little worried about that study.

DR. LIEBLER: It says with occasional edema. Is that literally the term taken from the text to the report? Usually, you would, I guess --

MS. FIUME: Yes. That would be something that was in the report.

DR. LIEBLER: So, I mean, stuff like that is just maddeningly imprecise. It just doesn't really allow you to hang a number on it and interpret it. And there wasn't, in the table, like checkmarks for the subjects, which --

MS. FIUME: I'm going to find it right now.

DR. LIEBLER: Okay.

DR. BELSITO: Yeah. And the other thing that worried me with the sensitization here was a fairly well documented outbreak in Finland with a moisturizing lotion. I'm just not sure that we have all the information on sensitization, and I was just wondering whether, from the HRIPTs -- let's see, Table 3. And then, also, the irritation data was sort of quirky. At 100 percent, sometimes it didn't seem to irritate. And then, others, it was corrosive. The information was sort of all over.

MS. FIUME: Don, there's a poster. So, I did want guidance from the panel whether anything from the poster, regarding that Finnish study, was available. I have a copy.

And actually, if you have any questions, Mike Fevola from INOLEX -- who INOLEX supplied a lot of the information -- is in the audience, if you have any specific questions. And then I don't know, Mike, if you'd like to identify yourself.

DR. FEVOLA: Good morning. Thank you. I'm Mike Fevola from INOLEX research and development. And yes, any questions you have related to any of these studies that we provided, we'd be happy to provide more background on.

The one document that Monice has mentioned, it was brought to our attention that the authors of the Finnish study presented a poster at the European Society of Contact Dermatitis last year in Milan. That was brought to our attention, so we've contributed that.

One of the things you'll see there is it offers very dramatic contrast in there from their initial conclusion based on the work they've done in follow-up.

DR. BELSITO: I'm sorry. I'm not following you because this poster essentially restates what they originally found. It doesn't contradict.

DR. FEVOLA: So their initial conclusion was that CHA or Caprylhydroxamic Acid was a sensitizer. And then, now, the final statement is that they just say that it may be. So, they've retreated from their initial publication, and they also have some contradictory data suggesting that where they believe there was associations with preservatives and Caprylhydroxamic Acid, they've now shown to the contrary that, in these follow-up subjects, that they can't make as distinct a correlation.

DR. BELSITO: Well, they say that, unfortunately, the products containing this could not be identified in products the patients are currently using. But they may have been sensitized from prior. I was at the Milan meeting; they were not retreating from the fact that they thought this was a sensitizer. They simply say that, in four subjects, they couldn't identify it.

It's just like when I test someone positive and they're found to be extremely reactive to neomycin. They probably aren't using it currently, but they've used it in the past and they became allergic. So, they were sensitized to it. It is a sensitizer.

If you want to take a look at this. I mean, I don't know that we have enough sensitization data on this. And I also thought the irritation data -- at least that's the note I have. Wasn't there somewhere that it was irritating? I thought, but I guess not. I'm not seeing it now in Table 3. I didn't mark it.

MS. FIUME: Don, while you're looking for that -- Dan, so the study where the conclusion states occasional edema is on PDF page 219 and the individual data follows. So far, it can find one "E," meaning edema, on day 3 of the challenge. It was in subject 42. But that's the only indication of edema that I am seeing. They had a .5, which corresponds to --

DR. BELSITO: Minimal irritation.

MS. FIUME: -- minimal irritation during the study occasionally. During induction patches, there was some minimal irritation in some subjects in one or two days in about two subjects, I believe. And one of those was the subjects with edema. But it wasn't prevalent throughout the raw data.

DR. LIEBLER: So I guess, Don, let's go back to you. What do you think about the wording, first of all, of the characterization of edema? Is there a better way to put it? And how does that influence your interpretation now?

DR. BELSITO: So it was subject 42. He or she, starting during the induction phase, had mild -- I'm having trouble reading this. I need to enlarge it. Sorry. TI; what is TI? I don't remember. Mild erythema. And then had edema on day 3 of the challenge which, to me, would represent a positive patch test. It had erythema and induration in edema. That would be a positive with a lot of suggestions that he was developing sensitization, or she, after the fourth induction. And then there were several others who were challenge-negative who developed erythema during the sensitization phases. It was mild. But I just -- I'm not happy with going with that.

DR. SNYDER: I certainly think it wouldn't be that out of line to ask for sensitization data at the max concentration and use. This was a 0.15. And we have a max concentration use of 0.3.

DR. BELSITO: But again, that's what got us into trouble with MI, if you remember. We had data, HRIPT in 100 patients, with 100 parts per million, that were negative. And it's going to depend upon -- you can't take highest concentration. It's not used in underarm deodorants, but it's used in baby products and it's used in lotions that could be applied to the underarm. I almost think that we need better data and possibly a QRA type approach with this as well, particularly given what the Finns found.

DR. SNYDER: Right. What you're basically saying is there's some cause for concern on the current data. So, let's just ask for it. This is just a draft, right?

DR. BELSITO: This is the first time we're seeing it.

DR. SNYDER: Yeah.

DR. BELSITO: I had a note about irritation, but I'm not finding it. No, I guess not. I basically said that we don't need dose responses for the metalloproteinases.

Dan, you'll write a sentence about that.

DR. LIEBLER: Right.

DR. BELSITO: We'll clarify the chelating binding. But I thought that we would need some type of QRA analysis or sensitization analysis on this. Basically, I said it could be safe when formulated to be non-sensitizing using methods such as the QRA. I guess irritation was not an issue.

MS. FIUME: I was wondering, was it where it showed up in that study in just a few subjects?

DR. BELSITO: Yeah. So, I think insufficient for sensitization and I'd like to see some type of QRA assessment, something similar to what we've done with MI and MCI/MI. Again, I'm concerned by that one patient and I'm concerned by the reports of the Finns. Anything else?

DR. LIEBLER: Thanks again, Mike, for your input.

DR. FEVOLA: Thank you.

DR. BELSITO: Okay. Alkanoyl Lactyl Lactates.

MS. FIUME: Just so I can clarify so when I do write up the IDA, are there specific parameters for the sensitization portion of the study that you would like to see?

DR. BELSITO: A NESIL and a calculation of the QRA. So, they can do dose per unit area and an HRIPT, come up with a NESIL, do it at the highest concentration being used, and then run it through a QRA.

MS. FIUME: Thank you.

Marks Team- June 6, 2019

DR. MARKS: Okay. Next is Caprylhydroxamic Acid. I feel like I'm in phonetics class. So, Monice, you're the writer again.

MS. FIUME: I am.

DR. MARKS: This is a draft report, meaning this is the first time we've seen this single ingredient. That's also rather rare. It's a chelating agent. We received, again, an unusual Wave 2 that only had data on one ingredient. That was this one. And it's absorbed through the skin.

The irritation and sensitization, from my viewpoint, look good. Ron, Tom, I'm not going to ask you if the ingredients are okay because we only have one ingredient. Any needs from your perspective, Tom or Ron?

DR. SLAGA: I didn't have any.

DR. SHANK: I think it's great. Monice asked the question in her cover letter, and I have my responses. There is ample HRIPT data to support skin sensitization is not a concern. Dr. Hill has a whole page, so let me see if I can digest this.

DR. SLAGA: It's almost lunchtime.

DR. MARKS: We have 20 minutes to go here. You may be hungry. I'm trying to remember. Which ingredient are you guys here for? Is it this one?

DR. FEVOLA: Yes.

DR. MARKS: Oh, so we did get to it before lunch.

DR. FEVOLA: Yes, thank you.

DR. MARKS: Thanks for staying. So we have some, perhaps, comments. I'll let you read Ron Hill, and then, based on -- so Ron Hill, as you've gathered, is absent today. He's our fourth panel team member, I should say, on this team. And Ron's a medicinal chemist, so he gets into the chemistry aspect.

DR. SHANK: Okay. He says there's information the compound would be significantly dermally penetrable from formulation. But rodent data shows rapid hydrolysis and liver homogenates. He says, consequently, the NICNAS margin of safety calculation is rendered questionable at best. And he feels there are needs: Need to assess the significance of dermal flux rates from (inaudible) cell experiments. As far as the potential for systemic toxicity, need information on systemic clearance sufficiency in humans as compared to rats. I guess that's the primary take. He doesn't think the N-nitroso boilerplate is needed. Basically, that's it.

DR. MARKS: So Ron Hill raises a question of the potential for systemic toxicity. We know it's absorbed, not only -- particularly with Wave 2 data. So Ron -- and I'm going to call on you in a minute. Ron Shank or Tom, you didn't have needs, so you weren't concerned about systemic toxicity?

DR. SHANK: Correct.

DR. MARKS: Do we need to bring that up tomorrow -- Ron Hill's concerns -- for the whole panel as a discussant point or not?

DR. SHANK: Well, we have repeated dose toxicity. It's oral. We have DART. It's oral. We have genotox, irritation sensitization. I think it's okay.

DR. MARKS: It will be in the minutes that we mentioned Ron Hill's concerns, and I think that's where it can stand at this point. Obviously, this is going to be the beginning of this ingredient, so there will be time in the future to comment again if needed.

And then, I presume you're from industry, manufacturer of this. Would you introduce yourself and then any comments that you have are welcome.

DR. FEVOLA: Yes. So my name is Michael Fevola. I'm from INOLEX. And we are a manufacturer and supplier of Caprylhydroxamic Acid. We've contributed a significant amount of data for this report. I'm happy to provide any additional context that may be helpful to the panel.

DR. MARKS: So tomorrow, I'm going to move that a tentative report be issued with safe conclusion.

Tom and Ron, any concerns with that?

DR. SLAGA: No.

DR. BERGFELD: I just want to ask a question about the quick hydrolysis. What does that -- how do you interpret that? That it's quickly dispersed, broken down to its component parts?

DR. SLAGA: Yeah.

DR. BERGFELD: And no toxicological sort of highlight there?

DR. MARKS: I assume you don't have any comments since at least our team feels that we can move forward with a safe conclusion? Usually, it's manufacturers want to clarify things if we come to a different conclusion or have insufficient data. But our team doesn't feel we need -- thank you for supplying the data you did. It helps us arrive at a conclusion.

DR. FEVOLA: You're welcome.

DR. MARKS: And, particularly the first round, it's very nice to have the data so we can make a conclusion and not have to issue an insufficient data announcement. Monice, you had something more?

MS. FIUME: Yeah. Actually, this was provided by INOLEX as well. This is just -- it's a follow-up to the Finnish study. It may be discussed tomorrow because Dr. Belsito also saw it. It's not in the report because it was from a poster, so it's not captured in the report right now. But it's just additional information that the other team saw as well. And it was just a follow-up to the Finnish study.

DR. FEVOLA: Yes. This was an additional data point that we ended up contributing. It was brought to our attention by a customer who attended the European Society for Contact Dermatitis meeting last fall. And this was a follow-up poster from the Finnish authors to their initial 2017 study.

DR. BERGFELD: So it doesn't have any cross-reactivity with the other preservatives here? Just the chelating agent across those who were positive MCI/MI, formaldehyde.

DR. MARKS: Well, I wouldn't put too much stock --

DR. BERGFELD: 12 out of 16.

DR. MARKS: -- about sensitized to other sources? I don't think we're talking about cross-reactivity.

DR. BERGFELD: No, but these are sensitive people. And to be hyper-reactive --

DR. MARKS: Oh, yeah. I know that, but -- let me go -- the thing that strikes me is they have 16 patients. So the question is -- let me go back in to where I looked. I didn't have a concern from an irritation or sensitization in the data we have, since it's -- let me go and review that one more time.

DR. BERGFELD: Is this going to be entered into the document?

MS. FIUME: It's a poster.

DR. BERGFELD: But it has a reference at the bottom.

MS. FIUME: So that study is in the document.

DR. BERGFELD: Okay.

MS. FIUME: It was actually that Finnish study that put this ingredient -- it came into Dr. Belsito's purview. He saw it, so that was added for cause to our priority list because of that Finnish study.

DR. BERGFELD: Okay.

DR. MARKS: I think what I based it on is there were a number of studies, like HRIPT, that did not show that this was a sensitizer. I'm glad you're here. How do you interpret this? And it's really interesting the title from the 2017 article is "An Epidemic Caused by a New Allergen." So how do you interpret that because, when I look at the background HRIPT

sensitization, irritation sensitization, lots of HRIPTs, they're all clean. No evidence of sensitization, not even a hint. How do you reconcile with the clinical report here?

DR. FEVOLA: So I'm a chemist, not a clinician. So I would defer to the clinicians on the interpretation. I can say our experience with this ingredient over a ten-year period, the Finnish report was the only complaint or adverse event that we've ever been notified or made aware of, with respect to Caprylhydroxamic Acid.

We've completed the HRIPT work in response to that specific event and submitted that data as part of our investigation in that report.

DR. BERGFELD: What did you find?

DR. FEVOLA: The HRIPT results that are presently in the report.

DR. MARKS: Yeah. There are a number of them.

DR. BERGFELD: Yeah. I saw those.

DR. MARKS: And they're all negative, correct?

DR. FEVOLA: Initially, for the NICNAS submission, we also conducted an earlier HRIPT that was actually on the neat material that was 50 subject HRIPT. The subsequent studies that are in the report were on --

COURT REPORTER: Can you speak louder?

DR. FEVOLA: Yes. The subsequent studies that were in the report are on in the ingredient in formulation and in blends with other ingredients.

DR. MARKS: I guess also reassuring to me is, if I have my numbers correctly, the highest concentration is 0.25 percent. And the human HRIPTs were at 15 percent, so markedly higher than what the use concentration is.

DR. FEVOLA: The HRIPTs, as tested, were 0.3 percent of the active. So there was a 15 percent in the blend diluted to a 0.3 percent.

DR. MARKS: So that's at the use concentration? Thank you for clarifying that. I think it will be interesting in the discussion tomorrow. I'll still move for a tentative report safe. We'll see what the Belsito team -- obviously, in the discussion, we have to note the clinical experience in Finland and the HRIPTs. It will be interesting if -- and these were whether another conclusion could be safe, as long as formulated to be non-sensitizing in a QRA. And then, that way, it gets into where there are specific uses in Finland. This was in -- what was the product? Eczema on the face?

MS. FIUME: It was a moisturizer.

DR. ANSELL: The Finnish was not actually based on patch testing. It was their deduction that it was caused by this product, which contained Caprylhydroxamic Acid.

MS. FIUME: The study is under provocative testing on PDF page 14. So it looks as if, when the positive results came across, it was because a moisturizer was reformulated for the preservative from parabens to using the Caprylhydroxamic Acid. And after reformulation, they saw an outbreak in some of the patients that were using the newly formulated moisturizer. And then they did do follow-up patch testing, and Table 4 has those results.

DR. MARKS: Yeah. And they're in the poster. They patch tested 1 percent, Jay. Caprylhydroxamic Acid, they patch tested 1 percent. And the moisturizer was Apobase. So it was really used not as a chelating agent in this case. It's used as a preservative.

DR. FEVOLA: It's a chelating agent that's a component of a preservative blend. The product also contained phenoxyethanol as a preservative with the chelating agent.

DR. MARKS: So this is clearly an alert.

DR. FEVOLA: Just one point on the Finnish study. I encourage the panel to look closer at that initial publication. When they were conducting their patch testing, because of their inability to obtain Caprylhydroxamic Acid in several cases, they used the potassium salt of the ingredient, which would be expected to have very different properties being a basic salt versus the acid. So that was one item of note in the 2017 paper that was noted about their patch testing.

DR. MARKS: Hmm. So Tom and Ron, your input? The safest would be formulated to be non-sensitizing. And that would cover. Otherwise, you'd have to -- we know at use concentration, from the HRIPT, that it was a non-sensitizer.

DR. SLAGA: And when it was, it was in --

DR. BERGFELD: Did you document that potassium salt, that that's what they used?

DR. FEVOLA: That is in their publication within their materials and methods.

DR. BERGFELD: We could cite it then in discussion?

MS. FIUME: Yes. In Table 4 -- I'd have to I look back at the paper. I don't think it's stated in the published paper when the salt was tested versus the acid itself, but I will look back. But on PDF page 21, the center rows of the table are patch testing with the Caprylhydroxamic Acid or its potassium salts. And it gives the range from 0.001 percent to 3.2 percent testing.

DR. SHANK: Yeah. The very last sentence in that report says the researchers really left it open. And they suggest that follow-up studies needed to clarify the significance that Caprylhydroxamic Acid is a contact allergen. So they didn't conclude it was.

DR. BERGFELD: Well, then the company gives a repeat insult patch test, and they showed it wasn't.

DR. MARKS: You don't have a local lymph node assay to say what's the potential sensitizing capacity?

DR. FEVOLA: We do not.

DR. MARKS: Because that would be very helpful to sort out as to is there a small potential, no potential, medium. And we don't have a guinea pig max either. We basically have human studies.

Well, I think we can move -- what I thought was going to be easiest turned out not to be quite as easy. Again, thanks for being here. We're going to move a tentative report be issued. At least, I will.

Then I think the question is do we just do safe and deal with this in the discussion, where we have the HRIPT that indicates that it is safe? Or do we take in -- we obviously will mention this clinic alert of sensitivity in this Apobase in Finland. That's correct? The Finnish product is Apobase in Finland? That one product moisturizer.

And if we took that in consideration, we could always say safe when formulated to be non-sensitizing based on a QRA -- something to that effect. Because when I look here, the diagnoses -- one was hand eczema, and they don't talk about anogenital in here. So I presume they're not wipes. But certainly based on the MI epidemic and MCI/MI, the quantitative risk assessment would have identified in those areas.

DR. SHANK: So the Finnish data, do they take precedence over the HRIPT studies?

DR. SLAGA: I don't see how it can.

DR. MARKS: My feeling would be the clinical alerts take precedent because you demonstrate patch testing 1 percent. Presumably, that's not an irritant -- that there were positive reactions. And despite -- I think it's like if any new drug when it's released, the FDA requires a certain amount of studies to be done. But then, when you get it out among a general population, there could be, now, toxicity that occurs which wasn't predicted or seen in the studies going up.

So even though the HRIPT is important, if we had already approved this ingredient as safe and three years from now we got this alert, I would have been in favor of considering reopening to look at this data and try and put it in perspective. And I'm not quite sure at this point. That's why I put the alternative is formulated to be non-sensitizing based on QRA -- that sort of thing. So it's up to the formulator to formulate it to be non-sensitizing.

Do you have any other comments from industry?

DR. FEVOLA: No, not at this time.

DR. MARKS: So we'll see what the Belsito team -- but I'm going to go ahead and recommend that we move forward with a tentative report. And we'll see. I'll give those two options. It's going to be a safe conclusion. It depends on whether it's safe with a QRA or not, I think. We'll see what the Belsito team says.

Does that clarify it, Ron, for you?

DR. SHANK: Yes, thank you.

DR. MARKS: You're welcome. Okay.

DR. FEVOLA: Thank you to the panel for the opportunity to contribute.

DR. SLAGA: Thank you.

DR. MARKS: You're welcome.

Probably the final note on that, Ron Shank, would be I would have liked to have seen an HRIPT with this Apobase, the actual moisturizer, and seen what came out of that.

DR. SLAGA: They had other things in it, too, though, right?

DR. BERGFELD: What?

DR. SLAGA: That was compared to potassium salt, is it?

DR. BERGFELD: They didn't do that. That's what it was. What about the vehicle? Did they test the vehicle? I didn't see that in that.

MS. FIUME: So on Table 4, they did look at the -- the positive results were seen in patients but not normal subjects. And they looked at the preservative mixture, as well as the Caprylhydroxamic Acid by itself, as well as the preservative system in different vehicles. And that's what it presented in that Table 4.

DR. BERGFELD: What page is that?

MS. FIUME: PDF Page 21.

DR. MARKS: That's why I actually -- 21.

DR. BERGFELD: Well, here's the vehicle responding.

MS. FIUME: That was the new formulation in the different vehicles.

DR. MARKS: It's because the investigator separated it out. Sometimes you get it that they had -- reacted to the whole product, and you don't know which ingredient it is. But they separated things out; so that, to me, holds more weight. That was again Table 21? I had closed --

MS. FIUME: PDF Page 21, Table 4.

DR. BERGFELD: The results are sort of interesting because the potassium salt is positive at 0.10 and up to 1 percent. And then the vehicles are positive, too -- reasonably high. The top box is the vehicle -- oily cream and lotion.

DR. MARKS: To me, that's everything.

MS. FIUME: That includes the preservatives.

DR. MARKS: So that's not surprising. That was the tip-off when the patients were using this new moisturizer, they started reacting. I think they did a very nice job of sorting this out.

DR. BERGFELD: So you don't think that's the vehicle? You just think that's the whole product?

DR. MARKS: Correct. And then when they broke it out, the Caprylhydroxamic Acid was positive down to 0.1 percent. And then the preservative mixture was positive also, but the preservative mixture, obviously -- if that was the only thing we had, we'd say, "Well, what else is in the preservative mixture?" But they separated it out.

DR. BERGFELD: But there seems to be a threshold for sensitization with those percentages.

DR. SLAGA: Yes.

DR. MARKS: For elicitation. I'm not sure of sensitization. Certainly, the elicitation is -- and not surprising if our maximum concentration is 0.25 percent, it's not surprising that they might react at a lower concentration on patch testing.

DR. BERGFELD: But then on Table 3, that's under irritation sensitization, you have a spread of the concentrations being tested from 0.45 down to 0.3.

DR. MARKS: Yeah.

DR. ANSELL: It really looks more like an irritation table than a sensitization table, doesn't it?

DR. BERGFELD: They said there was sensitization.

DR. MARKS: You mean Table 4? I didn't go back. Presumably, when they chose these concentrations, they had done that. Because what did you say, Monice? The controls had no reaction?

MS. FIUME: That's what it says, the normal controls had no reactions. But the reactions were seen in the patients.

DR. MARKS: Right. So that would indicate that, Jay, to me, they were patch testing with a concentration which was non-irritant.

DR. ANSELL: No. But it's concentration dependent. And typically, we don't think of elicitation in this.

DR. MARKS: Oh, I do. I think sensitization there's gradations, too, depending on the subject.

DR. BERGFELD: I agree.

DR. MARKS: That's why some people -- they just smell poison ivy. They say they're ten yards away, and they get poison ivy allergic contact dermatitis. And there are others that they're working like heck in it, and they might get just minimal reaction. So I think there's gradations of sensitivity among individuals. I don't think it's a yes/no. You're going to make another comment?

DR. FEVOLA: To the point on the potassium salt and where this introduces uncertainty. So the chemistry of Caprylhydroxamic Acid is that it has -- Hydroxamic Acid has a relatively high pKa, which other organic acids pKa is about nine and a half.

So, by testing the potassium salt, we have a very alkaline compound. So patching of the alkaline needed would be like patching soap, essentially -- that alkalinity. So something to consider when looking at the acid versus the salt compound.

DR. MARKS: Per Jay's comment about irritation, I hear you. But I'm reassured that the controls on the negative patch test with the concentrations they were using. Well --

DR. BERGFELD: Interesting.

DR. MARKS: I know Don's greatest fear is going to be is this going to be another MCI/MI story down the line. And obviously, one way of hopefully preventing that would be the utilizing a QRA and formulating it. But we'll see tomorrow what the discussion is.

Any other comments? So I'm going to move that it's safe. And then the question is do we add a proviso, safe when formulated to be non-sensitizing? And we have this, I would say, conflicting data that the irritation and sensitization is okay in the HRIPT. But then we have this small outbreak of allergic contact dermatitis, which seems to be well documented to the Caprylhydroxamic Acid in this Apobase moisturizer. Okay.

Any other comments? Sound good, Ron, Tom?

DR. SLAGA: Yes.

Full Panel – June 7, 2019

DR. MARKS: So this is the first review of this solo ingredient, which acts as a chelating agent. We know it's absorbed. That was sent to us in Wave 2. The irritation and sensitization data, including the HRIPT, were okay. But we had a clinical alert in that a moisturizer called Apobase, in Finland, caused allergic contact dermatitis, and patch testing with this ingredient revealed positive patch test.

So, we felt we could move forward with a tentative report. I'll move that a tentative report be issued. And the question is would it be safe, or do we have safe when formulated to be non-sensitizing based on a QRA or other method. And, our team was a little bit torn as to which way to move forward with that. If we did safe alone, then we would want in the discussion a robust --

DR. BERGFELD: Do you want a comment here?

DR. MARKS: Sure.

DR. FEVOLA: Thank you, Dr. Marks. Mike Fevola, from Inolex, and in the course of watching the panel discussions yesterday I just thought I can contribute some comments that may shed some insight, particularly around the Apobase publication from the Finnish team.

So, Caprylhydroxamic Acid is an ingredient that Inolex has marketed since 2008, so we have a great deal of experience with this compound. In addition to the VCRP, which reports 227 uses we also monitor it closely globally. I'll past around and submit for the record a report from the Mintel Global New Products database that documents 3,567 reported uses of Caprylhydroxamic Acid. And that's based on ingredient INCI label reporting. So I can submit that if anyone cares to have a look.

Based on that number of uses over the past 10 years, we were extremely puzzled when we saw the report of the Apobase case. We had never encountered any other adverse event report associated with contact dermatitis or allergenicity in all that time of marketing CHA. So we took it very seriously and delved into it. So I can share a little bit of insight into how we've looked at that.

We spoke with many of our customers. We do a lot of adverse event monitoring and reporting, and we inquired with them to see if they had ever experienced anything of that nature. They had never reported any incidents that were consistent with what the Finnish authors reported.

We commissioned an investigation of the paper ourselves, with some toxicologists who critically reviewed the paper, and noted that in the testing the potassium salt of CHA was used in some instances on the 39 subjects as well as on the eczema control group and on the healthy volunteer control group.

So, that introduces one confounding element because the potassium salt of Caprylhydroxamic Acid is an alkaline material, would have caustic characteristics. And the analogy would be the difference between patching fatty acid versus patching a soap on the skin. And the authors did not delineate that within their results.

The other piece is that the results for the healthy volunteers and eczema control group were not reported in that paper, and the authors also did not take into account the other ingredients. And Dr. Bergfeld made a comment yesterday on the potential of cross-sensitization. In looking at that formulation, we understood that it also contains Ceteareth-20 and Ceteareth-12 (phonetic) as emulsifiers. And it has been reported by Berg (phonetic) and co-authors in the past that atmospheric oxidation of

alcohol ethoxylates, so for example improperly stored or handled alcohol ethoxylates, can contribute to oxidation byproducts including formaldehyde. As we all know have potential sensitizing capabilities. So, that also was not accounted for in the Finnish study.

So, in light of, you know, these things that we've learned, with our experience with over 3500 products in market with Caprylhydroxamic Acid, and this being the only adverse event, our suggestion to the panel is to kind of weigh that and take into account the HRIPT evidence that has been contributed on both neat CHA, as well as on CHA in formulations, in coming to a conclusion regarding the sensitization potential of Caprylhydroxamic Acid. Thank you.

DR. BERGFELD: Thank you.

DR. MARKS: What happened to Apobase moisturizer? Was that reformulated? Is that a Finnish product?

DR. FEVOLA: Yes, Apobase is a Finnish product. There were two products.

DR. MARKS: Yeah, and what did they do?

DR. FEVOLA: They reformulated to another preservative system that included caprylyl glycol and phenoxyethanol.

DR. MARKS: So, Don, you could see where we were. I mean, we have a safe conclusion it's just whether --

DR. BELSITO: I would disagree with that. So the HRIPT, first of all this is used up to 0.25 percent in leave-ons. The HRIPT was done at 0.15%, and there was one individual who developed periodic episodes of erythema, and then developed edema at 48 hours after the challenged patch test. So there's something going on there. And I think we need to define -- we need to get a NESIL on this and do a QRA. I think this is a potential sensitizer.

The neat study was irritation. Irritation is not an issue that was not an epiderm. But the HRIPT was done at 0.15%, which is below the maximum level of leave-on. We don't know where those leave-ons necessarily can end up. I mean, I think that the Finns had a very strong signal. This was a very -- one of those buzzy things at the ESCD meeting in Milan last fall. Much like the glucosides, people were surprised. But one of reasons there may not be case reports is have you ever tested for this material? I haven't.

DR. MARKS: So you would propose an insufficient data announcement?

DR. BELSITO: Right.

DR. MARKS: So I withdraw my motion, and either I will second the insufficient data announcement or propose it, either way.

DR. BERGFELD: Why don't we say it's seconded? Don has proposed it.

DR. MARKS: Second.

DR. BERGFELD: All right. Any further discussion then?

DR. MARKS: And so we have the needs, the QRA and the NESIL.

DR. BELSITO: Yes. HRIPT to determine the NESIL. I'm not comfortable with this HRIPT given that -- and there were several other instances where during the induction there was faint erythema seen. So there was something going on there. I'm not sure what, but I would like further clarification, particularly given that cluster.

And as you know, the Scandinavians are much better than we are, and many other groups, in following up when they see a product, and identifying ingredients and testing with the ingredients. In their test they were positive both to the formulation and to the Caprylhydroxamic Acid, but not the old products. So, I think there's enough concern there that we need to be certain.

DR. BERGFELD: Curt?

DR. KLAASSEN: I agree.

DR. BERGFELD: Paul?

DR. SNYDER: I'm fine.

DR. BERGFELD: Dan?

DR. LIEBLER: Yep.

DR. BERGFELD: Ron?

DR. SHANK: Okay.

DR. BERGFELD: Tom?

DR. SLAGA: Okay.

DR. BERGFELD: Okay. All right, any other comments? Thank you very much for presenting.

DR. BELSITO: We need a vote?

DR. BERGFELD: All those in favor please indicate by raising your hand. Unanimous.

DECEMBER 2019 – SECOND REVIEW/DRAFT TENTATIVE REPORT

Belsito Team – December 9, 2019

DR. BELSITO: Caprylhydroxamic acid, we have been asked to table. Is that the one?

MS. FIUME: Yes.

DR. BELSITO: Yeah. I was fine with tabling it. They're doing an HRIPT and a QRA. This is the one that was creating the issues in Finnish products -- Finnish, the country, not finished. Okay, so we're tabling that. Curt, you're okay with that?

DR. KLAASSEN: Yes.

Marks Team – December 9, 2019

DR. MARKS: So caprylhydroxamic acid. Oh, this one could be short.

DR. SLAGA: Table.

DR. MARKS: Table until March when we will get the HRIPT, the QRA, and the NESIL. And that was the -- there was concern about sensitization from the caprylhydroxamic acid in a Finnish moisturizer, Lisa -- I don't know if you picked that up in reading this -- called Apobase. And so, that's what prompted the request for these further endpoints, toxicologic endpoints.

So, it's in process of getting the HRIPT by industry, the QRA calculation, the NESIL, and so, table. Anybody -- Ron, Tom? You already -- table? I agree, table. We'll be seconding it anyway.

DR. PETERSON: I thought it was table.

DR. MARKS: Yeah. I mean, that's --

DR. MARKS: Yeah, exactly. Ron Shank?

DR. SHANK: Yes, table.

DR. MARKS: Yep? Okay.

Full Panel – December 10, 2019

DR. BELSITO: Caprylhydroxamic Acid, at the last go around we had asked for HRIPT at maximum use concentration and a QRA. We've been notified that the company is doing these studies, but unfortunately they will not be available until our spring meeting, so, we will table this report.

DR. BERGFELD: And, there's no need for a second on a table. Call for a vote, all those in favor of tabling? Thank you, unanimous. So this ingredient is tabled until the spring meeting.

Safety Assessment of Caprylhydroxamic Acid as Used in Cosmetics

Status: Draft Tentative Report for Panel Review
Release Date: May 15, 2020
Panel Meeting Date: June 8 - 9, 2020

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

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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 in cosmetics. Nitrosamide formation is theoretically possible with Caprylhydroxamic Acid, but is unlikely; however, manufacturers should use good manufacturing practices to monitor for the formation of nitrosamides as a potential impurity. The Panel considered all the available data, and concluded [to be determined].

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* (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 the 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.

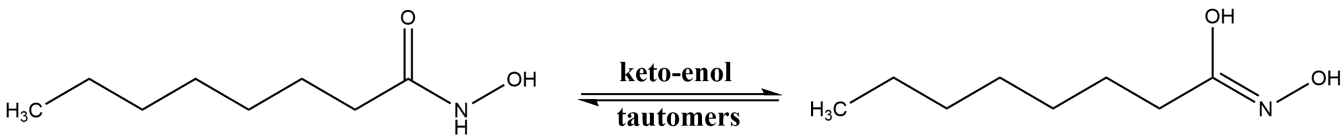

Figure 1. Caprylhydroxamic Acid

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 the inhibition of a 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.

Physical and Chemical Properties

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

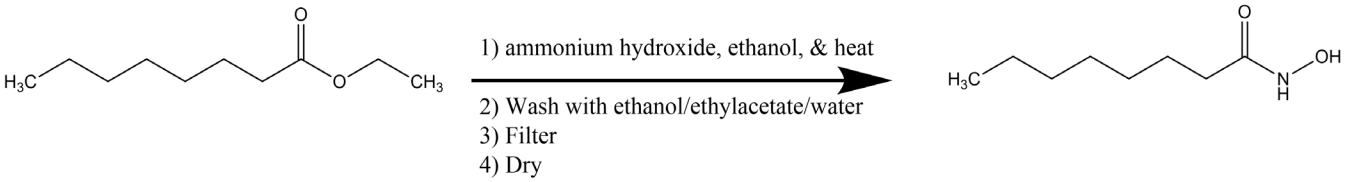

Figure 2. Example of a synthesis route for the commercial production of Caprylhydroxamic Acid, using ethyl caprylate

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.

Nitrosation

Nitrosamides are chemicals containing the R-C(O)-N=NO functional group. Due to the presences of a reactive *N*-hydrogen substituent (i.e., identity as a secondary amide), the theoretical potential for the formation of nitrosamides exists with hydroxamic acid derivatives. Of concern in cosmetics, is the conversion of secondary amides into nitrosamides that may be carcinogenic. In a group of *N*-nitroso compounds that have been tested, 79 of the 86 nitrosamides have been shown to produce cancer in laboratory animals.[8] Nitrosation can occur under physiologic conditions.[9] Depending on the nitrosating agent and the substrate, nitrosation can occur under acidic, neutral, or alkaline conditions. However, nitrosation occurs most commonly under acidic conditions. Atmospheric NO_2 may also participate in nitrosation in aqueous solution.[10]

However, while indirect test methods have supported the likelihood of formation, such *N*-nitrosated hydroxamic acid derivatives have yet to be isolated (likely due either to rapid decomposition or facile molecular rearrangement).[11] Also, no carcinogenicity studies specific to *N*-nitrosated hydroxamic acid derivatives were found in the publicly available literature.

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 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.[12] (Table 2) Information supplied to the Panel states that the Mintel Global New Products Database has reported the launch of at least 4356 marketed products containing Caprylhydroxamic Acid in a 10-year period, from 2009 - 2019.[13]

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.[14] 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 2 uses reported to the VCRP that could result in incidental ingestion (i.e., lipsticks), concentration of use data were 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, 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.[15,16] 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.[17,18] 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.[19-21]

Caprylhydroxamic Acid is not restricted from use in any way under the rules governing cosmetic products in the European Union.[22]

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

The margin of exposure (MOE) was then calculated using the total SED of 1.17 mg/kg bw/day and a no-observable-adverse-effect-level (NOAEL) of 50 mg/kg bw/day (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%.

Non-Cosmetic

Use of Caprylhydroxamic Acid as a growth-promoting feed additive was reported.[23] (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.[24] 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.[25] (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.[25] "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% 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.[26] (Further details were not available.)

Subchronic Toxicity Studies

Oral

Groups of 10 male and 10 female Wistar rats were dosed for 13 wks with 0, 100, 500, or 2500 mg/kg bw/day 10% Caprylhydroxamic Acid in lactose (corresponding to 0, 10, 50, and 250 mg/kg bw Caprylhydroxamic Acid, respectively) by gavage.[2,27] 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/day 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.[2,28] The vehicle was 5% gum arabic solution. 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 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 towards *E. coli* at concentrations up to 1000 µg/plate, but was not mutagenic to *S. typhimurium*.[23] 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.[29] 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^-.[23] (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.[30] 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-h 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.[13] 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) 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.[26] Tissue viability was 102.6%.

In human repeated insult patch tests (HRIPTs), cosmetic formulations containing 0.105% Caprylhydroxamic Acid (54 subjects; 24-h semi-occlusive patches),[31] 0.15% Caprylhydroxamic Acid (109 subjects, 48-h occlusive patches),[32] and 0.195% Caprylhydroxamic Acid (52 subjects; 24-h semi-occlusive patches),[33] an aqueous formulation containing 0.76% Caprylhydroxamic Acid (205 subjects; 24-h semi-occlusive patches),[34] Caprylhydroxamic Acid at 1.9% in petrolatum (95 subjects; 24-h occlusive patches),[35] and 100% Caprylhydroxamic Acid (52 subjects; 24-h semi-occlusive patches),[36] were not considered irritants or sensitizers. In eight HRIPTs completed concurrently in a shared panel (104 subjects; 24-h occlusive patches) in which 3 formulations containing 0.15% Caprylhydroxamic Acid were tested neat,[37-39] 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),[40-44] 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-h 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.[45]

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.[13] 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,[32,36] it was not possible to calculate the dose per unit area exposure, and the third study[34] 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 appropriate sensitization assessment factor (SAFs) were applied. For this assessment, QRA2 SAFs were used.

AEL = WoE NESIL/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, 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."

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.[46] 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 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.[47] 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.[48] 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 preservative mixture that consisted of 65 – 75% phenoxyethanol, 10 – 20% Caprylhydroxamic Acid, and 5 – 10% methylpropanediol, resulting in an actual concentration of 0.075 – 0.15% Caprylhydroxamic Acid 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; the preservative mixture itself diluted in petrolatum (pet.; test concentrations, 0.05% - 1.5%); and Caprylhydroxamic Acid (or its potassium salt) diluted in pet. (test concentrations, 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 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.[49] A total of 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 make-up 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.[50] 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. 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/day. Using this SED and an NOAEL of 50 mg/kg bw/day (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) containing 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 $^{14}CO_2$ 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-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 (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/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 (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 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.

Caprylhydroxamic Acid was not irritating or sensitizing in numerous studies. Tested neat, it was classified as non-irritant in an EpiDerm™ skin irritation test reconstructed human epidermis tissue containing keratinocytes. In HRIPTs, cosmetic formulations containing 0.105% Caprylhydroxamic Acid (54 subjects; 24-h semi-occlusive patches), 0.15% Caprylhydroxamic Acid (109 subjects, 48-h occlusive patches), and 0.195% Caprylhydroxamic Acid (52 subjects; 24-h semi-occlusive patches), an aqueous formulation containing 0.76% Caprylhydroxamic Acid (205 subjects; 24-h semi-occlusive patches), Caprylhydroxamic Acid at 1.9% in petrolatum (95 subjects; 24-h occlusive patches), and 100% Caprylhydroxamic Acid (52 subjects; 24-h semi-occlusive patches), were not considered irritants or sensitizers. In 8 HRIPTs completed concurrently (104 subjects; 24-h 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-h 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. The results of several HRIPTs were used to calculate a WoE NESIL of 1056 µg/cm^2. For each cosmetic product category, AELs were determined using this NESIL and appropriate QRA2 SAFs, and CELs were determined by for the reported maximum concentrations of use for Caprylhydroxamic 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.

DRAFT DISCUSSION

[*Please note, this discussion is in draft form and will be modified following the meeting.]*

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 straight alkyl chain, and the hydroxamates that are reported to be the most effective chelators are not straight chain molecules. Additionally, because Caprylhydroxamic Acid is a straight alkyl chain, concern about a potential effect on metalloproteinase enzymes was mitigated.

The Panel discussed that *N*-nitrosamide formation is theoretically possible with Caprylhydroxamic Acid, but such formation is unlikely. However, manufacturers should continue to use good manufacturing practices to monitor for the formation of *N*-nitrosamides as a potential impurity.

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, 95% – 99% of 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

[to be determined]

TABLES

Table 1. Physical and 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 @ 25ºC)	0.3413 (sample not compressed)	2,3
	0.4789 (sample tamped down)	
Vapor pressure (mm Hg @ 25 ºC)	2.50 x 10^{-6} (estimated)	2
Melting Point (ºC)	≥ 78 to ≤ 81	3
	81	2
	79 - 81	26
Boiling Point (°C)	343.32	26
Water Solubility (g/L @ 23ºC)	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

Table 2. Frequency (2020) and concentration (2018) of use of Caprylhydroxamic Acid

	# of Uses[12]	Max Conc of Use (%)[14]
Totals*	**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[a]; 83[b]	0.075 (aerosol and pump)
		0.075 - 0.23[a]
Incidental Inhalation-Powder	4; 83[b]; 4[c]	0.12[c]
Dermal Contact	243	0.11 – 0.3
Deodorant (underarm)	1[a]	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

*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 – not reported

Table 3. Dermal irritation and sensitization studies *

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%	26
HUMAN					
Irritation and Sensitization					
eyeliner formulation containing 0.105% Caprylhydroxamic Acid	applied neat; 0.2 ml induction and challenge conc:[13] 32.3 µg/cm^2	54 subjects	HRIPT induction: 24-h semi-occlusive patch (1 in^2) applied to the upper back 3 x/wk for 3 wks, for a total of 9 applications; test sites were evaluated 24 or 48 h after patch removal challenge: after a 2-wk non-treatment period, a 24-h 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	31
facial cream containing 0.15% Caprylhydroxamic Acid	applied neat; 0.02 ml dose/unit area could not be calculated[13]	109 subjects	HRIPT induction: 48-h occlusive patch applied 3x/wk for 3 wks challenge: after a 2-wk 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	32
brow thickening powder containing 0.195% Caprylhydroxamic Acid	applied neat; 200 mg product (0.39 mg Caprylhydroxamic Acid) induction and challenge conc:[13] 60.0 µg/cm^2	52 subjects	HRIPT induction: 24-h 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 wks, for a total of 9 applications; test sites were evaluated 24 or 48 h after patch removal challenge: after a 2-wk non-treatment period, a 24-h 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)	33

Table 3. Dermal irritation and sensitization studies *

Test Article	Concentration/Dose	Test Population/System	Procedure	Results	Reference
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 conc:[13] 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-h occlusive patch (¾ in^2) applied to the upper back 3 x/wk for 3 wks, for a total of 9 applications; test sites were evaluated 24 or 48 h after patch removal challenge: after a 2-wk non-treatment period, a 24-h 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 2and 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 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"	[37]
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 dipolyhydroxy-stearate; 3% glycerin; 2% beeswax) [concentrations stated as provided]	applied neat; 0.2 ml induction and challenge conc:[13] 83.3 µg/cm^2	(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 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	[38]

Table 3. Dermal irritation and sensitization studies *

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 conc:[13] 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	[39]
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 conc:[13] 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	[40]
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 conc:[13] 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	[41]

Table 3. Dermal irritation and sensitization studies *

Test Article	Concentration/Dose	Test Population/System	Procedure	Results	Reference
formulation containing 10% Caprylhydroxamic Acid (and 75% glyceryl caprylate and 15% glycerin)	tested as a 3% dilution with distilled water (resultant test concentration – 0.3% Caprylhydroxamic Acid); 0.2 ml induction and challenge conc:[13] 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: 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	[42]
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 conc:[13] 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	[43]

Table 3. Dermal irritation and sensitization studies *

Test Article	Concentration/Dose	Test Population/System	Procedure	Results	Reference
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 conc:[13] 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	[44]
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-h semi-occlusive patch (¾ in^2) applied to the upper back 3 x/wk for 3 wks, for a total of 9 applications challenge: after a 2-wk non-treatment period, a 24-h 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)	[34]
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 conc:[13] 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-h 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 wks, for a total of 9 applications challenge: after a non-treatment period of at least 10 days, a 24-h 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	[35]

Table 3. Dermal irritation and sensitization studies *

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 conc:[13] 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-h 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 wks, for a total of 9 applications challenge: after a non-treatment period of at least 10 days, a 24-h 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	[45]
Caprylhydroxamic Acid, 100%	amount applied not stated	52 subjects	HRIPT induction: 24-h semi-occlusive patch (1 in^2) applied to the upper back 3 x/wk for 3 wks, for a total of 9 applications; test sites were evaluated 24 or 48 h after patch removal challenge: after a 2-wk non-treatment period, a 24-h 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	[36]

*dose/unit area and induction and challenge concentrations portrayed in µg/cm^2 were not expressed explicitly in the submitted studies, bye were calculated separately[13]

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[37]	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[E1] (P4) 2[E2] (P5) disc (P6+)	1[E1] (P8) 0.5 (P9)		0.5 (P8-9) 0.5 (D1) 1[E1] (D2)			0.5 (P6)	0.5 (P4-5)	0.5 (P2)
water-in-oil (W/O) thick balm containing 0.15% Caprylhydroxamic Acid[38]	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[E1] (P4) 2[E2] (P5) disc (P6+)	0.5 (P8-9)		0.5 (P5-9) 1[E1] (D2)				0.5 (P4-5)	
"wipe juice" containing 0.15% Caprylhydroxamic Acid[39]	94.85% water; 3% propanediol; 2% polysorbate 20				0.5 (P 6,8) 1[E1] (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[40]	30% hexanediol; 65% propanediol		2[E1] (P7) (patching moved to adjacent site)	0.5 (P5)	0.5 (P4,8) 1 (P9) 0.5 (D1) 1[E1] (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[41]	92.5% propanediol		0.5 (P 8)		0.5 (P 4-8) 1[E1] (D2)		0.5 (P3)	0.5 (P6-8)	0.5 (P3) 1[E1] (P4-5) 0.5 (P6)	
formulation containing 10% Caprylhydroxamic Acid (tested as a 3% dilution)[42]	75% glyceryl caprylate; 15% glycerin		0.5 (P4-5)	0.5 (P5)	0.5 (P5-6, 8) 1 (P9) 0.5 (D1) 1[E1] (D2)	0.5 (P7) did not continue study	0.5 (P3-4)	0.5 (P5-7)	1[E1] (P3-5) 0.5 (P6-8)	
formulation containing 15% Caprylhydroxamic Acid (tested as a 2% dilution)[43]	70% phenoxyethanol; 7.5% methylpropanediol; 7.5% water		2[E1] (P 7) (patching moved to adjacent site	0.5 (P5)	0.5 (P5-6, 8) 1 (P9) 0.5 (D1) 1[E1] (D2)		0.5 (P3)	0.5 (P6-7)	1[E1] (P3-5) 0.5 (P6)	
formulation containing 15% Caprylhydroxamic Acid; tested as a 2% dilution[44]	71% caprylyl glycol; 14% glycerin		2[E1] (P 7) (patching moved to adjacent site		0.5 (P5-8) 0.5 (D2)			0.5 ((P6-8)	1[E1] (P3-5) 0.5 (P6-8)	

Abbreviations: D –day post-challenge; disc – discontinued patching for this formulation; E - edema; 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[13]

Product Category	Classification	Max Conc of Use (%)	Product Exposure (µg/cm²)	CEL (µg/cm²)
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

Table 6. MOS for skin sensitization by product category based on reported maximum concentrations of use of Caprylhydroxamic Acid[13]

Product Category	NESIL (µg/cm²)	QRA2 SAF	AEL (µg/cm²)	CEL (µg/cm²)	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

Table 7. Patch test results in patients with compromised skin that had suspected contact allergy to a new moisturizer formulation[48]

	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***

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2020 VCRP Data

CAPRYLHYDROXAMIC ACID	Baby Shampoos	2
CAPRYLHYDROXAMIC ACID	Baby Lotions, Oils, Powders, and Creams	4
CAPRYLHYDROXAMIC ACID	Other Baby Products	1
CAPRYLHYDROXAMIC ACID	Eyebrow Pencil	5
CAPRYLHYDROXAMIC ACID	Eye Lotion	6
CAPRYLHYDROXAMIC ACID	Mascara	1
CAPRYLHYDROXAMIC ACID	Other Eye Makeup Preparations	6
CAPRYLHYDROXAMIC ACID	Cologne and Toilet waters	1
CAPRYLHYDROXAMIC ACID	Hair Conditioner	3
CAPRYLHYDROXAMIC ACID	Shampoos (non-coloring)	9
CAPRYLHYDROXAMIC ACID	Tonics, Dressings, and Other Hair Grooming Aids	1
CAPRYLHYDROXAMIC ACID	Other Hair Preparations	8
CAPRYLHYDROXAMIC ACID	Face Powders	4
CAPRYLHYDROXAMIC ACID	Foundations	2
CAPRYLHYDROXAMIC ACID	Lipstick	2
CAPRYLHYDROXAMIC ACID	Other Makeup Preparations	2
CAPRYLHYDROXAMIC ACID	Bath Soaps and Detergents	2
CAPRYLHYDROXAMIC ACID	Deodorants (underarm)	1
CAPRYLHYDROXAMIC ACID	Other Personal Cleanliness Products	2
CAPRYLHYDROXAMIC ACID	Shaving Cream	1
CAPRYLHYDROXAMIC ACID	Cleansing	17
CAPRYLHYDROXAMIC ACID	Face and Neck (exc shave)	67
CAPRYLHYDROXAMIC ACID	Body and Hand (exc shave)	16
CAPRYLHYDROXAMIC ACID	Moisturizing	47
CAPRYLHYDROXAMIC ACID	Night	6
CAPRYLHYDROXAMIC ACID	Paste Masks (mud packs)	35
CAPRYLHYDROXAMIC ACID	Other Skin Care Preps	18

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: February 11, 2020

SUBJECT: Caprylhydroxamic Acid

Gerberick FG, Sminkey CS, and Fevola MJ. 2020. Quantitative Risk Assessment for Allergic Contact Dermatitis: Caprylhydroxamic Acid as Used in Cosmetics.

This risk assessment has been reviewed by the PCPC CIR Science and Support Committee (CIR SSC) and it is consistent with previous Quantitative Risk Assessments (QRA) for allergic contact dermatitis that have been submitted to CIR by the CIR SSC.

SGS Report. 2020. Repeat insult patch test study - Caprylhydroxamic Acid 1.9%.

SGS Report. 2020. Repeat insult patch test study - Caprylhydroxamic Acid 3.8%.

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Quantitative Risk Assessment for Allergic Contact Dermatitis: Caprylhydroxamic Acid as Used in Cosmetics

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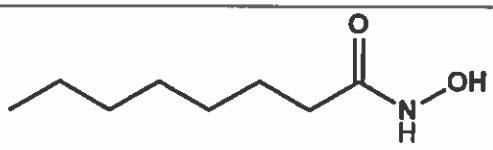
27 January 2020

Summary:

This document provides an exposure-based quantitative risk assessment (QRA) for allergic contact dermatitis for caprylhydroxamic acid (CHA) as used in a variety of cosmetic products. This document also reviews the available data used to generate the critical inputs needed to conduct a QRA. The results of the QRA clearly show that all product categories evaluated have an acceptable margin of safety. Thus, formulation of these products at their maximal concentration of CHA would present a negligible risk of inducing skin sensitization.

Caprylhydroxamic acid (CHA), CAS# 7377-03-9	

Methods:

The QRA approach is a well-established process for assessing the skin sensitization safety of individual ingredients used in cosmetic products (Robinson et al., 2000; Gerberick and Robinson, 2000; Gerberick et al., 2001; Api et al., 2008). The approach defines an Acceptable Exposure Level (AEL) for daily consumer exposure based on a Weight of Evidence No Expected Sensitization Induction Level (WoE NESIL), to which various Sensitization Assessment Factors (SAFs) are applied, determined by the product type. The AEL = WoE NESIL/Total SAF. The Consumer Exposure Level (CEL) is determined by using maximum CHA usage levels which were provided by CIR/PCPC survey and published habits and practices data. The assurance of skin sensitization safety is assessed by evaluating the AEL/CEL ratio. AEL/CEL ratios ≥ 1.0 provide an acceptable margin of safety from the induction of allergic contact dermatitis. Aggregate exposure is not considered in this assessment.

Skin Sensitization Hazard Assessment of CHA:

In silico analysis - *In silico* SAR modeling was employed to evaluate the hazard potential of CHA as a skin sensitizer (Toxservices, 2018). The report concludes that predictive modeling using three different tools (Toxtree, v2.6.13; OECD Toolbox, v4.0.0.26167; and CAESAR), the weight of *in silico* evidence suggests that CHA is not likely to be a skin sensitizer in humans. Using Toxtree, no skin sensitization reactivity domains were identified in the chemical structure of CHA and no alerts were identified using the OECD Toolbox. CHA was predicted to be a sensitizer using CAESAR, but the prediction had low reliability. It is important to note that *in silico* evidence alone is not adequate to fully predict sensitization potential. However, the modeling results are important elements in conducting a weight-of-evidence determination of a chemical's skin sensation potential, especially along with *in vitro* and/or *in vivo* data.

In vitro Data - The four key mechanistic events covered in the skin sensitization adverse outcome pathway (AOP) include: (1) binding of haptens to endogenous proteins in the skin, (2) keratinocyte activation, (3) dendritic cell activation, and (4) proliferation of antigen specific T cells. *In chemico* and *in vitro* methods addressing the first three mechanistic events of the skin sensitization AOP have been adopted by the OECD including the Direct Peptide Reactivity Assay (DPRA, OECD TG 442C), the ARE-Nrf2 Luciferase Test Method (KeratinoSens™ and LuSens, OECD TG 442D) and the human Cell Line Activation Test (h-CLAT, OECD TG 442E). One simple approach has been to use a 2 out of 3 approach using OECD approved methods: DPRA, KeratinoSens™ or LuSens, and h-CLAT, U937-CD86, or mMUSST (e.g., Urbisch et al., 2015). Placed in the context of the AOP, the DPRA evaluates key event 1– the protein/peptide reactivity of a substance, the KeratinoSens™ and LuSens assays represent key event 2 and give a measure of keratinocyte activation, and the h-CLAT, U937- CD86 and mMUSST describe key event 3, namely dendritic cell activation. When used together, these assays cover the first three of the four key events of the sensitization AOP, and as such are of mechanistic relevance and supports the scientific rationale for using a combination of these methods in an AOP-based integrated testing strategy. Substances causing at least two positive results in tests addressing Key events 1–3 are rated positive, while chemicals with none or only one positive outcome are rated negative.

In each of the three alternative skin sensitization assays, the DPRA, KeratinoSens™, and h-CLAT (IIVS DPRA, 2018; IIVS h-CLAT, 2018; IIVS, 2018, KerationSens™), CHA was positive. Thus, these hazard results would indicate that CHA is a potential skin sensitizer. The results of these three assays do not give any indication of the CHA's skin sensitization potency. However, it is worth nothing that DPRA results show low reactivity which is consistent with a less potent sensitizer.

Conclusion – The non-animal alternatives data supports that CHA has potential to cause skin sensitization. Although the conclusion of the *in silico* work did not predict CHA to be a human skin sensitizer, it was positive in each of 3 *in vitro* assays that have been validated for hazard identification of skin sensitizers. The conclusion that CHA has potential to cause skin sensitization is also supported by clinical reports in the literature where CHA was suspected to be the cause of allergic contact dermatitis in a group of individuals with compromised skin who used a moisturizer formulation containing CHA (Ackerman et al, 2017; Kluger, 2018; Virtanen et al, 2018). It is important to note that the data used to identify CHA as a potential skin sensitization hazard are not useful for assessing its skin sensitization potency.

Establishment of the WoE NESIL for CHA

Human data should always take priority in setting a WoE NESIL, if available. For CHA, there are a number of human repeat insult patch test (HRIPT) studies available for consideration (Table 1). Twelve test materials containing CHA were evaluated with 8 of them tested together in the same panel of subjects (104 subjects). For two of the test materials, it was not possible to calculate the CHA dose per unit area exposure, so those studies were not used in determining a WoE NESIL. Dose of ingredient per unit area of exposed skin is considered the most relevant dose metric for a QRA for skin sensitization (Kimber et al, 2008). Of the remaining 10 studies, the conclusion for each was that no clinically significant potential for allergic contact dermatitis was observed. However, in the shared panel (104 subjects) 7 of the 8 study reports showed one subject (#42) who presented with reactions that were indicative of the induction of skin sensitization. The reactions were not severe, but they started to present later in the induction period and persisted through the challenge phase along with edema. It is critical to note that no other subjects had suspicious reactions and the great majority presented with no reactions, specifically during the challenge phase. It would have been helpful to determine the significance of these responses with a rechallenge protocol at a later time to see if the individual maintained reactions indicative of skin sensitization. There is no way to know the significance of the individual's response, but one could

speculate that the responses may be the result of being patched with eight (8) products containing CHA and potentially involving the same draining lymph nodes that potentiated the immune response. Thus, one could speculate that if these studies were performed on separate panels of subjects, no sensitization, at any of the doses tested, would have been observed.

Recently, two additional exclusive HRIPTs were conducted with CHA at concentrations of 1.9% (1056.6 µg/cm^2) and 3.8% (2111.1 µg/cm^2). In the HRIPT conducted with 1.9% CHA in petrolatum (SGS Test Report C19-6637.01), no subjects exhibited reactions consistent with the induction of allergic contact dermatitis (Table 1). However, the HRIPT study conducted in a separate HRIPT panel with 3.8% CHA in petrolatum (SGS Test Report C19-6279.01) showed three individuals who, upon challenge, presented with reactions suggestive of allergic contact dermatitis. Based on the totality of the HRIPT test results presented in Table 1, the highest concentration tested where no positive responses were observed (NOEL) was 1055.6 µg/cm^2, whereas the lowest concentration tested where skin sensitization response were observed (LOEL) was 2111.1 µg/cm^2.

Dose per unit area was calculated according to the following example:

$$\frac{1.9\ g\ CHA}{100\ g\ dispersion} \times \frac{0.2\ g\ dispersion\ applied}{3.6\ cm^2\ patch\ area} \times \frac{1000\ mg\ CHA}{1\ g\ CHA} \times \frac{1000\ \mu g\ CHA}{1\ mg\ CHA} = 1056\ \mu g\ CHA/cm^2$$

Conclusion – Taking a WoE approach and favoring the human data over the *in silico* and *in vitro* data, a WoE NESIL of 1056 µg/cm^2 was chosen.

Table 1 – CHA Human Repeat Insult Patch Test Data Summary

Test Article	Vehicle, Dose Volume, Patch Size	Induction Conc. (µg/cm^2)	Challenge Conc. (µg/cm^2)	Positive Responses	Reference
eyeliner formulation containing 0.105% CHA (1.05 mg/ml) Subjects = 54	0.2 ml neat test material; 1 sq. in. patch (200 µl and 6.5 cm^2), semi-occlusive	32.3 µg/cm^2	32.3 µg/cm^2	No responses noted	Consumer Product Testing Company. 2014. Repeated insult patch test of an eyeliner containing 0.105% CHA.
brow thickening powder containing 0.195% Caprylhydroxamic Acid Subjects = 52	applied neat; 200 mg product (0.39 mg Caprylhydroxamic Acid) dose/unit area: 0.06 mg/cm^2	60.0 µg/cm^2	60.0 µg/cm^2	Report states no clinically significant potential for irritation or ACD. However, individual scores not shown.	Anonymous. 2019. Summary of an HRIPT on a brow thickening powder containing 0.195% CHA.
lotion containing 0.15% (1.5 mg/ml) Caprylhydroxamic Acid (also, 72.35% water; 5% caprylic/ capric triglyceride; 5% isopropyl	0.2 ml; ¾ in. X ¾ in. (200 µl and 3.6 cm^2), occlusive	83.3 µg/cm^2	83.3 µg/cm^2	Report states no clinically significant potential for irritation or ACD. However, Subject #10 showed rxns	Consumer Product Testing Company. 2018. Repeated insult patch test. Protocol No.: CP-01.01S.

myristate; 4.5% arachidyl alcohol (and) behenyl alcohol (and) arachidyl glucoside; 4% petrolatum; 3% cetyl alcohol; 3% stearyl alcohol; 3% glycerin) Subjects = 104				during induction and was removed, pre-hypersensitivity. Subject #42 exhibited response potentially indicative of sensitization. Rechallenge should have been performed.	Lotion (lot: 647-081-7J) containing 0.15% CHA, tested undiluted.
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 dipolyhydroxystear ; 3% glycerin; 2% beeswax) (concentrations stated as provided] Subjects = 104	0.2ml; ¾ in. X ¾ in. (200 µl and 3.6 cm^2), occlusive	83.3 µg/cm^2	83.3 µg/cm^2	Report states no clinically significant potential for irritation or ACD. However, Subject #10 showed rxns during induction and was removed, pre-hypersensitivity. Subject #42 exhibited response potentially indicative of sensitization. Rechallenge should have been performed.	Consumer Product Testing Company. 2018. Repeated insult patch test. Protocol No.: CP-01.01S. W/O thick balm (lot: 617-109-7J), containing 0.15% CHA, tested undiluted.
"wipe juice" containing 0.15% Caprylhydroxamic Acid containing 0.15% Caprylhydroxamic Acid (also, 94.85% water; 3% propanediol; 2% polysorbate 20) Subjects = 104	0.2 ml; ¾ in. X ¾ in. (200 µl and 3.6 cm^2), occlusive	83.3 µg/cm^2	83.3 µg/cm^2	Report states no clinically significant potential for irritation or ACD. However, Subject #42 exhibited response potentially indicative of sensitization. Rechallenge should have been performed.	Consumer Product Testing Company. 2018. Repeated insult patch test. Protocol No.: CP-01.01S. Wipe juice (lot: 647-080-7J) containing 0.15% CHA, tested undiluted.
formulation containing 5% Caprylhydroxamic Acid (and 30%	tested as a 6% dilution with distilled water (resultant test	166.6 µg/cm^2	166.6 µg/cm^2	Report states no clinically significant potential for	Consumer Product Testing Company. 2018. Repeated insult

hexanediol; 65% propanediol) Subjects = 104	concentration – 0.3% Caprylhydroxamic Acid); 0.2 ml; ¾ in. X ¾ in. (200 µl and 3.6 cm^2), occlusive			irritation or ACD. However, subject #42 exhibited response potentially indicative of sensitization. Rechallenge should have been performed.	patch test. Protocol No.: CP-01.01S. CHA blend #3 (lot: GH5355) containing 5% CHA, tested as a 6% dilution.
formulation containing 7.5% Caprylhydroxamic Acid (and 92.5% propanediol) Subjects = 104	tested as a 4% dilution with distilled water (resultant test concentration – 0.3% Caprylhydroxamic Acid); 0.2 ml; ¾ in. X ¾ in. (200 µl and 3.6 cm^2), occlusive	166.6 µg/cm^2	166.6 µg/cm^2	Report states no clinically significant potential for irritation or ACD. However, subject #42 exhibited response potentially indicative of sensitization. Rechallenge should have been performed.	Consumer Product Testing Company. 2018. Repeated insult patch test. Protocol No.: CP-01.01S. CHA blend #5 (lot: GK9324) containing 7.5% CHA, tested as a 4% dilution.
formulation containing 10% Caprylhydroxamic Acid (and 75% glyceryl caprylate and 15% glycerin) [concentrations stated as provided] Subjects = 104	tested as a 3% dilution with distilled water (resultant test concentration – 0.3% Caprylhydroxamic Acid); 0.2 ml; ¾ in. X ¾ in. (200 µl and 3.6 cm^2), occlusive	166.6 µg/cm^2	166.6 µg/cm^2	Report states no clinically significant potential for irritation or ACD. However, subject #42 exhibited response potentially indicative of sensitization. Rechallenge should have been performed.	Consumer Product Testing Company. 2018. Repeated insult patch test. Protocol No.: CP-01.01S. CHA blend #2 (lot: GK9325) containing 10% CHA, tested as a 3% dilution.
formulation containing 15% Caprylhydroxamic Acid (and70% phenoxyethanol; 7.5% methylpropanediol; 7.5% water) Subjects = 104	tested as a 2% dilution with distilled water (resultant test concentration – 0.3% Caprylhydroxamic Acid); 0.2 ml; ¾ in. X ¾ in. (200 µl and 3.6 cm^2), occlusive	166.6 µg/cm^2	166.6 µg/cm^2	Report states no clinically significant potential for irritation or ACD. However, subject #42 exhibited response potentially indicative of sensitization. Rechallenge should have been performed.	Consumer Product Testing Company. 2018. Repeated insult patch test. Protocol No.: CP-01.01S. CHA blend #1 (lot: GK9326) containing 15% CHA, tested as a 2% dilution.

formulation containing 15% Caprylhydroxamic Acid (and 71% caprylyl glycol and 14% glycerin) Subjects = 104	tested as a 2% dilution with distilled water (resultant test concentration – 0.3% Caprylhydroxamic Acid); 0.2 ml; ¾ in. X ¾ in. (200 µl and 3.6 cm^2), occlusive	166.6 µg/cm^2	166.6 µg/cm^2	Report states no clinically significant potential for irritation or ACD. In this study, subject #42 only exhibited barely perceptible erythema.	Consumer Product Testing Company. 2018. Repeated insult patch test. Protocol No.: CP-01.01S. CHA blend #4 (lot: GK9322) containing 15% CHA, tested as a 2% dilution.
facial cream containing 0.15% Caprylhydroxamic Acid Subjects = 109	0.2 ml Patch area unknown	Not possible to calculate	Not possible to calculate	Individual scores not available so not able to interpret results.	Anonymous. 2019. Summary of an HRIPT of a facial cream containing 0.15% CHA.
Caprylhydroxamic Acid Subjects = 52	undiluted; no vehicle indicated. 0.2 g solid (dampened), no vehicle ¾ in. x ¾ in. = 3.6 cm^2	55096 µg/cm^2 (estimated)	55096 µg/cm^2 (estimated)	Report states no clinically significant potential for irritation or ACD. With application of solid it is difficult to know extent of bioavailability.	Clinical Research Laboratories Inc. 2008. Repeated insult patch test of undiluted CHA.
Caprylhydroxamic Acid, 1.9% in petrolatum Subjects = 95	0.2 g; ¾ in. X ¾ in. (200 mg and 3.6 cm^2), occlusive	1055.6 µg/cm^2	1055.6 µg/cm^2	No responses at challenge noted	SGS, 2019. C19-6637.01.
Caprylhydroxamic Acid, 3.8% in petrolatum Subjects = 104	0.2 g; ¾ in. X ¾ in. (200 mg and 3.6 cm^2), occlusive	2111.1 µg/cm^2	2111.1 µg/cm^2	3 responses at challenge were suggestive of causing allergic contact sensitization	SGS, 2019. C19-6279.01.

Derivation of Sensitization Assessment Factors (SAFs)

The use of SAFs for skin sensitization QRA were originally published in Api et al., 2008. However, recently there has been an effort to update and improve the SAFs used in QRA (Basketter and Safford, 2016; SCCS, 2018). These updated SAFs are used in what is referred to informally as "QRA2". The SAFs for QRA2 have not yet been published (manuscript is in progress) but those values listed in Table 2 are consistent with the ones being used by the Research Institute for Fragrance Materials (RIFM) QRA Expert Group for fragrance materials. Table 2 lists both QRA1 and QRA2 SAFs, but only QRA2 SAFs were used for conducting the CHA skin sensitization QRA.

Table 2 – Product Category Sensitization Assessment Factors (SAFs)

Product Type	QRA1 SAF[1]	QRA2 SAF
Baby lotions, oils and creams - Not powder	300	300
Eyebrow pencils	100	100
Eyeliners	300	100
Eye shadows	300	100
Other eye makeup preparations	300	100
Hair conditioners, rinse-off	100	100
Hair conditioners, leave-on	100	100
Hair sprays Aerosol Pump spray	100	30
Shampoos (non-coloring)	100	300
Tonics, dressings and other hair grooming aids	100	100
Other hair preparations (non-coloring)	100	100
Bath soaps and detergents (added to the bath water)	100	300
Body wash, shower gel	100	300
Facial skin cleansing (rinse-off)	100	100
Facial skin cleansing (wipe-off)	100	100
Face and neck products Not spray	Men 300 Women 100	100
Body creams and lotions	300	300
Hand creams and lotions	100	100
Paste masks and mud packs	100	100

[1]Api AM, Basketter DA, Cadby PA, Cano M-F, Ellis G, Gerberick GF, Greim P, McNamee PM, Ryan CA, Safford R. Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. (2008). *Regulatory Toxicology and Pharmacology*, 52(1):3-23.

Derivation of CEL

It is critical to have accurate exposure estimates for the chemical being evaluated in the context of specific product usage for the QRA for the induction of allergic contact dermatitis. In the present assessment for CHA, a standard approach was used where the highest reported use concentration of CHA in the various cosmetic product categories was used along with habits and practices data for the cosmetic product type. The maximum concentrations of CHA used for each product were provided by the CIR/PCPC use survey. The product exposure levels for each product category were based on Api et al., 2008 or from other references that are indicated in Table 3. The CHA CELs range from as low as 0.013 $\mu g/cm^2$ for bath soaps and detergents to as high as 10.5 $\mu g/cm^2$ for leave-on body and hand products (Table 3).

Table 3 – Consumer Exposure Level (CEL) based upon maximum CHA use levels

Product Category	Classification	Maximum Concentration of Use	Product Exposure ($\mu g/cm^2$)[1]	Ingredient CEL ($\mu g/cm^2$)
Baby lotions, oils and creams Not powder	Leave-on	0.15%	2421[2]	3.63
Eyebrow pencils	Leave-on	0.2%	647[3]	1.29
Eyeliners	Leave-on	0.11%	1563[4]	1.72
Eye shadows	Leave-on	0.19%	2170	4.12
Other eye makeup preparations (assumed to be used similar to an eye shadow)	Leave-on	0.2%	2170	4.34
Hair conditioners	Rinse-off	0.15%	200	0.3
Hair conditioners	Leave-on[5]	0.15%	2000	3.0
Hair sprays Aerosol Pump spray	Leave-on	 0.075% 0.075%	 1390 2200	 1.04 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)	Assumed Leave-on – similar to above	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)	Rinse-off	0.12-0.15%	150	0.18-0.225
Facial skin cleansing (wipe-off)	Wipe-off	0.12-0.15%	900[6]	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

[1] Product exposure data taken from Api et al., *Reg. Tox. Pharm.*, 2008, unless noted otherwise.

[2] Dornic et al., 95th percentile babies moisturizing cream.

[3] Calculated with the use amount of 7.76 mg/day is the 95th percentile taken from Jung et al., 2018. Surface area of 12 cm^2 is assumed to be ½ eyeshadow application area from Bremmer, 2003.

[4] SCCS (Scientific Committee on Consumer Safety), SCCS Notes of Guidance for the Testing of Cosmetic Ingredients and their Safety Evaluation 10th revision, 24-25 October 2018, SCCS/1602/18.

[5] Rinse-off hair conditioner has a retention factor of 0.01; Leave-on has a retention factor of 0.1.

[6] Facial cleansing Wipe-off based on Api et al., *Reg. Tox. Pharm.*, 2008 value for make-up remover which has a retention factor of 0.1.

Results of CHA QRA

Table 4 reports the margins of safety for CHA when used according to the concentrations and product categories reported in Table 3. Using the NESIL value of 1056 $\mu g/cm^2$, values of AEL are calculated by dividing the NESIL value by the appropriate QRA2 SAF (Table 2). The margins of safety are reported as the

ratio of AEL/CEL (using the CEL values from Table 3), with AEL/CEL ratios ≥ 1.0 providing an acceptable margin of safety from the induction of skin sensitization.

Table 4 - Margin of safety for skin sensitization (AEL/CEL) based on industry reported maximum use levels of CHA

Product	CHA WoE NESIL (µg/cm2)	QRA 2 SAF	CHA AEL (µg/cm2)	CHA CEL (µg/cm2)	Margin of Safety (AEL/CEL)[1]
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 spray	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	0.74-2.28	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 (rinse-off)	1056	100	10.6	0.18-0.225	58.9-47.1
Facial skin cleansing (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

[1]Values were rounded to one decimal.

Conclusion

A skin sensitization QRA was conducted using reported maximum use levels of CHA in a variety of cosmetic products. A WoE NESIL of 1056 μg/cm^2 was chosen for CHA based on review of the available human repeat insult patch test data (Table 1). The CELs for the various products are listed in Table 3 with references supporting the exposure calculations. In Table 4, the margin of safety value is reported for each product using 1056 μg/cm^2 as the NESIL and the Acceptable Exposure Level (AEL) derived by dividing the NESIL by the appropriate QRA2 SAF (Table 2). The AEL is compared to the CEL (Table 4). It is clear that all of the product categories have an adequate margin of safety as indicated by the AEL/CEL ratio values ≥ 1. Thus, formulation of these products at their maximal concentration of CHA would present a negligible risk of inducing skin sensitization.

Continued monitoring of clinical results from the dermatology community and marketed product surveillance data is recommended to confirm the effectiveness of the QRA-based approach to risk management. Consistent with this recommendation, it is noted that the *Mintel Global New Products Database*, has reported the launch of at least 4,356 marketed products containing Caprylhydroxamic Acid in the 10-year period from 2009-2019 (Mintel GNPD, 2020). During this period, the report of allergic contact dermatitis specific to the Apobase® brand cream and lotion products (Ackermann 2017) remains the only documented account of skin sensitization associated with CHA in marketed products.

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Consumer Product Testing Company. 2018. Repeated insult patch test. Protocol No.: CP-01.01S. Wipe juice (lot: 647-080-7J) containing 0.15% Caprylhydroxamic Acid, tested undiluted. Experiment Reference No.: C17-5522.06. (Unpublished data submitted by INOLEX on April 9, 2019.)

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Consumer Product Testing Company. 2018. Repeated insult patch test. Protocol No.: CP-01.01S. CHA blend #5 (lot: GK9324) containing 7.5% Caprylhydroxamic Acid, tested as a 4% dilution. Experiment Reference No.: C17-5522.04. (Unpublished data submitted by INOLEX on April 9, 2019.)

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This report 4529277-CPCH04R1 supersedes all previous versions of report

Test Report

No. 4529277-CPCH04R1 Date: February 10, 2020 Page 1 of 10

[redacted]

The following sample(s) was/were submitted and identified by/on behalf of the client as	:	One (1) [redacted] Sample(s): • [redacted] CHA Caprylhydroxamic Acid powder, 98+%
Item No	:	[redacted]
Batch No/Lot No	:	[redacted]
Expiration Date	:	Recommended re-evaluation date is 24 months
Manufacturer/Supplier	:	[redacted]
Country of Origin	:	USA
Destination Country	:	USA
Initiation Date	:	**10/02/2019**
Completion Date	:	**11/15/2019**
Panel #	:	**20190379**
Reference Study No	:	**C19-6637.01**
Reason for Revision	:	**Amendment to the "Test Summary" section of report on sample preparation.**

Test Requested : Repeat Insult Patch Test (RIPT) – 100 Subjects Caprylhydroxamic Acid tested at 1.9%

Test Method & Results : Please refer to next page(s).

Result Summary :

Test Requested	Conclusion:
Repeated Insult Patch Test Protocol No.: CP-01.01S	See below.

Testing performed at an SGS partner lab

Signed for and on behalf of SGS North America, Inc.

Melissa Perez
Laboratory Supervisor, CPCH Laboratory

Prepared By:

Candace Jandura
Business Coordinator, CPCH Laboratory

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SGS

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Sample Description(s):

Lot #	Description (as submitted by the client)
[redacted]	[redacted] CHA Caprylhydroxamic Acid powder, 98+%

Execution Summary:

Quality Assurance Statement	:	This trial has been conducted in accordance with the Declaration of Helsinki, the ICH Guideline E6 for Good Clinical Practice, the requirements of 21 CFR Parts 50 and 56, other applicable laws and regulations, Partner Lab Standard Operating Procedures, and the approved protocol.
Objective	:	To determine by repetitive epidermal contact the potential of a test material to induce primary or cumulative irritation and/or allergic contact sensitization.
Participants	:	**One hundred nine (109)** qualified subjects, male and female, ranging in age from **16** to **79** years, were selected for this evaluation. **Ninety-five (95)** subjects completed this study. The remaining subjects discontinued their participation for various reasons, none of which were related to the application of the test material.
Inclusion Criteria	:	a. Male and female subjects, age 16* to 79 years, inclusive. b. Panelists must have read, signed, and dated an Informed Consent Form that included a HIPPA statement. c. Panelists were considered reliable and capable of understanding and following directions. d. Panelists aged 16 or 17 years must have read, signed and date an Adolescent Assent Form after their parent or legal guardian had read, signed, and dated an Informed Consent Form.
Exclusion Criteria	:	a. Ill health. b. Under a doctor's care or taking medication(s) which could influence the outcome of the study. c. Panelists who used an prescribed or OTC anti-inflammatory, antihistamine, corticosteroid, immunosuppressant, or antibiotic drug within 7 days prior to initiation of the trial or during their participation on this trial. d. Females who are pregnant, planning to become pregnant, or nursing. e. Panelists with any visible disease, sunburn, scars, excessive tattoos, that might be confused with a skin reaction to the test material or, as determined by the Principal Investigator, might interfere with the evaluation f. A history of adverse reactions to cosmetics, adhesive tapes, OTC drugs, or other personal care products g. Panelists who introduced the use of any new cosmetic, toiletry, or personal care products during the trial.

***With parental or guardian consent.**

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Methodology:

Test Summary:	Prior to the initiation of this study, 98.1 g of slightly warmed petroleum jelly was added to 1.9 g of test material followed by 5 minutes of mixing. The upper back between the scapulae served as the treatment area. Approximately 0.2 g of the test material was applied to the 3.6 cm^2 absorbent pad portion of an adhesive dressing. This was then applied to the appropriate treatment site to form an occlusive patch.
Induction Phase:	Patches were applied three (3) times per week (e.g., Monday, Wednesday, and Friday) for a total of nine (9) applications. The site was marked to ensure the continuity of patch application. Following supervised removal and scoring of the first Induction patch, participants were instructed to remove all subsequent Induction patches at home, twenty-four hours after application. The evaluation of this site was made again just prior to re-application. If a participant was unable to report for an assigned test day, one (1) makeup day was permitted. This day was added to the Induction period. With the exception of the first supervised Induction Patch reading, if any test site exhibited a moderate (2-level) reaction during the Induction Phase, application was moved to an adjacent area. Applications were discontinued for the remainder of this test phase, if a moderate (2-level) reaction was observed on this new test site. Applications would also be discontinued if marked (3-level) or severe (4-level) reactivity was noted. Rest periods consisted of one day following each Tuesday and Thursday removal, and two days following each Saturday removal.
Challenge Phase:	At least 10 days following the final Induction patch application, a Challenge patch was applied to a virgin test site adjacent to the original Induction patch site, following the same procedure described for Induction. The patch was removed and the site scored at the clinic Day 1 and Day 3 post-application.
Evaluation Criteria (Erythema and additional Dermal Sequelae):	0 = No visible skin reaction 0.5 = Barely perceptible E= Edema V = Vesicles 1 = Mild D= Dryness B = Bullae 2 = Moderate S= Staining U = Ulceration 3 = Marked P= Papules Sp = Spreading 4 = Severe Erythema was scored numerically according to this key. If present, additional Dermal Sequelae were indicated by the appropriate letter code and a numerical value for severity.

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Adverse Events:	There were no adverse events
Amendments:	There were no amendments.
Deviations:	There were no deviations.
Results:	The results of each participant are appended (Table 1). Observations remained negative throughout the test interval. Subject demographics are presented in Table 2.
Summary:	Under the conditions of this study, test material, Item No [redacted] – [redacted] CHA [redacted], indicated no potential for dermal irritation or allergic contact sensitization.
Reviewed By:	Richard R. Eisenberg, M.D. Medical Director Board Certified Dermatologist

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Test Results:

TABLE 1 – INDIVIDUAL RESULTS

PANEL #: 20190379

		Induction Phase									Virgin Challenge Site	
Subject Number	Day 1*	1	2	3	4	5	6	7	8	9	Day 1*	Day 3
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0
24	WITHDREW CONSENT											
25	0	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	WITHDREW CONSENT				
27	0	0	WITHDREW CONSENT									
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	WITHDREW CONSENT			

Day 1* = Supervised removal

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TABLE 1 (Continued) -- INDIVIDUAL RESULTS												
PANEL #: 20190379												
		Induction Phase									Virgin Challenge Site	
Subject Number	Day 1*	1	2	3	4	5	6	7	8	9	Day 1*	Day 3
30	0	0	0	0	0	0m	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	WITHDREW CONSENT				
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	SUBJECT NUMBER NOT ASSIGNED											
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0m	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	WITHDREW CONSENT									

Day 1* = Supervised removal

m = Additional makeup day granted at the discretion of the clinic supervisor

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TABLE 1 (Continued) – INDIVIDUAL RESULTS

PANEL #: 20190379

		Induction Phase									Virgin Challenge Site	
Subject Number	Day 1*	1	2	3	4	5	6	7	8	9	Day 1*	Day 3
58	0	0	0	0	0	0	WITHDREW CONSENT					
59	0	0	0	0	0	0	0	0	0[m]	WC		
60	0	0	0	0	0	0	0	0	0	0	0	0
61	0	0	0	0	0	WITHDREW CONSENT						
62	0	0	0	0	0	0	0	0	0	0	0	0
63	0	0	0	0	0	0	0	0	0	0	0	0
64	0	0	0	0	0	0	0	0	0	0	0	0
65	0	0	0	0	0	0	0	0	0	0	0	0
66	0	0	0	0	0	0	0	0	0	0	0	0
67	0	0	0	0	0	WITHDREW CONSENT						
67	0	0	0	0	0	0	0	0	0	0	0	0
68	0	0	0	0	0	0	0	0	0	0	0	0
69	0	0	0	0	0	0	0	0	0	0	0	0
70	0	0	0	0	0	0	0	0	0	0	0	0
71	0	0	0	0	0	0	0	0	0	0	0	0
72	0	0	0	0	0	0	0	0	0	0	0	0
73	0	0	0	0	0	0	0	0	0	0	0	0
74	0	0	0	0	0	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0	0	0	0	0	0
76	0	0	0	0	0	0	0	0	0	0	0	0
77	0	0	0	0	0	0	0	0	0	0	0	0
78	0	0	0	0	0	0	0	0	0	0	0	0
79	0	WITHDREW CONSENT										
80	0	0	0	0	0	0	0	0	0	0	0	0
81	0	0	0	0	0	0	0	0	0	0	0	0
82	0	0	0	0	0	0[m]	WITHDREW CONSENT					
83	0	0	0	0	0	0	0	0	0	0	0	0
84	0	0	0	0	0	0	0	0	0	0	0	0
85	0	0	0	0	0	0	0	0	0	0	0	0
86	0	0	0	0	0	0	0	0	0	0	0	0

Day 1* = Supervised removal

WC = Withdrew Consent

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m = Additional makeup day granted at the discretion of the clinic supervisor

TABLE 1 (Continued) – INDIVIDUAL RESULTS

PANEL #: 20190379

		Induction Phase									Virgin Challenge Site	
Subject Number	Day 1*	1	2	3	4	5	6	7	8	9	Day 1*	Day 3
87	0	0	0	0	0	0	0	0	0	0	0	0
88	0	0	0	0	0	0	0	0	0	0	0	0
89	0	0	0	0	0	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0	0	0	0	0	0
91	0	0	0	0	0	0	0	0	0	0	0	0
92	WITHDREW CONSENT											
93	0	0	0	0	0	0	0	0	0	0	0	0
94	0	0	0	0	0	0	0	0	0	0	0	0
95	0	0	0	0	0	0	0	0	0	0	0	0
96	0	0	0	0	0	0	0	0	0	0	0	0
97	0	0	0	0	0	0	0	0	0	0	0	0
98	0	0	0	0	0	0	0	0	0	0	0	0
99	0	0	0	0	0	0	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0	0	0	0	0
101	0	0	0	0	0	0	0	0	0	0	0	0
102	0	0	0	0	0	0	0	0	0	0	0	0
103	0	0	0	0	0	0	0	0	0	0	0	0
104	0	0	0	0	0	0	0	0	0	0	0	0
105	0	0	0	0	0	0	0	0	0	0	0	0
106	0	0	0	0	0	0	0	0	0	0	0	0
107	0	0	0	0	0	0	0	0	0	0	0	0
108	0	0	0	0	0	0	0	0	0	0	0	0
109	0	0	0	0	0	0	0	0	0	0	0	0
110	0	0	0	0	0	0	0	0	0	0	WC	

WC = Withdrew consent
Day 1* = Supervised removal

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TABLE 2 -- SUBJECT DEMOGRAPHICS									
PANEL #: 20190379									
Subject Number	ID#	Age	Gender	Fitzpatrick Skin Type	Subject Number	ID#	Age	Gender	Fitzpatrick Skin Type
1	81715	60	F	IV	29	88952	24	M	II
2	61110	68	F	IV	30	76633	47	F	IV
3	34236	60	F	II	31	49596	60	M	III
4	40428	33	F	III	32	14430	79	F	III
5	87196	51	F	II	33	84683	76	M	I
6	79343	30	F	III	34	35809	52	F	IV
7	88394	66	M	III	35	85660	76	F	I
8	80815	67	M	I	36	66021	73	F	III
9	72658	74	F	III	37	78258	72	M	III
10	18887	47	M	II	38	2601	75	F	IV
11	76666	64	F	I	39	56551	79	F	II
12	26201	69	F	III	40	83812	50	M	II
13	75910	65	M	II	41	3585	61	F	II
14	27605	71	F	II	42	84049	44	F	III
15	11431	69	M	I	43	66549	39	F	IV
16	75544	58	F	III	44	43312	45	F	II
17	81588	54	F	I	45	-	-	-	-
18	75159	65	M	II	46	82495	46	F	II
19	63354	25	M	II	47	87714	54	M	I
20	76908	45	F	IV	48	76097	59	F	IV
21	88144	56	F	II	49	82661	39	F	III
22	74288	63	F	IV	50	88624	59	F	II
23	88427	61	M	II	51	34490	73	M	I
24	89774	23	M	IV	52	74686	65	F	IV
25	55933	77	F	I	53	71160	75	F	II
26	88128	66	M	IV	54	73437	28	F	II
27	89498	61	M	II	55	79066	49	F	II
28	40879	73	F	III	56	89167	30	F	II

- = Subject number not assigned

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TABLE 2 (CONTINUED) – SUBJECT DEMOGRAPHICS									
PANEL #: 20190379									
Subject Number	ID#	Age	Gender	Fitzpatrick Skin Type	Subject Number	ID#	Age	Gender	Fitzpatrick Skin Type
57	12016	73	F	IV	84	58170	51	F	II
58	87786	37	M	III	85	84115	66	M	I
59	88274	20	F	I	86	88380	53	F	I
60	87787	37	F	III	87	53358	65	F	II
61	85558	56	F	IV	88	6928	55	F	II
62	53359	38	F	IV	89	69968	61	F	I
63	75625	74	F	I	90	78964	58	F	III
64	89529	31	F	III	91	31345	40	F	III
65	80886	73	F	I	92	85488	57	F	IV
66	47333	24	F	III	93	86010	56	M	I
67	73347	19	F	I	94	85029	22	F	III
68	11229	46	F	II	95	79396	29	F	IV
69	78582	42	M	I	96	83981	67	F	I
70	11353	62	F	IV	97	83992	63	M	I
71	61969	50	F	II	98	86458	65	F	IV
72	81045	23	M	III	99	86709	66	M	III
73	89747	30	F	IV	100	3653	53	F	II
74	77267	30	F	I	101	89787	31	F	III
75	85315	52	F	II	102	51891	71	F	III
76	49712	50	F	II	103	83275	21	F	II
77	60579	61	F	IV	104	88994	32	M	IV
78	2162	61	F	II	105	89785	79	F	III
79	87033	22	M	II	106	66790	58	M	I
80	88966	16	M	III	107	87135	53	F	IV
81	36802	20	F	I	108	88902	16	F	I
82	81106	24	F	I	109	57310	65	F	I
83	85082	62	F	III	110	85590	48	M	IV

**** End of Report ****

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Test Report

No. 4529277-CPCH03R1 Date: February 10, 2020

[redacted]

The following sample(s) was/were submitted and identified by/on behalf of the client as	:	One (1) [redacted] Sample(s): • [redacted] CHA Caprylhydroxamic Acid powder, 98+%
Item No	:	[redacted]
Batch No/Lot No	:	[redacted]
Expiration Date	:	Recommended re-evaluation date is 24 months
Manufacturer/Supplier	:	[redacted]
Country of Origin	:	USA
Destination Country	:	USA
Initiation Date	:	**10/09/2019**
Completion Date	:	**11/15/2019**
Panel #	:	**20190386**
Reference Study No	:	**C19-6638.01**
Reason for Revision	:	**Amendment to the "Test Summary" section of report on sample preparation.**

Test Requested : Repeat Insult Patch Test (RIPT) – 100 Subjects Caprylhydroxamic Acid tested at 3.8%

Test Method & Results : Please refer to next page(s).

Result Summary :

Test Requested	Conclusion:
Repeated Insult Patch Test Protocol No.: CP-01.01S	See below.

Testing performed at an SGS partner lab

Signed for and on behalf of SGS North America, Inc.

Melissa Perez
Laboratory Supervisor, CPCH Laboratory

Prepared By:

Candace Jandura
Business Coordinator, CPCH Laboratory

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Sample Description(s):

Lot #	Description (as submitted by the client)
[redacted]	[redacted] – [redacted] CHA Caprylhydroxamic Acid powder, 98+%

Execution Summary:

Quality Assurance Statement	:	This trial has been conducted in accordance with the Declaration of Helsinki, the ICH Guideline E6 for Good Clinical Practice, the requirements of 21 CFR Parts 50 and 56, other applicable laws and regulations, Partner Lab Standard Operating Procedures, and the approved protocol.
Objective	:	To determine by repetitive epidermal contact the potential of a test material to induce primary or cumulative irritation and/or allergic contact sensitization.
Participants	:	**One hundred twelve (112)** qualified subjects, male and female, ranging in age from **16** to **78** years, were selected for this evaluation. **One hundred four (104)** subjects completed this study. The remaining subjects discontinued their participation for various reasons, none of which were related to the application of the test material.
Inclusion Criteria	:	a. Male and female subjects, age 16* to 79 years, inclusive. b. Panelists must have read, signed, and dated an Informed Consent Form that included a HIPPA statement. c. Panelists were considered reliable and capable of understanding and following directions. d. Panelists aged 16 or 17 years must have read, signed and date an Adolescent Assent Form after their parent or legal guardian had read, signed, and dated an Informed Consent Form.
Exclusion Criteria	:	a. Ill health. b. Under a doctor's care or taking medication(s) which could influence the outcome of the study. c. Panelists who used an prescribed or OTC anti-inflammatory, antihistamine, corticosteroid, immunosuppressant, or antibiotic drug within 7 days prior to initiation of the trial or during their participation on this trial. d. Females who are pregnant, planning to become pregnant, or nursing. e. Panelists with any visible disease, sunburn, scars, excessive tattoos, that might be confused with a skin reaction to the test material or, as determined by the Principal Investigator, might interfere with the evaluation f. A history of adverse reactions to cosmetics, adhesive tapes, OTC drugs, or other personal care products g. Panelists who introduced the use of any new cosmetic, toiletry, or personal care products during the trial.

***With parental or guardian consent.**

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Methodology:

Test Summary:	Prior to the initiation of this study, 96.2 g of slightly warmed petroleum jelly was added to 3.8 g of test material followed by 5 minutes of mixing. The upper back between the scapulae served as the treatment area. Approximately 0.2 g of the test material was applied to the 3.6 cm^2 absorbent pad portion of an adhesive dressing. This was then applied to the appropriate treatment site to form an occlusive patch.
Induction Phase:	Patches were applied three (3) times per week (e.g., Monday, Wednesday, and Friday) for a total of nine (9) applications. The site was marked to ensure the continuity of patch application. Following supervised removal and scoring of the first Induction patch, participants were instructed to remove all subsequent Induction patches at home, twenty-four hours after application. The evaluation of this site was made again just prior to re-application. If a participant was unable to report for an assigned test day, one (1) makeup day was permitted. This day was added to the Induction period. With the exception of the first supervised Induction Patch reading, if any test site exhibited a moderate (2-level) reaction during the Induction Phase, application was moved to an adjacent area. Applications were discontinued for the remainder of this test phase, if a moderate (2-level) reaction was observed on this new test site. Applications would also be discontinued if marked (3-level) or severe (4-level) reactivity was noted. Rest periods consisted of one day following each Tuesday and Thursday removal, and two days following each Saturday removal.
Challenge Phase:	At least 10 days following the final Induction patch application, a Challenge patch was applied to a virgin test site adjacent to the original Induction patch site, following the same procedure described for Induction. The patch was removed and the site scored at the clinic Day 1 and Day 3 post-application.
Evaluation Criteria (Erythema and additional Dermal Sequelae):	0 = No visible skin reaction 0.5 = Barely perceptible E= Edema V = Vesicles 1 = Mild D= Dryness B = Bullae 2 = Moderate S= Staining U = Ulceration 3 = Marked P= Papules Sp = Spreading 4 = Severe Erythema was scored numerically according to this key. If present, additional Dermal Sequelae were indicated by the appropriate letter code and a numerical value for severity.

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Adverse Events:	There were no adverse events
Amendments:	There were no amendments.
Deviations:	There were no deviations.
Results:	The results of each participant are appended (Table 1). Observations remained within normal limits throughout the test interval. Subject demographics are presented in Table 2.
Summary:	Subject #s 13 and 65 exhibited evaluation scores of 1 for erythema and for edema on Day 3 Challenge Phase suggesting induction of allergic contact sensitization. Subject #56 exhibited an evaluation score of 2 for erythema and edema on Day 3 Challenge Phase indicative of allergenic contact sensitization induction. Under the conditions of this clinical trial, test material, Item No [redacted] – [redacted] CHA [redacted], indicated no potential for dermal irritation or allergic contact sensitization noting these three exceptions.
Reviewed By:	Richard R. Eisenberg, M.D. Medical Director Board Certified Dermatologist

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Test Results:

TABLE 1 – INDIVIDUAL RESULTS

PANEL #: 20190386

		Induction Phase									Virgin Challenge Site	
Subject Number	Day 1*	1	2	3	4	5	6	7	8	9	Day 1*	Day 3
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	WITHDREW CONSENT								
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0.5	0.5	0.5	1[E1]	0	1[E1]
14	0	0	0	0	0	0	0[m]	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0.5
20	0	0	0	WITHDREW CONSENT								
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0.5	0.5	0.5	0	0
29	0	0	0	0	0	0	0	0.5	0	0	0	0

Day 1* = Supervised removal **E = Edema**
m = Additional makeup day granted at the discretion of the clinic supervisor

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TABLE 1 (Continued) – INDIVIDUAL RESULTS

PANEL #: 20190386

		Induction Phase									Virgin Challenge Site	
Subject Number	Day 1*	1	2	3	4	5	6	7	8	9	Day 1*	Day 3
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0.5	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	WITHDREW CONSENT											
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	WC	
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0.5	1[E1]	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0
51	_+	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0.5	0.5	1[E1]	0	2[E2]
57	0	0	0	0	0	0	0	0	0	0	0	0

Day 1* = Supervised removal

E = Edema

WC = Withdrew Consent

_+ = Subject not present for supervised removal

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TABLE 1 (Continued) – INDIVIDUAL RESULTS

PANEL #: 2019035

		Induction Phase									Virgin Challenge Site	
Subject Number	Day 1*	1	2	3	4	5	6	7	8	9	Day 1*	Day 3
58	0	0	0	0	0	0	0	0	0	0	0	0
59	0	0	0	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0	0	0	0	0	0
61	0	0	0	0	0	0	0	0	0	0	0	0
62	0	0	0	0	0	0	0	0	0	0	0	0
63	0	WITHDREW CONSENT										
64	0	0	0	0	0	WITHDREW CONSENT						
65	0	0	0	0	0	0	0	0.5	0	0.5	0	1[E1]
66	0	0	0	0	0	0	0	0	0.5	0.5	0	0
67	0	0	0	0	0	0	0	0	0	0	0	0
68	0	0	0	0	0	0	0	0.5	0.5	0.5	0	0
69	0	0	0	0	0	0	0	0	0	0	0	0
70	0	0	0	0	0	0	0	0	0	0	0	0
71	0	0	0	0	0	0	0	0	0.5	0	0	0
72	0	0	0	0	0	0	0	0	0	0	0	0
73	0	0	0	0	0	0	0	0	0	0	0	0
74	0	0	0	0	0	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0	0	0	0	0	0
76	0	0	0	0	0	0	0	0	0	0	0	0
77	0	0	0	0	0	0	0	0	0	0	0	0
78	0	0	0	0	0	0	0	0	0	0	0	0
79	0	0	0	0	0	0	0	0	0	0	0	0
80	0	0	0	0	0	0	0	0	0	0[m]	0	0
81	0	0	0	0	0	0	0	0	0	0	0	0
82	0	0	0	0	0	0	0	0	0	0	0	0
83	0	0	0	0	0	0	0	0	0	0	0	0
84	0	0	0	0	0	0	0	0	0	0	0	0
85	0	0	0	0	0	0	0	0	0	0	0	0
86	0	0	0	0	0	0	0	0.5	0	0	0	0

Day 1* = Supervised removal

E = Edema

m = Additional makeup day granted at the discretion of the clinic supervisor

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TABLE 1 (Continued) – INDIVIDUAL RESULTS												
PANEL #: 20190386												
		Induction Phase									Virgin Challenge Site	
Subject Number	Day 1*	1	2	3	4	5	6	7	8	9	Day 1*	Day 3
87	0	0	0	0	0	0	0	0	0	0	0	0
88	0	0	0	0	0	0	0	0	0	0	0	0
89	0	0	0	0	0	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0	0	0	0	WC	
91	0	0	0	0	0	0	0	0	0	0	0	0
92	0	0	0	0	0	0	0	0	0	0	WC	
93	0	0	0	0	0	0	0	0	0	0	0	0
94	0	0	0	1[E1]	0.5	0	0	0	0	0	0	0
95	0	0	0	0	0	0	0	0	0	0	0	0
96	0	0	0	0	0	0	0	0	0	0	0	0
97	0	0	0	0	0	0	0	0	0	0	0	0
98	0	0	0	0	0	0	0.5	0.5	0.5	0.5	0	0.5
99	0	0	0	0	0	0	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0	0	0	0	0
101	0	0	0	0	0	0	0	0	0	0	0	0
102	0	0	0	0	0	0	0	0	0	0	0	0
103	0	0	0	0	0	0	0	0	0	0	0	0
104	0	0	0	0	0	0	0	0	0	0	0	0
105	0	0	0	0	0	0	0	0	0	0	0	0
106	0	0	0	0	0	0	0	0	0	0	0	0
107	0	0	0	0	0	0	0	0	0	0	0	0
108	SUBJECT NUMBER NOT ASSIGNED											
109	0	0	0	0	0	0.5	1[E1]	1[E1]	0.5	0.5	0	0
110	0	0	0	0	0	0	0	0	0.5	0	0	0
111	0	0	0	0	0	0	0	0	0	0	0	0
112	0	0	0	0	0	0	0	0	0	0	0	0
113	0	0	0	0	0	0	0	0	0	0	0	0

WC = Withdrew consent
Day 1* = Supervised removal
E = Edema

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TABLE 2 – SUBJECT DEMOGRAPHICS									
PANEL #: 20190386									
Subject Number	ID#	Age	Gender	Fitzpatrick Skin Type	Subject Number	ID#	Age	Gender	Fitzpatrick Skin Type
1	84925	53	M	IV	29	68040	30	F	IV
2	89303	24	F	II	30	22464	71	F	III
3	78116	25	F	III	31	54477	35	F	IV
4	85264	33	F	IV	32	79905	35	M	IV
5	60438	75	M	IV	33	63027	71	F	III
6	413	55	F	III	34	70764	74	M	III
7	74119	73	M	III	35	82652	58	F	II
8	29453	59	F	IV	36	75892	63	F	III
9	62141	27	F	III	37	77314	46	F	III
10	87088	72	F	III	38	77808	50	M	III
11	62087	52	F	I	39	89739	47	F	III
12	81834	66	M	III	40	89341	58	F	II
13	15348	38	F	IV	41	49380	66	F	II
14	86585	34	F	IV	42	41133	58	M	IV
15	89760	33	F	II	43	23019	52	F	II
16	27320	63	F	IV	44	43449	42	M	III
17	20242	65	F	III	45	83461	52	F	II
18	14585	75	F	III	46	89827	55	F	IV
19	81736	36	F	III	47	87400	35	F	III
20	88585	44	F	IV	48	66000	42	F	III
21	83574	67	F	III	49	88163	34	F	IV
22	83586	73	M	III	50	89044	35	F	III
23	67492	71	M	III	51	89828	72	F	IV
24	85301	49	F	IV	52	81721	29	F	III
25	89797	43	F	IV	53	85606	27	M	II
26	54356	62	F	IV	54	72582	50	M	III
27	89222	78	F	III	55	59202	61	F	II
28	89769	63	F	IV	56	89830	26	M	II

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TABLE 2 (CONTINUED) – SUBJECT DEMOGRAPHICS									
PANEL #: 20190386									
Subject Number	ID#	Age	Gender	Fitzpatrick Skin Type	Subject Number	ID#	Age	Gender	Fitzpatrick Skin Type
57	72031	55	M	III	86	52036	60	F	III
58	80543	29	M	II	87	34027	54	M	III
59	69618	54	F	III	88	82374	48	F	III
60	75104	56	F	III	89	61196	25	M	II
61	89168	64	F	I	90	89825	27	F	IV
62	84556	26	F	III	91	88262	38	F	III
63	78673	53	F	I	92	77433	32	M	IV
64	72026	31	F	IV	93	26875	62	F	III
65	87351	70	F	II	94	80280	64	F	III
66	83745	73	F	II	95	87064	39	F	I
67	48122	54	F	III	96	62979	72	F	II
68	69145	56	F	III	97	79085	54	M	IV
69	81707	61	M	III	98	89808	21	F	III
70	80059	51	M	IV	99	89836	42	F	II
71	11500	54	F	III	100	77227	23	F	IV
72	71896	60	M	III	101	84993	22	F	III
73	29874	20	F	III	102	89540	46	F	IV
74	28142	59	F	III	103	85488	57	F	IV
75	74337	31	M	IV	104	89535	49	F	I
76	86276	68	M	III	105	58757	37	F	V
77	34263	61	M	III	106	57398	39	F	III
78	85842	59	F	III	107	57169	60	F	III
79	89823	25	M	III	108	-	-	-	-
80	84404	48	F	IV	109	75231	63	F	IV
81	84155	46	F	III	110	88229	49	F	IV
82	87095	46	M	IV	111	89513	16	F	IV
83	80267	57	F	IV	112	89543	35	M	IV
84	89834	30	F	IV	113	88618	33	F	III
85	75254	58	F	IV					

- = Subject number not assigned

**** End of Report ****

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: February 14, 2020

SUBJECT: Caprylhydroxamic Acid

Anonymous. 2020. Summary - HRIPT aqueous formulation containing 0.76% Caprylhydroxamic Acid.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

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February 2020

Summary – HRIPT Aqueous Formulation Containing 0.76% Caprylhydroxamic Acid

This study was conducted in two different phases (Phase A and B). Phase A was initiated with 115 subjects while Phase B was initiated with 116 subjects.

0.76% Caprylhydroxamic Acid in an aqueous formulation was evaluated in a Human Repeat Insult Patch Test (HRIPT). Based on the test population of 205 subjects and under the conditions of the study, 0.76% Caprylhydroxamic Acid in aqueous formulation did not demonstrate a potential for eliciting dermal irritation or inducing sensitization.

For the HRIPT, each of 231 human subjects received a semi-occlusive 3/4" x 3/4" (approximately 2 cm) absorbent pad with 0.2 ml of test material on the upper back area and 205 subjects completed this study. No subject(s) dropped out based on a reaction to the test material. The approximate dose of Caprylhydroxamic Acid was 380 $\mu g/cm^2$.

Following a 24-hour exposure period, test patches were removed and sites were scored for erythema and edema. A series of nine induction patches was applied three times a week for three weeks. Following a two-week rest period, challenge patches were applied to a virgin site on the back and allowed to remain in skin contact for 24 hours. Challenge sites were scored for erythema and edema at 24, 48, 72, and 96 hours post patching. No significant dermal reactions were exhibited during either the induction phase or challenge phase of the study.

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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: May 30, 2019

SUBJECT: Draft Report: Safety Assessment of Caprylhydroxamic Acid as Used in Cosmetics (June meeting draft)

The Council respectfully submits the following comments on the draft report, Safety Assessment of Caprylhydroxamic Acid as Used in Cosmetics.

Acute - Is reference 21 (EpiDerm skin irritation test) the correct reference for the acute oral LD_{50} in rats?

Dermal Irritation and Sensitization; Table 3 - As they are necessary for completing a quantitative risk assessment for sensitization, please provide the dose/unit area. e.g., $\mu g/cm^2$, for the HRIPT studies.

References 20 and 22 - In the reference section, when only an English abstract is available, it would be helpful to state the language in which the study is written.

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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: December 3, 2019

SUBJECT: Draft Tentative Report: Safety Assessment of Caprylhydroxamic Acid as Used in Cosmetics (draft prepared for the December 2019 CIR Expert Panel meeting)

The Personal Care Products Council respectfully submits the following comments on the draft tentative report, Safety Assessment of Caprylhydroxamic Acid as Used in Cosmetics.

Abstract - The ingredient name still needs to be added to the first sentence of the Abstract.
Physical and Chemical Properties - Please correct: "1.66=2.827" to "1.66-2.827"
Cosmetic Use, Exposure Assessment - As NICNAS calculated a margin of exposure in addition to estimating exposure from cosmetic use, this assessment should be called a "Risk Assessment". The CIR outline at https://www.cir-safety.org/sites/default/files/CIR%20Report%20Format%20Outline.pdf indicates that risk assessments should be presented in the relevant section of the report. Since this risk assessment is based on a NOAEL from a subchronic rat study, the risk assessment should be presented in the Subchronic section after the study identifying the NOAEL is described. This would make it consistent with the outline of the CIR report format.
Dermal Penetration - As the composition of the receptor fluid affects dermal penetration, the identity of the receptor fluid should be stated.
ADME; Reference 21 - For reference 21, it is misleading to state that "Only an abstract was available". It should be made clear that this study is not just an abstract, it is in Japanese, only the abstract, tables and figure titles are in English.
Subchronic; Summary - As dilution may change the outcome of a toxicity study, it is not correct to state: "the NOAEL of undiluted Caprylhydroxamic Acid is expected to be 50 mg/kg bw/day" when 50 mg/kg bw/day was tested in a 10% dosing solution, e.g., total dose of solution administered 500 mg/kg bw/day. As was done for the DART study, it would be better to describe the dose as "corresponding to 50 mg/kg bw Caprylhydroxamic acid".
Summary - As the dose of Caprylhydroxamic Acid in the DART study was up to 50 mg/kg bw, it is not correct to state: "Caprylhydroxamic Acid (10% in 5% gum arabic solution) was

administered to groups of 18 mated rats at doses up to 500 mg/kg bw/day..." Either the dose needs to be corrected to 50 (the dose of Caprylhydroxamic Acid; the last sentence could also be deleted), or it should state that a "Solution of Caprylhydroxamic Acid" was tested at doses up to 500 mg/kg bw/day (50 mg/kg bw/day Caprylhydroxamic Acid).

Table 4 - The difference between the first two test materials (finished formulations) and the last 5 test materials (mixtures of cosmetic ingredients that are added to finished formulations) should be made clear.