
Safety Assessment of Caprylhydroxamic Acid as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: August 21, 2020
Panel Meeting Date: September 14-15, 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.



Commitment & Credibility since 1976

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Monice M. Fiume *MMF*
Senior Director, CIR
Date: August 21, 2020
Subject: Safety Assessment of Caprylhydroxamic Acid as Used in Cosmetics

Enclosed is the Draft Final Report of the Safety Assessment of Caprylhydroxamic Acid as Used in Cosmetics. (It is identified in this report package as *caphyd092020rep.*) At the June 2020 meeting, the Panel issued a Tentative Report for public comment with the conclusion that Caprylhydroxamic Acid is safe in cosmetics in the present practices of use and concentration described in this safety assessment.

The Panel was concerned with inconsistent outcomes regarding dermal sensitization. Upon further review, the Panel determined that studies that had positive sensitization results were those in which the test substance included a penetration enhancer. Additionally, the Panel noted that cases of increased sensitization with use of a moisturizer in Finland, that had been reformulated to include Caprylhydroxamic Acid, appeared to be related to use on damaged skin, and most likely resulted in increased penetration. Therefore, the Panel stated that caution should be taken with use of Caprylhydroxamic Acid in a manner that would result in increased penetration, such as with the inclusion of penetration enhancers in formulations containing Caprylhydroxamic Acid.

Two sets of comments on the Tentative Report were received from the Council. The comments received in the first submission (*caphyd092020pcpc_1*) were addressed, as appropriate. However, most of the comments received in the second submission (*caphyd092020pcpc_2*) require input from the Panel, so please review these and be prepared to discuss these comments.

The following are also included as a part of this report package:

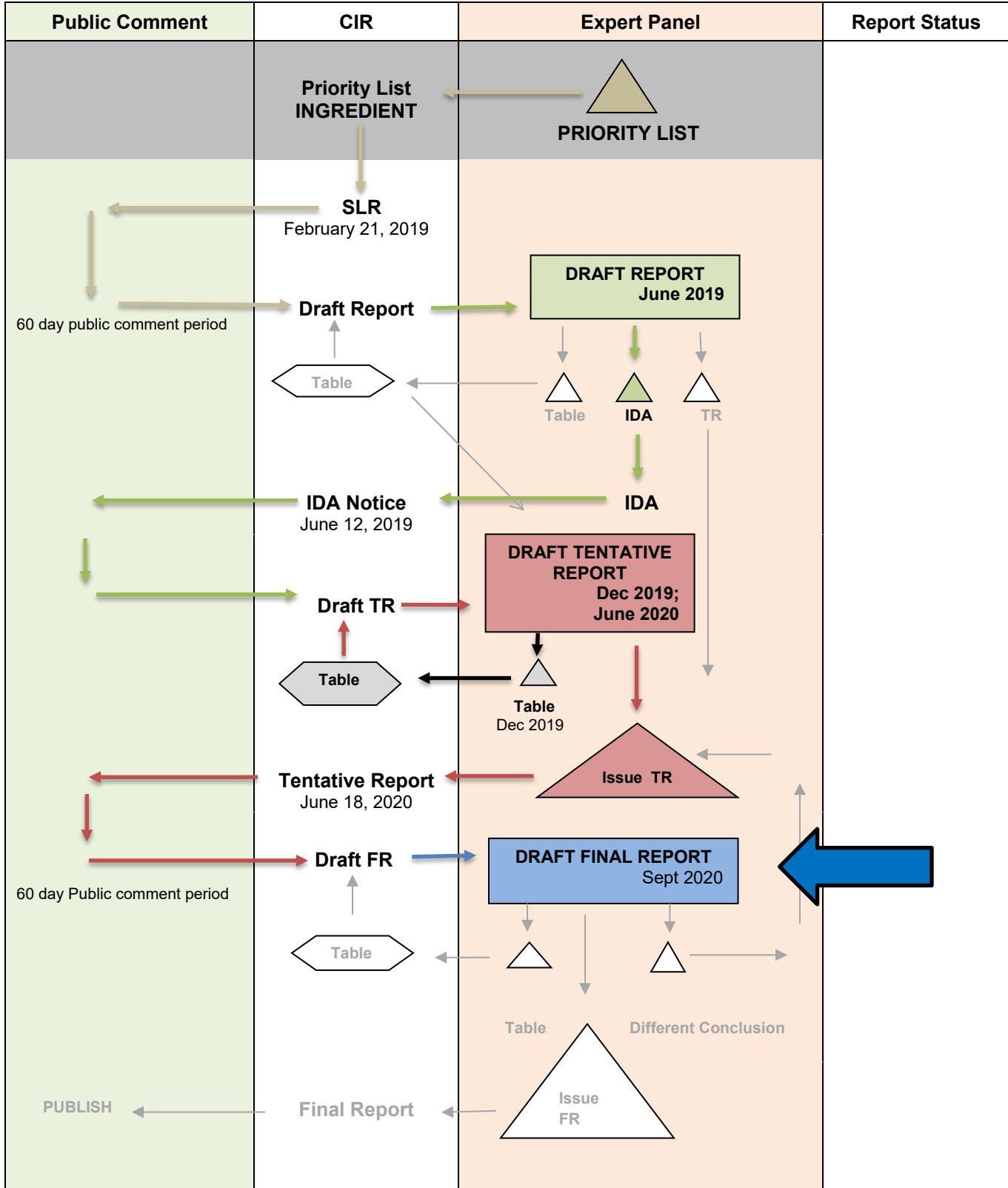
caphyd092020flow: report flowchart
caphyd092020hist: report history
caphyd092020prof: data profile
caphyd092020strat: search strategy
caphyd092020min: transcripts
caphyd092020FDA: FDA VCRP data

The Panel should carefully review the Abstract, Discussion, and Conclusion, and issue a Final Report.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Caprylhydroxamic Acid

MEETING September 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.

The Panel issued a Tentative Report with the conclusion that Caprylhydroxamic Acid is safe in cosmetics in the present practices of use and concentration described in this safety assessment.

Draft Final Report: September 14-15, 2020

Caprylhydroxamic Acid* – September 14-15, 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/fcnavigation.cfm?rpt=cafuslisting&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 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 Cetareth-20 and Cetareth-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.

JUNE 2020 MEETING – THIRD REVIEW/DRAFT TENTATIVE REPORT

Belsito Team – June 8, 2020

DR. BELSITO: Okay. Last one, caprylhydroxamic acid. So this is the one where there was all that data on that one product coming out of Finland. And we asked for additional data. Here it is. And quite honestly, I don't know what to do with all of this additional data because it's -- so this is on skin-sensitization -- because it's sort of all over the board. And I also don't like the NESIL that they chose to come up with the QRA, which puts baby products right on the border with a level of one.

So I think the best table to look, if I remember, is Table 7? Where's the one where they did all the summary -- summary of reactions? Here are all the HRIPTs. No, it's Table 3, dermal irritation and sensitization data. So if you look, they're getting reactions -- they chose a NESIL of 1600 or something. But, if you look at that table, they're getting reactions as low as 83 in induction and challenge and even at 60. No, not at 60.

So the one thing that I started to note -- and then I just gave up -- is that, if you look at the top ones in Table 3, on PDF 32, were at 83 mgs per centimeter squared they're getting reactions during induction of erythema and one reaction of erythema and edema but not at challenge. And then, in the other, they're again getting these funny reactions during induction. And in one, subject 42, they got the same reaction at day two post-challenge, and one subject dropped out because of reactions during the induction period. Anyway, the bottom line was that these two studies at 83 mgs per centimeter squared had penetration enhancers. One had isopropyl myristate; one had isopropyl palmitate, which are known penetration enhancers.

So depending upon how this is formulated, the way I'm reading it, I mean, you cannot go with the NESIL that they chose to use, which, again, I think was 1600 and something, right, for their QRA? You know, particularly given the fact that 1600 is right on the fence with baby products.

DR. HELDRETH: Dr. Belsito?

DR. BELSITO: Yeah?

DR. HELDRETH: I think Mike Fevola, from INOLEX, the company who was behind this data, is wanting to provide some support possibly to this.

DR. BELSITO: Okay.

DR. FEVOLA: Good afternoon. Yes, I'd just like to clarify where the NESIL came from, and that was derived from the two subsequent studies that were in response to the insufficient data announcement from last June's meeting. So we developed N equals 100 patch test cells at two different concentrations. And those corresponded to a LOAEL and a NOAEL. So the NESIL came from the NOAEL. And it should be noted that that CHA was tested neat, and it was formulated into a petrolatum vehicle, so kind of an occlusive vehicle under an occlusive patch, for the delivery in those subsequent studies. So just to clarify where that 1056 NESIL value came from. It was derived from those two subsequent studies.

DR. BELSITO: Right. I mean, I understood that. But in looking at all of the studies that are summarized in Table 3, you're getting some sensitization -- or indication of sensitization, at 83 mgs per centimeter squared in a formulation that is penetration enhancers. That's my point. The NESIL almost depends upon the formulation. And to just not state that, I think, is a mistake, you know, particularly when you're right at an AEL/CEL of one for baby products.

DR. FEVOLA: Yes. And that's noted that that's the same subject throughout all of those tests. And that was the same subject, same series of tests.

DR. LIEBLER: So, Don, is a HRIPT done with penetration enhancers a valid test? I normally don't hear us considering that in the context of our safety evaluations. We sort of tend to assume that the only component in the tested mixture that is relevant to the outcome is the ingredient under consideration. But we often don't have -- we may not even have full information about what else is in the test mixture. Here you know that they're penetration enhancers in the 83 study. And then, the study that we're hearing about from Mike, where we're getting NESIL around 1000, is just petrolatum.

DR. BELSITO: Well, I mean, you're right.

DR. LIEBLER: It's considered. Yeah?

DR. BELSITO: I mean, well, from the fragrance industry, of course, the study we look at for our HRIPTs is always ethanol/DEP, right? Not petrolatum.

DR. LIEBLER: Uh-huh.

DR. BELSITO: We look at, you know, the more typical vehicle for a fragrance. I don't know. I'm just pointing it out that -- and I agree. I was, like, you ran a huge number of HRIPTs on the same cohort of 114 people.

DR. LIEBLER: And I think the penetration enhancers will stack the deck in favor of a sort of higher degree of sensitization potency, just by helping more test chemical get into the epidermis. And because with this particular molecule, this is one where the absorption is going to be, you know, a fraction of what's applied. In fact, we may have data on that somewhere else in the report.

I don't know if we accept the newer NESIL that's at a higher level and then consider the others but explain that this is with penetration enhancers. And, then, maybe roll that all into the discussion. But then, what's the proper level for the calculation of the QRA?

DR. BELSITO: Well, I mean, I think that it's almost like you have to do a QRA on the finished product, or you -- you know, I mean, I don't know what the answer is. It just bothered me that suddenly things dropped when you get a penetration enhancer added into formulation.

DR. LIEBLER: Yeah. I mean, it makes sense. I'm just looking at PDF 23, which is the dermal penetration in vitro. And the last paragraph on that page indicates total absorbed dose, which is in the receptor fluid, and the receptor chamber was about 42 percent, 32 percent and 23 percent of applied doses at the three different doses. So it's dose-dependent, and not surprising that it could be enhanced by a penetration enhancer.

So we usually do take data from an HRIPT, and we very seldom actually talk about the vehicle, although you may read it and note that. And I don't pay that close attention. But we very seldom discuss it. And I think the underlining assumption is there's sort of a constancy of vehicle that's appropriate to the context of cosmetic use. And then we go from there to calculate our NESIL if we need to.

So here we have a situation where we could calculate a NESIL from a vehicle that at least is not a penetration enhancer, which gives us around 1000 for the NOAEL. Whereas with the penetration enhancers, it goes down by about a little more than 10-fold, maybe about, you know, 12-fold lower. So do we pick the higher NESIL, use that in our calculation, and then note that the effect of the penetration enhancer and the fact that these are about somewhere between one third and a half absorbed, formulation particularly important to be done in the context of a QRA? Is that how we deal with it?

DR. BELSITO: I don't know. Was it ever explained why they had that outbreak in Finland?

DR. LIEBLER: Oh, I don't know.

DR. BELSITO: I'm addressing, I guess the gentleman from the industry. Mike?

DR. FEVOLA: Yes. So in follow ups that we have had, we've never heard any additional information other than what appeared in the publication and in the poster presented at European Society. Recall that that was on patients with compromised skin who were using a highly occlusive formulation that contained phenoxyethanol and caprylhydroxamic acid. The subjects that were run as a control as part of that Finnish study, that were the non-eczema group, did not demonstrate any sensitization. It was just in the compromised skin patients that that outbreak occurred.

DR. BELSITO: So I guess this brings up the issue of what we did with PEGs and, then, subsequently undid when we did the tape-stripped-skin. Not to be used on damaged skin. In conclusion, not to be used with -- caution with penetration enhancers in the discussion and diseased skin in the discussion.

DR. LIEBLER: Yeah. That's right. I think we end up going with this.

DR. BELSITO: So safe as used, but in the discussion point out that formulators should take care when formulating products that are designed to be used on diseased skin and/or contain penetration enhancers?

DR. LIEBLER: Yeah. That's what I think we need to do.

DR. BELSITO: Is that what we do? I mean, I don't know.

DR. LIEBLER: I mean, that sounds reasonable to me, but I'd like to hear from the other guys on our team.

DR. BELSITO: Curt, Paul?

DR. SNYDER: Yeah. I was talking the whole time. My headphone was on mute, sorry. No, I think this is exactly what we need to do. It's the easiest path forward, and it most likely would be the resulting conclusion, even if we ask for more data. I think we have enough data. I think we have a pretty good understanding of what's going on.

DR. BELSITO: Okay. So just put it into the discussion?

DR. LIEBLER: Yeah.

DR. SNYDER: But I think it would be nice, Monice, to look at that PEG wording -- of how we did that wording and where we placed that in that document.

DR. BELSITO: Well, we eventually got rid of it. It was in the conclusion, but then we got the data on tape-stripped --

DR. SNYDER: Yeah. That's right.

DR. BELSITO: -- and got rid of it all.

DR. LIEBLER: Yeah.

DR. BELSITO: Because it was in third degree burn patients, where essentially it was given intravenously.

DR. HELDRETH: We can certainly model the language after the new PEGs discussion.

DR. BELSITO: What did that say? I thought we basically said that, after looking at it, it wasn't a concern.

DR. HELDRETH: Right. And, you know, I mean, here we're saying we want to make sure people aren't using it for diseased skin. That sounds more like a drug than a cosmetic anyway. We're always assuming healthy skin for our products, as well. I'm going to bringing that up.

Okay. So in the newer PEGs report, from 2010, we had that “The Expert Panel has further considered one issue of concern that PEGs used on severely damaged skin, as in burned skin, can be associated with renal toxicity. Clearly to be able to demonstrate non-sensitive renal toxicity when PEGs are applied to normal skin, da, da, da, da, da.”

You can see it up here on the screen. “The Panel then considered the newly available dermal penetration data for normal skin and for skin in which the stratum corneum has substantially been removed. These data demonstrated that dermal penetration of (Inaudible) PEGs is increased when the stratum corneum barrier is removed. The question the Panel then addressed was the significance of that finding, using assumptions that would maximize the risk. A margin of safety over 100 was maintained between the renal tox and no observable effect level in the exposure that could result from the use of leave-on cosmetics.”

So instead of having the “burned” in there we could talk about, you know, skin penetration enhancers, something similar to that, if that’s --

DR. BELSITO: I think it has to be in there to explain why we’re getting some of that quirky data. Also, it was very unusual, I think, to try and do -- what -- five, six, seven, eight different concentration HRIPTs in the same panel? I mean, on the same ingredient. I’ve seen -- I mean, it’s not unusual that they’ll run five or six or seven or eight different ingredients on the same panel. But I’ve never seen different concentrations being used on the same group of individuals, which could end up creating, quote/unquote, some type of synergistic effects.

But it was just curious that the stuff that popped up it always seem to be at lower levels. It always seems to be when there was a penetration enhancer in the finished product or in the vehicle.

DR. SNYDER: Well, Don, this would also be highly relevant that in context of the baby products where the margin of safety is only one.

DR. BELSITO: Right. Exactly. That’s what particularly concerned me. You know, if we were at AEL/CELs of, you know, two, three, four, you know, that would be fine. But when we get down to one for baby products -- although, it’s still very conservative. Although, this was QRA1. It wasn’t QRA2 with accumulative exposure.

DR. SNYDER: It’s QRA2. Sorry.

DR. BELSITO: It did consider accumulative exposures?

DR. SNYDER: Yes.

DR. BELSITO: Okay.

DR. LIEBLER: Hi, Monice.

MS. FIUME: Hi, everyone.

DR. BELSITO: I’m just looking back. I thought it said this one did not include accumulative exposure. So the quantitative risk assessment for allergic contact dermatitis as used was conducted -- aggregate exposure was not considered in this assessment. This is PDF page 26.

DR. SNYDER: On PDF 54, it says the 1056 was QRA2. The conclusion, PDF 54.

DR. BELSITO: Well, then there’s a contradiction, right?

DR. EISENMANN: This is Carol. I believe the assay asked for QRA2, but it didn’t do the accumulative, like you do for a fragrance. But the assay asked for QRA2.

DR. BELSITO: Okay. Okay. I mean, I’m fine. I just think that we need to point that out that, with a penetration enhancer in the formulation, it could lower the level of induction for sensitization -- or it may lower. So Bart, just similar language to what we had for the PEGs except for, here, instead of damaged skin or diseased skin, you know, when formulated with penetration enhancer.

DR. HELDRETH: Did you catch that Monice?

MS. FIUME: Parts of it. If someone wouldn’t mind repeating it, I would appreciate that.

DR. HELDRETH: All right. So I put up on the screen the PEGs conclusion -- the discussion section. And we have -- this is the newer conclusion from 2010, where we talked about why the Panel no longer needed to consider damaged skin in the conclusion.

MS. FIUME: Okay.

DR. HELDRETH: And the Belsito team was talking about the possibility of maybe using very similar language to this but instead of “severely damaged skin,” having a case of penetration enhancers.

DR. SNYDER: When formulated with a penetration enhancer.

DR. HELDRETH: Because many of these HRIPTs that we got recently used significant amount of penetration enhancers.

MS. FIUME: Okay. Now I'm caught up. Thank you.

DR. BELSITO: So our conclusion is safe as used, but in the discussion we caution formulators when they're formulating with penetration enhancers, particularly in products that come close to the AEL/CEL of one. Anything else to add here? No? We're all set?

DR. SNYDER: It looks like we're done.

Marks Team – June 8, 2020

DR. MARKS: And I guess -- oh, yeah. I have a lot of comments about that. But first, Tom, Ron, Lisa -- or Lisa, Ron, Tom, if I do it alphabetically -- how are things going with Microsoft Team? They seem to be going pretty smoothly, and we're interfacing with each other, including with Thomas and Monice. Wilma's rather quiet. Alex has commented, but it seems like it's going pretty smoothly.

DR. SHANK: Except for the sound. The audio seems broken up.

MS. KOWCZ: I think the sound is not good from Tom.

DR. MARKS: Yeah, exactly. That's the only thing I have is, Tom, I don't know whether -- get UTS Data to give him another computer with a better mic.

MS. KOWCZ: Right.

DR. SLAGA: Yeah. I will do that.

DR. MARKS: Yeah. It's kind of tough. Okay. I will ask you to clarify, Tom, if I can't hear. It sounds like we all have the same problem. We're having difficulty with your audio portion. It's not that you don't have the audio; it's just it doesn't --

DR. SLAGA: I do have problems with hearing Ron, mainly. I can hear you pretty well. Lisa is pretty good.

DR. MARKS: I can hear Ron Shank quite easily when I talk. It's Tom. It's just you in which -- so if, Tom, in our discussions, there's something which you really want to insert, you can try the chat. Although, I got to say I have not been going on the chat. So, you know, maybe raise your hand and wave at like this, Tom, and say hold. You see me. Give me the non-verbal hold, and we'll figure out a way if we don't hear you that well, to do it. Okay.

DR. PETERSON: So I just have a -- can I just if -- it helps me a lot. I'm using the attachment for my phone, and I don't know if, Tom, you have a headset that goes with your phone. You could plug it into the computer and use it as headphones. It might help.

DR. SLAGA: I don't have one right now, but I can get one.

DR. PETERSON: Okay.

MS. FIUME: I was also going to add I don't know if your computer's the same, but in my settings, I actually have a microphone volume which I think --

DR. PETERSON: Oh, yeah. That's true.

MS. FIUME: -- that's my outgoing sound so that people can hear me more easily if I turn up my microphone volume.

DR. SLAGA: I've got the volume as high as it'll go.

MS. FIUME: Okay.

DR. MARKS: Yeah.

MS. FIUME: And I am watching the chat. So Tom, if you have something that doesn't get picked up, if you -- in the bar across the bottom -- when you can get it -- where there's a different actions, there's a little conversation bubble and if you go there and want to do a chat, I'll pick it up and make sure that Jim hears it or knows that it's there.

DR. MARKS: Yeah. Thanks, Monice. I'm afraid if I pay attention to that along with the two screens -- actually three screens that I have up here -- I would lose track of what's going on a little bit. So yeah. Thanks, Monice.

So Tom, if you really have something -- well, anything you say is important -- but if it's really important, you can do the chat and Monice will pick that up. You can just type in your response or question, and then as I said -- I can see your forehead. I'm glad you washed this morning -- and just raise your hand if there's something you want me to halt. Okay. And I think I see a new -- maybe a couple of new faces on the screen, so I'll be probably expecting your participation.

So this is Caprylhydroxamic Acid, if I'm saying that correctly, and there was concern with this one ingredient because there was an outbreak of contact dermatitis due to an Apobase moisturizer in Finland. Remember at the June meeting of last year, we found insufficiencies to determine the safety, and it all really revolved around this concern about sensitization to this

ingredient. And so there was an ask for some sensitivity endpoints, and in that memo, you can see we got a lot of sensitivity information. There was in chemico and in vitro assays that suggested that this ingredient was a weak sensitizer.

HRIPT gave mostly non-sensitizing results. However, at 3.8 percent, there were a few mild reactions in a couple of subjects. The quantitative risk assessment results found that present formulations at maximum concentration -- there was a negligible risk of insensitivity. Let me see. And then I assume that Dr. -- and I may not be pronouncing this right -- Fevola or Fevola, the chemist.

MS. KOWCZ: It's Mike Fevola.

DR. MARKS: -- might have some comments. Are you on with us?

DR. FEVOLA: Yes, I'm here. Good morning.

DR. MARKS: Good. Okay. So in a minute, I'll ask for your comments to put that in perspective. Monice, probably the only thing that I had a comment is Tables 5 and 6. At the bottom, there were abbreviations like CEL, AEL, et cetera. This is a minor editorial comment but possibly if the abbreviations could be spelled out. Alex had some comments, which will be incorporated.

So we're at the stage now of moving to issue a tentative report, and perhaps the conclusion would be safe when formulated to be nonsensitizing based on quantitative risk assessment or other methods. Lisa, Ron, Tom, your comments with this? And what would you -- moving on to a tentative report, what conclusion would you like to make and maybe comments? Should we first start -- Yeah. Let's first start with Lisa, Ron, and Tom, and then we can ask -- how do I say your last name? I know I didn't get that right.

DR. FEVOLA: Fevola.

DR. MARKS: Fevola.

DR. FEVOLA: Yes. Thank you.

DR. MARKS: Fev-o-la. Okay. A real Irish name. Okay. Lisa, Ron, Tom, your comments. We added data that we now -- we received a lot. Do you feel comfortable moving onto a tentative report and maybe an alert to the cosmetic formulators about the sensitization issue and have that in the conclusion as I put there, formulate -- safe when formulated to be nonsensitizing?

DR. SHANK: Is sensitization an issue? The highest at --

DR. MARKS: And that's a --

DR. SHANK: -- HRIPT test was at 0.3 percent. The highest leave on is 0.25 percent. I think you could just say safe as used. The QRA says the current concentrations would be okay.

DR. MARKS: They hedge a little bit. They say negligible risk. It would have been nice to say no risk.

DR. SHANK: Okay.

DR. MARKS: So Ron, you think we could just go with safe and not even mention -- obviously, all this is going to be detailed in the discussion.

DR. SHANK: Right.

DR. MARKS: Lisa, Tom, what's your sense? Do you want to go just safe or safe when formulated to be nonsensitizing?

DR. SLAGA: Tom, here. I think we should go with safe.

DR. MARKS: So if I heard you right, Tom, go with safe.

DR. SLAGA: Right.

DR. MARKS: Okay.

DR. PETERSON: And I had safe with qualifications. I guess, looking at all the data -- and there is this thing in Finland. I guess I was wondering if it's possible that there is an ingredient-ingredient interaction that's in that particular formulation that's causing the sensitization to the chemical. So that's why I would go for the qualification.

DR. MARKS: Okay. So we have sort of a split.

DR. SHANK: Where is that that you just referred to?

DR. PETERSON: Well, the study -- I have to get the --

DR. SHANK: What page?

DR. PETERSON: Um.

DR. MARKS: I guess, Ron and Tom, while Lisa's looking that up -- and she's trying to explain the outbreak in Finland from the Apobase whether there was an interaction chemically to change things -- the in chemico and in vitro assays suggest it's a weak sensitizer. And as I said in the QRA, it was a negligible risk. HRIPT gave mostly nonsensitizing, so, I guess, to me it was put a qualifier. But Dr. Fevola, why don't we have your input and anybody else from industry go ahead and put it in your perspective because you've done that in the last meeting. We discussed, and I thought it was quite helpful.

DR. FEVOLA: Great. Thank you. So following last June and here we are a year later, based on the insufficient data announcement, our company, INOLEX, undertook the goal of getting the HRIPT completed. And, to do that and ensure that we designed the study correctly, we engaged Dr. Frank Gerberick as a consultant to help guide the design of the studies and then complete the quantitative risk assessment. So many of you are probably familiar with Dr. Gerberick's work and him kind of being one of the chief architects of the present QRA approach that we use today.

We designed the study so that we could achieve both LOEL and NOEL values, and, based on the reported function concentrations, set our levels according to those multiples. We have submitted the data, which you've seen for the HRIPT, and then conducted the quantitative risk assessment. And when used according to the concentrations reported, well, our finding was that there is -- we say negligible risk because there's probably -- it's very difficult to say that there is zero risk and that we do acknowledge that there was the Apobase case. But according to the QRA, it doesn't appear that there would be risk in the present practices of use.

We also, prior to submission actually, coordinated with the CIR SSC at PCPC to kind of ensure that that QRA was robust, and indeed we had input from the Science and Support Committee that was aligned to go with the conclusion as it was presented. So we feel that there's a very strong, based on the data, support to say that there's no risk. But then again, it's really difficult to say, you know, is that zero?

I don't think there could be (inaudible) zero risk. But in perspective based on the QRA, I believe it would be prudent to say it could be safe. And again, that's based on the feedback from multiple toxicologist and other subject matter experts within PCPC.

DR. MARKS: So as you can tell, our team feels we will move forward with the tentative report that it's safe. The question is whether we have a qualifier or not, although, this may not change how we view the conclusion. How difficult from your point of view and a formulator's point of view would it be if there's a qualifier saying that it's formulated to be nonsensitizing based on a QRA or other methods that takes care of the future?

Since you already have the data, we're referring back that your QRA would indicate that it's safe. Is having that qualifier inhibit or create a problem from a formulator's point of view, since we already have the data that'll be in the report?

DR. FEVOLA: Yeah. In a practical sense, I think, if that formulator has access to someone with toxicological expertise, then it's typically not a problem. In a broader sense, when people don't have the context around that qualification, it does sometimes become a little bit more challenging. What I would point out is that the recommended uses that our company recommends are actually below the reported uses.

So I think having that statement in there could be a little bit challenging because it does kind of create a conflict with how people normally use the product. And if they're going to use it beyond our recommended concentrations, then they would probably want to conduct that quantitative risk assessment.

DR. MARKS: I've got to say that part of it, I think, is really crucial because they've have been limits set on Methylisothiazolinone and Methylchlorisothiazolinone and Methylisothiazolinone -- that combination. Even though the manufactured recommended limits, when those limits were exceeded, we got into problems with sensitization. So I think it's important -- when we put our report, it's relevant to the current use concentration and that we would want to have data that support why it would be a higher concentration. Back to Ron and Tom.

DR. SHANK: Can I ask a question?

DR. MARKS: Ron, would you comment?

DR. SHANK: Yes, this is a single chemical, and usually, when we deal with sensitization from single chemicals, we talk about a concentration limit. We don't say "when formulated to be nonsensitizing." That phrase -- that qualification, we have used for mixtures, especially botanicals.

So I don't think it's necessary in this case. We have the data to support that the concentrations of use currently are below those which could produce serious sensitization. And it's not necessary --

DR. BERGFELD: May I (inaudible)?

DR. SHANK: -- it's not necessary to confuse it by saying when formulated to be nonsensitizing. That's putting the burden on the formulator. And if we feel that there is a problem, then we should give a concentration limit that's a maximum limit on how high it could go.

DR. MARKS: Wilma, did I see you raise your hand?

DR. BERGFELD: Yeah. I just wanted to say I agree with Ron Shank totally. I think that this is so clear cut as presented in the information and in the discussion to put that into a -- to create an extra quantitative and qualitative remark in the conclusion maybe puts a company in a medical/legal risk here if something were to happen, and it involves us.

DR. MARKS: Well, Ron and Wilma, you've convinced me, and that's also, obviously, taking into consideration that comments Dr. Fevola made. So I will move tomorrow a tentative report be issued with a conclusion that it's safe. Lisa, is that okay with you hearing?

And then sometimes we do have individuals who do not fully agree with the conclusion, and you're perfectly free, as you know, to comment. And then you're obviously also perfectly free to vote against the conclusion if you don't feel convinced that we're moving forward appropriately. So I don't want you to feel the least bit inhibited.

DR. PETERSON: No, I won't feel inhibited. I just want to follow up; it's a case study on page 27. And I think, if we can say that there's an upper limit to the concentration, I'm fine with that because I still feel like, you know -- you look at all the data, it's possible that there is something about that formulation in Finland that made those individuals sensitive to the chemical. And so perhaps it was the concentration that they used. There's not enough information here to make a judgment on that, but I'm comfortable if there's an upper limit. It's safe as used up to this concentration because that's where all the data are.

DR. MARKS: So the way the reports always are constructed when we say safe as used, it's the concentration -- the highest concentration -- in this report.

DR. PETERSON: Okay.

DR. MARKS: So we expect the formulators would look at the use and concentration tables and see what the highest concentration is. So we normally don't put a concentration limit, I don't think. Wilma, you were going to jump in.

DR. BERGFELD: We could put it in the discussion.

DR. MARKS: Pardon?

DR. BERGFELD: We could put it in our discussions.

DR. MARKS: Oh, yeah. We could emphasize in the discussion that this is the highest use. Yeah. I think the discussion's going to be really important in this.

DR. PETERSON: Yeah.

DR. MARKS: Nobody's going to come out and, I think, feel like, well, you can willy-nilly just use this at large concentrations and not worry about causing allergic contact dermatitis. We know there's an alert to that. I feel comfortable, Ron and Tom, that you've addressed it, along with you, Wilma. You've allayed my concerns dealing with the sensitivity issue. Thomas, I detect non-verbal communication even though we're doing this virtually.

MR. GREMILLION: Yeah. I just wanted to ask if the concentration -- and I apologize if this in there and I didn't see it -- but the concentration for that Apobase, the Finnish product, is that -- what was that? I mean, is it reasonable to presume that it was just a high concentration that caused that incident, or is it kind of a mystery?

DR. FEVOLA: I believe the Apobase concentration was 0.15 percent, and that was formulated into a highly occlusive -- basically a petrolatum mineral oil type emollient base, so a very highly therapeutic cream that was -- the observed incidences of contact dermatitis were observed in patients with compromised skin and eczema.

MR. GREMILLION: Sorry, and remind me, the highest concentration -- so that was 0.15 percent, and that's below the maximum concentration of the products. So it's more of the makeup of the product than the concentration of this ingredient?

DR. FEVOLA: Correct. So according to the QRA, the safety data from these HRIPTs demonstrated that there was an acceptable margin of safety for exposure in leave-on body lotions, which has the highest exposure area, and it was still a margin of safety of one.

MR. GREMILLION: I guess, I'm just trying to understand -- and maybe this is what Dr. Peterson was getting at -- the best way to communicate this in a way that prevents a repeat of that incident in Finland.

DR. FEVOLA: Correct. So --

DR. PETERSON: Is there some language that could go in the discussion that talks about -- I mean, I guess it's hard for me to ignore that Finnish situation? And that if there's some information that's known about what was specific about that formulation that caused the harm, then it's worth having -- I mean, I think our goal is to protect people. So if there's some information that's known that we could put in there then -- the data are the data, and so this is an outlier.

But it means it's telling us something, and I think I have a hard time ignoring it because there's something special, then, about -- if all the other tests say that it's safe, what's different about that product that made it potentially unsafe based on the data that we have?

MS. KOWCZ: Dr. Marks, you have some people that want to speak. I think Carol wants to say something and Don Bjerke as well.

DR. MARKS: Thank you. Go ahead.

DR. EISENMANN: Don, you can go first.

DR. BJERKE: Okay. Yeah. Thanks. This is a great discussion. I think the caution I would give about listing a concentration is that it's really dependent on the cosmetic exposure. So it's dose per unit area, which is critically important, and that's different given the different cosmetic applications. So that's why I think the QRA is so important because the QRA incorporates both the concentration of use, as well as a particular cosmetic application and the dose per unit area. So I think the most appropriate way to handle this would be, as Dr. Marks had noted -- is to refer to the data tables in the QRA.

DR. MARKS: And we would do that basically in the discussion. I think we've come to the conclusion that we won't have a qualifier in the conclusion at this point, but it will be in the discussion. And then, Carol -- Alex, thanks for inserting. You know, it's interesting. When I'm looking at my screen here, I don't see Carol at all.

DR. EISENMANN: Because I don't have my camera.

DR. MARKS: So Carol, jump in now. Again, and Monice, don't hesitate since we're obviously doing a new platform. Normally, when our panels breakout -- or our group breaks out, I can see everybody around the table and in the audience. I have a bit of -- what can I say -- a handicap with that, so Monice and Alex, don't hesitate. Dr. Fevola, your image came up, so that's why I figured you were here. So Carol, what comments did you have?

DR. EISENMANN: Don said very well what I wanted to also say. Just to say, in the past, you have had individual ingredients when you've done a QRA that you've used the QRA in the conclusion. So you can do it that way if you want to, but either way is fine. But you have had it in the conclusion for single ingredients when you've done a QRA.

DR. MARKS: Uh-oh, Ron. Well, we'll see tomorrow what the Belsito team wants to do. You've convinced me, Ron, Tom, and Wilma, to move to have no qualifiers in the conclusion. But I think tomorrow, if the Belsito team feels strongly to have a qualifier, I don't have any strong feelings that that shouldn't be included. Is that okay, Ron, Tom?

We usually -- normally, we're sitting next to each other, and I look next to you. Tom's sitting next to me. I might give Tom a little nudge or Ron, and Lisa and I look at you and say, "Is that okay?" It's a little harder virtually to do it -- what would I say -- rather quietly. But if that scenario comes tomorrow, do you have any issues with having -- strong issues, I'd say -- with having a qualifier? We'll see what happens.

DR. SHANK: Not a strong issue, no.

DR. MARKS: Okay. Okay. So tomorrow, I'm going to move in our review what I fit is the prep for this. And then I don't think Dr. -- I think tomorrow, Dr. Fevola, I'm going to leave Wilma -- Wilma's the one who is facilitating tomorrow's meeting. So if you have some comments, Monice and Bart can alert Wilma. Wilma, you may be more adept at navigating through this platform than I am, but I'm not going to specifically call on you when I make the motion.

I'll let things play out with the Belsito reaction and their team's conclusions. And then, if we're at the same conclusion of safe as used, then there probably will not be much of a discussion, if any, tomorrow. But we'll see how that plays out.

Thomas, that gives you 24 hours to think about it and perhaps ask for anymore clarification. Okay. Let's move on to the next ingredient then.

MS. FIUME: Jim?

DR. MARKS: Oh, Monice.

MS. FIUME: Can I jump in? And then I see Don Bjerke would also like to comment.

DR. MARKS: Oh, sure.

MS. FIUME: But first I just want to get clarification for this --

DR. MARKS: Where am I miss --

MS. FIUME: There's a little --

DR. MARKS: Oh, I see. I see Don's symbol coming up there now. Okay.

MS. FIUME: Yeah. On the screen.

DR. MARKS: Monice.

MS. FIUME: So I just wanted to clarify because I need to add language to the discussion about the sensitization issue. And so Lisa, did I hear you say there was -- one of the items to possibly discuss would be concern of not knowing why that Finnish formulation had issues, and if it was -- did you say ingredient to ingredient interaction was possible?

DR. PETERSON: Well, I mean I think about that way because I think about mixtures and, you know, that sometimes things are more active in a mixture than they are as a single ingredient. And so, yeah. I've had something -- I'm just curious what's special about that particular formulation that made people sensitive to the specific chemical.

DR. MARKS: So I think, Dr. Fevola, again remind me, what was the concentration in the Apobase?

DR. FEVOLA: We believe it was 0.15 percent.

DR. MARKS: Okay. And the highest use concentration we have now is 0.25 percent, so I think that can be brought out. I'm pretty sure I'm correct on that -- am I not, Monice -- that was 0.25 percent is the highest use concentration now. We have an HRIPT that 0.3 percent, so as Ron Shank mentioned, right at the get-go, we have HRIPT that supports the safety of it.

I think for me, Lisa, what we did was we got an alert from this outbreak in Finland with Apobase. And then the reason we delved into the sensitivity issue much greater than perhaps on some of the other ingredients is because we had this alert that there was a sensitizer in Apobase. And so we wanted to be sure we were moving forward with a proper conclusion. And all that'll appear for the discussion. Any other comments? There was one more. Don, do you have --

DR. BJERKE: Yeah. Just a couple of things to maybe add some clarity. I think when it comes to choosing a concentration, I think if you incorporate all of the existing skin sensitization data, that's all included into the NESIL, which is the no expected sensitization induction level. So I think when you create a limit, that is really the limit that gets applied to the various cosmetic usages. So that's the first point. So I think having that NESIL included in the QRA, I think, is quite appropriate because that includes all the data.

Secondly, with regards to formulation effect, that is considered as part of the sensitization assessment factors. So those formulation differences are accounted for by adding an additional uncertainty factor. And then I think what Dr. Fevola made a very good comment on is that I think that, if you have a patient population that has compromised skin and using an occlusive patch, then the exposure can be greater.

So one way that you might consider handling that is to basically say -- reaffirm that this assessment is for normal skin. With compromised skin, this assessment would not hold.

DR. MARKS: I think if you delve into that area, we then will be moving on for a whole another discussion. We've done that in the past -- when you talk about applying it to damaged skin. And oftentimes, moisturizers are applied to eczematous skin. So I don't think I'd really go there.

DR. BJERKE: Okay. That could be included in the uncertainty factors.

DR. MARKS: That's why I'm thinking. Ron and Tom and Lisa?

DR. BERGFELD: That's my opinion.

DR. MARKS: Pardon?

DR. BERGFELD: That's my opinion. Don't touch that one.

DR. MARKS: Yeah, exactly.

DR. BERGFELD: Assumed it's most (inaudible).

DR. MARKS: Okay. That was robust and a good discussion. Again, I'll move tomorrow that we issue a safe conclusion as used.

DR. FEVOLA: Thank you.

Full Panel – June 9, 2020

DR. MARKS: Oh, don't worry, Wilma. I knew that was your microphone, you're breaking up. I'll refer you to the memo from Monice, dated February 21st. At the June meeting last year, the panel found the data were insufficient to determine sensitivity. There was some (audio skip) for sensitization in the HRIPTs that were submitted at that time.

So, we requested more sensitivity data, and that was particularly -- that's because there was an outbreak of allergic contact dermatitis to a product called Apobase, which is a moisturizer that had been marketed in Finland, and the allergy within this moisturizer was Caprylylhydroxamic Acid.

So, we asked for several different data needs, which in that memo from Monice are highlighted. Submissions include a quantitative risk assessment (inaudible). So, we had a structural activity group analysis, and that conclusion was it was a non-sensitizer.

We had input with a chemico/vitro assays, and that suggested that this ingredient could be a weak sensitizer. And then we had HRIPTs, which mostly resulted in non-sensitizer, but at 3.8 percent there were mild reactions in a few subjects. QRA results found at the present formulations, at maximum concentration, there would be a negligible risk for inducing sensitization.

So, our team felt, with this new data, and obviously all that being handled in the discussion, that we could move forward with a tentative report, and a conclusion safe as used. That's a motion.

DR. BERGFELD: Okay. Comment by the Belsito team, or Dr. Belsito?

DR. BELSITO: No, we're going to go ahead with that conclusion, but we have some very important points to make in the discussion, particularly since with the QRA analysis your AEL to CEL for baby products ends right at one. If it had gone any lower, it would not be safe for baby products. So, we'll go ahead with the conclusion, but there are some important points in the discussion if you want me to get into them now.

DR. BERGFELD: Why don't we take the vote, then be done with that, and then give the discussions. I'd like to have any other comments regarding this, quickly, and then we can come back and comment if it would change the vote.

All right, I'm going to call for the vote. All those in favor of safe conclusion, please indicate by raising your hand. Those oppose, be verbal. It passed unanimously. Now, back to our discussion.

DR. BELSITO: So, I went back and looked at all of those reports where we're getting quirky data on lower concentrations, and it turns out that they were all formulations containing penetration enhancers. And, when I inquired about the outbreak in Finland, apparently this Apobase was being used on damaged skin in those cases. So, it does appear that at dosages below what we're approving, if you increase penetration to the stratum corneum, either because the skin is damaged or because you add a penetration enhancer, it can sensitize at a lower dose.

I would also point out that no one knows how to predict potency of an allergen from in vivo assays. That's the \$90 million question. All you can tell is that there's a hazard; you cannot determine the risk, so, saying that just because the DPRA was not high it may suggest that it's not a strong sensitizer, is a leap of faith that has not really been shown yet.

So, that's just an aside, but, having said that, I think that we need a very robust discussion that the outbreak in Finland appeared to be related to application of Apobase to diseased skin, and in some of the reports where we had quirky data at lower concentrations, the hydroxycinnamic acid was in a formulation that had a penetration enhancer, isopropyl myristate in one case, isopropyl palmitate in another.

DR. LIEBLER: Don, we also discussed, somewhat of a discussion related to PEGs on a tape strip.

DR. BELSITO: Right, using the same type of language we had in the discussion for PEGs, in this discussion.

DR. BERGFELD: Nice pickup, thank you. Any other discussion points or comments? So, Don, your discussion, we'll have to deal with the QRA, the low dose on damaged skin, and what else are we missing?

DR. BELSITO: Formulation with penetration enhancers.

DR. BERGFELD: Formulation with penetration enhancers. Thank you.

DR. BELSITO: Particularly in product categories that come close to one in the AEL/CEL on a QRA.

DR. BERGFELD: And, did you want to mention baby products?

DR. BELSITO: I mean, you could, assuming that that data for the QRA is part of the publication, they'll see what the AEL/CEL are for the various product categories.

DR. BERGFELD: Okay. So, we won't include specifically babies, but just the results. Okay. All right. So, we have voted on this, I believe. I've got all of the discussion. And, this is the (inaudible) in the discussion. Dr. Marks?

DR. MARKS: Yeah, one comment. Hey, Don? I agree with everything you've said. Was Dr. Fevola in your discussion group when you reviewed this? Just so that we had industry's input.

DR. BELSITO: Yes.

DR. MARKS: Good. Okay.

Safety Assessment of Caprylhydroxamic Acid as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: August 21, 2020
Panel Meeting Date: September 14-15, 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.

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of Caprylhydroxamic Acid as used in cosmetic formulations; this ingredient is reported to function as a chelating agent. Positive sensitization results appeared to be related to use of a penetration enhancer in formulation; additionally, sensitization that occurred with the use of a moisturizer containing Caprylhydroxamic Acid appeared to correlate with use on damaged skin. Therefore, the Panel cautioned against the use of Caprylhydroxamic Acid in a manner that would result in increased penetration. A quantitative risk assessment (QRA) was performed, using weight-of-evidence no-expected-sensitization-induction-level (WoE NESIL) of 1056 $\mu\text{g}/\text{cm}^2$. Nitrosamide formation is theoretically possible with Caprylhydroxamic Acid, but unlikely; however, manufacturers should use good manufacturing practices to monitor for the formation of nitrosamides as potential impurities. The Panel concluded that Caprylhydroxamic Acid is safe in cosmetics in the present practices of use and concentration described in this safety assessment.

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 Expert Panel for Cosmetic Ingredient Safety (Panel) typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (<https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites>; <https://www.cir-safety.org/supplementaldoc/cir-report-format-outline>). Unpublished data were provided by the cosmetics industry, as well as by other interested parties.

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

CHEMISTRY

Definition and Structure

According to the *Dictionary*, Caprylhydroxamic Acid (CAS No. 7377-03-9) is the organic compound that conforms to the keto form depicted in Figure 1.¹ However, hydroxamic acids may exist in both keto and enol tautomeric forms.⁴ The keto form is likely to predominate in acidic formulation, while the enol may dominate under alkaline conditions.

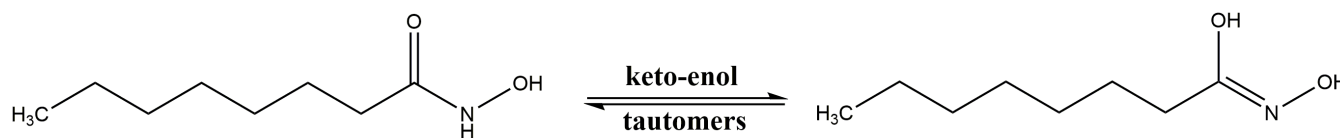


Figure 1. Caprylhydroxamic Acid

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 inhibiting 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.

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 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.

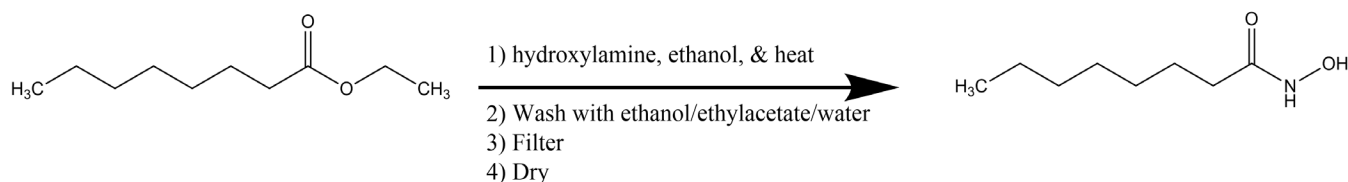


Figure 2. Example of a synthesis route for the commercial production of Caprylhydroxamic Acid, using ethyl caprylate

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(R')-N=O R functional group. Due to the presence 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 NO₂ 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 (Table 2).¹² 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.¹³ 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.^{14,15} 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.^{16,17} 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.¹⁸⁻²⁰

Caprylhydroxamic Acid is not restricted from use in any way under the rules governing cosmetic products in the European Union.²¹

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

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

A use concentration of 0.3% was then considered in the calculations because an MOE greater than or equal to 100 was not achieved with a concentration of 0.5%. Using 0.3% as the maximum concentration of use, the MOE was calculated to be 71. NICNAS stated that even though this MOE is still below 100, given that the exposure estimate is based on the conservative assumption of 100% dermal absorption of the amount left on the skin following application and the simultaneous use of various products containing the maximum concentration of Caprylhydroxamic Acid, the risk to the public is not considered unreasonable if products contain a maximum of 0.3%.² Actual data support a maximum of 42% absorption, as described in the Dermal Penetration section, below.²²

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.²² 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-[¹⁴C]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/cm²), 31.75% (2747 ng equiv/cm²), and 22.93% (1824 ng equiv/cm²) of the applied dose, respectively. Dermal delivery (absorbed dose + epidermis + dermis + clingfilm) using these preparations was 51.45% (3649 ng equiv/cm²), 43.84% (3793 ng equiv/cm²), and 36.87% (2933 ng equiv/cm²) of the applied dose, respectively. The total unabsorbed dose (total dislodgeable dose + stratum corneum + unexposed skin) was 43.99% (3120 ng equiv/cm²), 52.67% (4558 ng equiv/cm²), and 60.23% (4792 ng equiv/cm²) 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.²⁴ (Only an English abstract was available for this Japanese paper; therefore, additional details are not presented.)

Animal

Oral

Following oral administration of 1-[¹⁴C]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.²⁴ "Considerable amounts" of radioactivity were found in the liver and the heart, but most was excreted as expired [¹⁴C]CO₂; approximately 25% of the total radioactivity was excreted as [¹⁴C]CO₂ 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 LD₅₀ of Caprylhydroxamic Acid is reported to be > 8820 mg/kg in rats.² Another source reported that the oral LD₅₀ in rats is > 10,700 mg/kg.²⁵ (Further details were not available.)

Subchronic Toxicity Studies

Oral

Groups of 10 male and 10 female Wistar rats were dosed for 13 wk with 0, 100, 500, or 2500 mg/kg bw/d 10% Caprylhydroxamic Acid in lactose (corresponding to 0, 10, 50, and 250 mg/kg bw Caprylhydroxamic Acid, respectively) by gavage.^{2,26} The vehicle was 5% aqueous (aq.) gum arabic. There was no mortality attributed to the test article; however, 2 female animals of the mid-dose group died due to dosing errors. Signs of toxicity were observed only in the high dose group, and all the following observations were reported for this group. Clinical observations included "slowness in activity." There were significant decreases in alanine aminotransferase activity and glucose and potassium levels in males, and there was a significant increase in leukocyte count and significant decreases in erythrocyte, hematocrit, and hemoglobin values in males and females. Spleen weights (absolute and relative to bw) were increased in males and females, and adrenal weights were significantly decreased in males. Slight atrophy in the epithelial cells of the renal glomeruli and hemosiderin deposits in the spleen were reported upon microscopic examination. The NOAEL of the test article (10% Caprylhydroxamic Acid in lactose) was determined to be 500 mg/kg bw/(corresponding to up to 50 mg/kg bw Caprylhydroxamic Acid).²

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oral

Groups of 18 mated female Wistar rats were dosed with 0, 50, 250, and 500 mg/kg bw/d 10% Caprylhydroxamic Acid (corresponding to 0, 5, 25, and 50 mg/kg bw Caprylhydroxamic Acid, respectively) by gavage on days 9 through 14 of gestation.^{2,27} The vehicle was 5% gum arabic solution. Twelve dams of the 0, 50, and 250 mg/kg bw/d groups, and all of the dams of the 500 mg/kg bw/d group, were killed on day 20 of gestation. The remaining dams were allowed to litter naturally. There was no mortality during the study, and there were no clinical signs of maternal toxicity. Body weight gains and feed consumption of the 250 and 500 mg/kg bw/d groups were "a little lower" than those of the controls; fetal weights in these groups were also lower than those in the control group, subsequently resulting in delayed ossification. Neonatal body weights from dams of the 250 mg/kg bw/d dose group were significantly lower at birth and at weaning. Decreased growth that was observed for fetuses and neonates of the higher dose groups 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.²⁸ 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 487.²⁹ 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.³⁰ 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.²⁵ 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.³⁰ 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 study³⁴ 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/cm²; the lowest-observable-effect-level (LOEL) was 2111.1 µg/cm². Therefore, a WoE NESIL of 1056 µg/cm² was chosen.

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

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

Consumer exposure levels (CELs) for each product category were determined for the reported maximum concentrations of use for Caprylhydroxamic Acid, as provided in the Council's concentration of use survey, along with published habits and practices data (Table 5). The MOS was then determined by evaluating the AEL/CEL ratio; ratios ≥ 1 provide an acceptable MOS. Using a NESIL of 1056 µg/cm² for Caprylhydroxamic Acid, MOS values ranged from 1.0 (for baby lotions, oils, and creams, not powder) to 269.2 (for bath soaps and detergents; Table 6). Based on the results of this QRA 2.0, the study authors stated that "formulation of these products at their maximal concentration of [Caprylhydroxamic Acid] would present a negligible risk of inducing skin sensitization."

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 ET₅₀ (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; 0.05% - 1.5% of the preservative mixture itself (in petrolatum (pet.)); and 0.001% - 3.2% Caprylhydroxamic Acid (or its potassium salt; in pet.). Occlusive patches were applied for 2 d, and the test sites were scored upon patch removal and on days 4 and 5. A control group of 20 eczema patients, who had not used the new moisturizer formulation that contained the preservative mixture, was patched-tested with the preservative mixture and with Caprylhydroxamic Acid. A second control group of 13 subjects, all with uncompromised skin, was patch-tested with all the test materials.

Patch test results for the test group are presented in Table 7. In the test group of patients with compromised skin that developed contact allergy, positive reactions were seen with the new moisturizer formulation (that contained the preservative mixture), Caprylhydroxamic Acid, and the preservative mixture itself; however, reactions were not reported with the old

moisturizer formulation (which was preserved with parabens), the formulation with phenoxyethanol only, or the preservative-free cream. For Caprylhydroxamic Acid, +++ reactions were reported with test concentrations $\geq 0.1\%$, ++ reactions with concentrations $\geq 0.032\%$, and + reactions with concentrations $\geq 0.01\%$. 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 In total, 16 patients with a positive patch test reaction were identified, three with a (++)-reaction and the remainder with a (+)-reaction. Twelve of the 16 patients that presented with atopic dermatitis, hand eczema, or psoriasis had previously used the moisturizer. Of the remaining 4 patients (2 of which had a ++ reaction), 3 presented with eczema of the face or eyelids, and 1 was a hairdresser with hand eczema. The use of products containing Caprylhydroxamic Acid could not be identified, but 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/d. Using this SED and an NOAEL of 50 mg/kg bw/d (that was derived in a subchronic oral toxicity study in rats), an MOE of 43 was calculated. Because this is not an acceptable MOE, the calculations were again performed with a maximum use concentration of 0.3% in formulations. With this concentration, the MOE was calculated to be 71. Even though this MOE is still below the generally acceptable value of 100, NICNAS stated, given that the exposure estimate is based on the conservative assumption of 100% dermal absorption, and the simultaneous use of various products containing the maximum concentration of Caprylhydroxamic Acid, the risk to the public is not considered unreasonable if products contain a maximum of 0.3%.

The rate and extent of dermal absorption following topical application of three suspensions containing (oil-in-water, silicone-in-water, and clear lotion) 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/cm²), followed by the silicone-in-water suspension (31.75%; 2747 ng equiv/cm²), and then the clear lotion (22.93%; 1824 ng equiv/cm²). Dermal delivery using these preparations was 51.45% (3649 ng equiv/cm²), 43.84% (3793 ng equiv/cm²), and 36.87% (2933 ng equiv/cm²) of the applied dose, respectively.

Caprylhydroxamic Acid was rapidly hydrolyzed by rat liver homogenates to caprylic acid and hydroxylamine. In rats orally administered 1-[¹⁴C]Caprylhydroxamic Acid, approximately 25% of the radioactivity was excreted as [¹⁴C]CO₂ after 2 h, and by 24 h, 6.9% and 0.6% was excreted in the urine and the feces, respectively.

The oral LD₅₀ 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/d 10% Caprylhydroxamic Acid in lactose, with 5% aq. gum arabic as the vehicle, the NOAEL of the test article was determined to be 500 mg/kg bw/d (corresponding to up to 50 mg/kg bw Caprylhydroxamic Acid). Changes in some clinical chemistry parameters and organ weights (specifically an increase in absolute and relative spleen weight) were observed in the high dose group.

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

In the Ames test, Caprylhydroxamic Acid in DMSO (at up to 5000 µg/plate) was not mutagenic to *S. typhimurium*, with or without metabolic activation, but there was weak but clear dose-dependent mutagenic activity 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, and the NESIL was chosen based on the highest dose/cm² that did not cause any sensitization. The results of all of the applicable HRIPTs were examined, and accordingly, the highest concentration tested in which no positive responses were observed (NOEL) was 1055.6 µg/cm²; the LOEL was 2111.1 µg/cm². Therefore, a WoE NESIL of 1056 µg/cm² was chosen. For each cosmetic product category, AELs were determined using this NESIL and appropriate QRA 2.0 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.

DISCUSSION

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

The Panel was concerned with the inconsistent outcomes regarding dermal sensitization. However, upon further review, the Panel determined that studies that had positive sensitization results were those in which the test substance included a penetration enhancer. Additionally, the Panel noted that cases of increased sensitization with the use of a moisturizer in Finland, a product that had been reformulated to include Caprylhydroxamic Acid, appeared to be related to use on damaged skin, which most likely resulted in increased penetration. Therefore, the Panel stated that caution should be taken with use of Caprylhydroxamic Acid in a manner that would result in increased penetration, such as formulation with penetration enhancers. This is especially important in product types with an MOS, based on an AEL/CEL ratio at or near 1, as calculated in a QRA. According to the results of a QRA that was submitted to CIR, product types with an AEL/CEL of 1 include baby lotions, oils, and creams; the WoE NESIL used in the QRA was 1056 µg/cm².

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

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

TABLES**Table 1. Chemical properties**

Property	Value	Reference
Physical Form	crystalline solid	2,3
Color	white	3
	white to tan	2
Odor	mild, characteristic	3
Molecular Weight (Da)	159.23	6
Density (g/ml @ 25°C)	0.3413 (sample not compressed) 0.4789 (sample tamped down)	2,3
Vapor pressure (mm Hg @ 25 °C)	2.50×10^{-6} (estimated)	2
Melting Point (°C)	≥ 78 to ≤ 81	3
	81	2
	79 - 81	25
Boiling Point (°C)	343.32	25
Water Solubility (g/l @ 23°C)	1.55	2,3
log K_{ow} (@ 25°C)	1.66 (estimated)	2,3
	2.827 ± 0.191 (estimated)	6
Disassociation constants pKa (@ 25°C)	9.56 ± 0.20 (estimated)	6

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

	# of Uses ¹²	Max Conc of Use (%) ¹³
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%	²⁵
HUMAN					
Irritation and Sensitization					
eyeliner formulation containing 0.105% Caprylhydroxamic Acid	applied neat; 0.2 ml induction and challenge dose: ³⁰ 32.3 µg/cm ²	54 subjects	HRIPT <u>induction</u> : 24-h semi-occlusive patch (1 in ²) applied to the upper back 3 x/wk for 3 wk, for a total of 9 applications; test sites were evaluated 24 or 48 h after patch removal <u>challenge</u> : 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 1 st 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 ³⁰	109 subjects	HRIPT <u>induction</u> : 48-h occlusive patch applied 3x/wk for 3 wk <u>challenge</u> : after a 2-wk non-treatment period, patches were applied to induced 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 dose: ³⁰ 60.0 µg/cm ²	52 subjects	HRIPT <u>induction</u> : 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 wk, for a total of 9 applications; test sites were evaluated 24 or 48 h after patch removal <u>challenge</u> : 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 dose: ³⁰ 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 <u>induction</u> : 24-h occlusive patch (¼ in ²) applied to the upper back 3 x/wk for 3 wk, for a total of 9 applications; test sites were evaluated 24 or 48 h after patch removal <u>challenge</u> : 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 2 and 3); mild erythema with mild edema (induction patch 4); moderate erythema with moderate edema (induction patch 5), resulting in the discontinuation of subsequent patch applications; it was the opinion of the researchers that this pattern of skin reactivity was indicative of a pre-existing hypersensitivity to 1 or more ingredients in the formulation 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 dipolyhydroxystearate; 3% glycerin; 2% beeswax) [concentrations stated as provided]	applied neat; 0.2 ml induction and challenge dose: ³⁰ 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 dose: ³⁰ 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 dose: ³⁰ 166.6 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 dose: ³⁰ 166.6 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 dose: ³⁰ 166.6 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 dose: ³⁰ 166.6 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 dose: ³⁰ 166.6 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 <u>induction</u> : 24-h semi-occlusive patch (¾ in ²) applied to the upper back 3 x/wk for 3 wk, for a total of 9 applications <u>challenge</u> : 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 dose: ³⁰ 1055.6 µg/cm ²	95 subjects Fitzpatrick skin types: I – 23 subjects II – 30 subjects III – 25 subjects IV – 17 subjects	HRIPT <u>induction</u> : 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 wk, for a total of 9 applications <u>challenge</u> : after a non-treatment period of at least 10 d, 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 dose: ³⁰ 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 <u>induction</u> : 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 wk, for a total of 9 applications <u>challenge</u> : after a non-treatment period of at least 10 d, 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 perceptible erythema; 5 subjects had one incident of barely perceptible erythema	⁴⁵
Caprylhydroxamic Acid, 100%	amount applied not stated	52 subjects	HRIPT <u>induction</u> : 24-h semi-occlusive patch (1 in ²) applied to the upper back 3 x/wk for 3 wk, for a total of 9 applications; test sites were evaluated 24 or 48 h after patch removal <u>challenge</u> : 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 doses portrayed in µg/cm² were not expressed explicitly in the submitted studies, but were calculated separately³⁰

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; HRIPT – human repeated insult patch test; P – induction patch

Key to reaction scores: 0.5 = barely perceptible; 1 = mild; 2 = moderate

Table 5. CEL by product category based upon reported maximum concentrations of use for Caprylhydroxamic Acid³⁰

Product Category	Classification	Max Conc of Use (%)	Product Exposure (µg/cm ²)	CEL (µg/cm ²)
baby lotions, oils, and creams (not powder)	leave-on	0.15	2421	3.63
eyebrow pencils	leave-on	0.2	647	1.29
eyeliners	leave-on	0.11	1563	1.72
eye shadows	leave-on	0.19	2170	4.12
other eye makeup preparations	leave-on	0.2	2170	4.34
hair conditioners	rinse-off	0.15	200	0.3
hair conditioners	leave-on	0.15	2000	3.0
hair sprays; aerosol	leave-on	0.075	1390	1.04
hair sprays; pump spray	leave-on	0.075	2200	1.65
shampoos (non-coloring)	rinse-off	0.2	170	0.34
tonics, dressings, and other hair grooming aids	leave-on	0.075 – 0.23	990	0.74 – 2.28
other hair preparations (non-coloring)	leave-on	0.15	990	1.49
bath soaps and detergents	rinse-off	0.13 – 0.3	10	0.013 – 0.03
body wash, shower gel	rinse-off	0.13 – 0.3	15	0.02 – 0.045
facial skin cleansing	rinse-off	0.12 – 0.15	150	0.18 – 0.225
facial skin cleansing	wipe-off	0.12 – 0.15	900	1.08 – 1.35
face and neck products (not spray)	leave-on	0.12	2700 (face cream)	3.24
body creams and lotions	leave-on	0.12 – 0.25	1120	1.34 – 2.80
hand creams and lotions	leave-on	0.12 – 0.25	4200	5.04 – 10.5
paste masks and mud packs	rinse-off	0.15	4200	6.3

Abbreviation: CEL - consumer exposure level

Table 6. MOS for skin sensitization by product category based on reported maximum concentrations of use of Caprylhydroxamic Acid³⁰

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

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

Table 7. Patch test results in patients with compromised skin that had suspected contact allergy to a new moisturizer formulation⁴⁸

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					
<i>no. tested</i>	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
<i>no. tested</i>	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				
<i>no. tested</i>	39	39	39	39				

REFERENCES

1. Nikitakis J, Kowcz A. Web-Based International Cosmetic Ingredient Dictionary and Handbook. <http://webdictionary.personalcarecouncil.org/jsp/Home.jsp>. Washington, DC: Personal Care Products Council. Last Updated 2020. Accessed 2/19/2020.
2. National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Public Report: Octanamide, N-hydroxy- (INCI name: Caprylhydroxamic Acid) (File No.: LTD/1543) 2012 https://www.nicnas.gov.au/_data/assets/word_doc/0005/6773/LTD1543FR.docx Accessed 02/01/2019
3. European Chemicals Agency (ECHA). N-Hydroxyoctanamide (CAS No. 7377-03-9) <https://echa.europa.eu/en/registration-dossier/-/registered-dossier/25355> Last Updated 2018. Accessed 02/08/2019
4. Ganeshpurkar A, Kumar D, Singh SK. Strategies for the Synthesis of Hydroxamic Acids *Current Organic Synthesis*. 2017;14(0):1-12.
5. Muri E, Nieto M, Sindelar R, Williamson J. Hydroxamic Acids as Pharmacological Agents. *Current Medicinal Chemistry*. 2002;9(17):1631-1653.
6. Advanced Chemistry Development (ACD/Labs). CAS Registry No. 7377-03-9 Software 11.02. 2019.
7. Inolex. 2019. Method of Manufacture for Caprylhydroxamic Acid. Unpublished data received from Inolex on March 20, 2019.
8. Shank RC, Magee PN. Chapter 1. Toxicity and carcinogenicity of N-nitroso compounds. In: *Mycotoxins and N-Nitroso Compounds: Environmental Risks*. Boca Raton, FL: CRC Press, Inc; 1981. 185-217.
9. Rostkowska K, Zwierz K, Rózański A, Moniuszko-Jakoniuk J, Roszczenko A. Formation and metabolism of N-nitrosamines. *Polish Journal of Environmental Studies*. 1998;7(6):321-325.
10. Challis BC, Shuker DE, Fine DH, Goff EU, Hoffman GA. Amine nitration and nitrosation by gaseous nitrogen dioxide. *IARC Sci Publ*. 1982;41:11-20.
11. Shiota FN, DeMaster EG, Lee MJ, Nagasawa HT. Generation of nitric oxide and possibly nitroxyl by nitrosation of sulfohydroxamic acids and hydroxamic acids. *Nitric Oxide*. 1999;3(6):445-453.
12. US Food and Drug Administration (FDA) Center for Food Safety & Applied Nutrition (CFSAN). 2020. Voluntary Cosmetic Registration Program (VCRP) - Frequency of Use of Cosmetic Ingredients. College Park, MD Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 6, 2020; received January 13, 2020.
13. Personal Care Products Council. 2018. Council Concentration of Use Survey: Caprylhydroxamic Acid. Unpublished data submitted by the Personal Care Products Council on October 25, 2018.
14. Johnsen MA. The influence of particle size *Spray Technol Marketing*. 2004;14(11):24-27.
15. Rothe H. Special Aspects of Cosmetic Spray Evaluation. 2011. Unpublished data presented at the 26 September Expert Panel meeting. Washington, D.C.
16. Bremmer HJ, Prud'homme de Lodder LCH, Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 2006. RIVM 320104001/2006. Pages 1-77.
17. Rothe H, Fautz R, Gerber E, et al. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett*. 2011;205(2):97-104.
18. Aylott RI, Byrne GA, Middleton J, Roberts ME. Normal use levels of respirable cosmetic talc: Preliminary study. *Int J Cosmet Sci*. 1976;1(3):177-186.
19. CIR Science and Support Committee of the Personal Care Products Council (CIR SSC). 2015. Cosmetic Powder Exposure. Unpublished data submitted by the Personal Care Products Council on November 3, 2015.
20. Russell RS, Merz RD, Sherman WT, Siverston JN. The determination of respirable particles in talcum powder. *Food Cosmet Toxicol*. 1979;17(2):117-122.
21. European Commission. CosIng database; following Cosmetic Regulation No. 1223/2009. <http://ec.europa.eu/growth/tools-databases/cosing/>. Last Updated 2018. Accessed 02/08/2019.
22. Charles River Laboratories. 2016. The *in vitro* percutaneous absorption of radiolabelled Caprylhydroxamic Acid in three formulations through human skin. Test Facility Study No. 798232. Report No. 37551. Unpublished data submitted by Inolex on May 10, 2019.

23. Ohta T, Moriya M, Kaneda Y, et al. Mutagenicity screening of feed additives in the microbial system. *Mutat Res, Genet Toxicol Test.* 1980;77(1):21-30.
24. Kobashi K, Takebe S, Hase J. Distribution, metabolism and excretion of caprylo- and nicotinohydroxamic acid. [English abstract only.] *Yakugaku Zasshi.* 1973;93(12):1564-1572.
25. MatTek Corporation. 2018. Evaluation of the Skin Irritation Potential of Diheptyl Succinate and Caprylhydroxamic Acid Using the EpiDerm Skin Irritation Test OECD TG 439. Study No. 034-18. Unpublished data submitted by Inolex on April 16 2019.
26. Sugiyama K, Sagami F, Chiba T. Chronic toxicity test of Taselin in rats. (English abstract only) *Jpn J Vet Sci.* 1974;36(6):525-538.
27. Suzuki Y, Okada F, Chiba T. Negative result of teratological study on caprylo-hydroxamic acid in rats. *Nihon Juigaku Zasshi.* 1975;37(5):307-309.
28. Nelson Laboratories Inc. 2007. The *Salmonella typhimurium* reverse mutation assay (Ames test), liquids or soluble chemicals, with caprylohydroxamic acid. Procedure No. STP0098 REV 01. Laboratory No. 373535. Unpublished data submitted by Inolex on April 9, 2019.
29. BioReliance. 2013. *In Vitro* Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL) with Caprylhydroxamic Acid. BioReliance Study No. AD64VD.348REACH.BTL. Unpublished data submitted by Inolex on April 9, 2019.
30. Gerberick FG, Sminkey CS, Fevola MJ. 2020. Quantitative risk assessment for allergic contact dermatitis: Caprylhydroxamic Acid as used in cosmetics. Unpublished data submitted by the Personal Care Products Council on February 11, 2020.
31. Consumer Product Testing Company. 2014. Repeated insult patch test of an eyeliner containing 0.105% Caprylhydroxamic Acid. Unpublished data submitted by the Personal Care Products Council on February 26, 2019.
32. Anonymous. 2019. Summary of an HRIPT of a facial cream containing 0.15% Caprylhydroxamic Acid. Unpublished data submitted by the Personal Care Products Council on March 8, 2019.
33. Anonymous. 2019. Summary of an HRIPT of a brow thickening powder containing 0.195% Caprylhydroxamic Acid. Unpublished data submitted by the Personal Care Products Council on March 14, 2019.
34. Anonymous. 2020. Summary of an HRIPT of an aqueous formulation containing 0.76% Caprylhydroxamic Acid. Unpublished data submitted by the Personal Care Products Council on February 14, 2020.
35. SGS. 2020. Repeated insult patch test study - Caprylhydroxamic Acid tested at 1.9%. Test Report No. 4529277-CPCH04R1. Unpublished data submitted by the Personal Care Products Council on February 11, 2020.
36. Clinical Research Laboratories Inc. 2008. Repeated insult patch test of undiluted caprylohydroxamic acid. CRL study number: CRL16108. Unpublished data submitted by Inolex on April 9, 2019.
37. Consumer Product Testing Company. 2018. Repeated insult patch test. Protocol No.: CP-01.01S. Lotion (lot: 647-081-7J) containing 0.15% Caprylhydroxamic Acid, tested undiluted. Experiment Reference No.: C17-5522.07. Unpublished data submitted by Inolex on April 9, 2019.
38. 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% Caprylhydroxamic Acid, tested undiluted. Experiment Reference No.: C17-5522.08. Unpublished data submitted by Inolex on April 16, 2019.
39. 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.
40. Consumer Product Testing Company. 2018. Repeated insult patch test. Protocol No.: CP-01.01S. CHA blend #3 (lot: GH5355) containing 5% Caprylhydroxamic Acid, tested as a 6% dilution. Experiment Reference No.: C17-5522.05. Unpublished data submitted by Inolex on April 9, 2019.
41. 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.
42. Consumer Product Testing Company. 2018. Repeated insult patch test. Protocol No.: CP-01.01S. CHA blend #2 (lot: GK9325) containing 10% Caprylhydroxamic Acid, tested as a 3% dilution. Experiment Reference No.: C17-5522.01. Unpublished data submitted by Inolex on April 16, 2019.

43. Consumer Product Testing Company. 2018. Repeated insult patch test. Protocol No.: CP-01.01S. CHA blend #1 (lot: GK9326) containing 15% Caprylhydroxamic Acid, tested as a 2% dilution. Experiment Reference No.: C17-5522.03. Unpublished data submitted by Inolex on April 9, 2019.
44. Consumer Product Testing Company. 2018. Repeated insult patch test. Protocol No.: CP-01.01S. CHA blend #4 (lot: GK9322) containing 15% Caprylhydroxamic Acid, tested as a 2% dilution. Experiment Reference No.: C17-5522.02. Unpublished data submitted by Inolex on April 9, 2019.
45. SGS. 2020. Repeated insult patch test study - Caprylhydroxamic Acid tested at 3.8%. Test Report No. 4529277-CPCH03R1. Unpublished data submitted by the Personal Care Products Council on February 11, 2020.
46. MB Research Laboratories. 2011. Bovine Corneal Opacity and Permeability Test (BCOP) with a 20% solution of Caprylhydroxamic Acid. MB Research Project #: MB 10-19564.09. Unpublished data submitted by Inolex on April 9, 2019.
47. MB Research Laboratories. 2010. MatTek EpiOcular™ MTT Viability Assay with CHA (Caprylhydroxamic Acid), lot/batch# HJ4059. MB Research Project #: MB 10-18732.19. Unpublished data submitted by Inolex on April 9, 2019.
48. Ackermann L, Virtanen H, Korhonen L, et al. An epidemic of allergic contact dermatitis caused by a new allergen, caprylhydroxamic acid, in moisturizers. *Contact Dermatitis*. 2017;77(3):159-162.
49. Virtanen H, Ackermann L. Posters: P-058. Contact allergy from caprylhydroxamic acid - follow-up. *Contact Dermatitis*. 2018;79:80.
50. Kluger N. Contact allergy to moisturizers in Finland: The tale of the lurking tube in the medicine cupboard. *Contact Dermatitis*. 2018;78(4):289-290.

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



Memorandum

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

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

DATE: July 10, 2020

SUBJECT: Tentative Report: Safety Assessment of Caprylhydroxamic Acid as Used in Cosmetics
(Release Date: June 18, 2020)

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

Abstract - In the Abstract, it would be helpful to indicate that a QRA for sensitization has been completed and to mention the NESIL.

Summary - If only one rat LD₅₀ is mentioned in the Summary, it should be the greater value >10,700 mg/kg rather than >8820 mg/kg (if these were actual LD₅₀ values, e.g., = 8820 mg/kg, the lower value would be most appropriate).

Discussion - Please revise: "reported to be the most inhibitors of metalloproteinase enzymes" (either delete most or add "active").

Please add the NESIL to the Discussion.

Table 3 - Throughout this table (in the Concentration/Dose column) units of $\mu\text{g}/\text{cm}^2$ should be called "dose" rather than "concentration". This correction also needs to be completed in the footnote to this table. The footnote also states: "bye were calculated separately", which needs to be corrected.



Memorandum

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

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

DATE: August 5, 2020

SUBJECT: Caprylhydroxamic Acid

Inolex, Inc. 2020. Comments on the CIR tentative report: Safety Assessment of
Caprylhydroxamic Acid as Used in Cosmetics

Comments on Safety Assessment of Caprylhydroxamic Acid as Used in Cosmetics

CIR Tentative Report for Public Comment released on June 18, 2020



Tentative Report
062020 Caprylhydro:

(Page numbers refer to PDF page number)

General comments

Edits are recommended to ensure clear and unambiguous communication of the points made by the CIR and the Expert Panel for Cosmetic Ingredient Safety. Emphasis should be placed on precise language and context to ensure complete understanding by various stakeholder audiences, especially for audiences whose primary language is not English and/or where translation may be required. For clarity, language that is speculative and/or contradictory to the conclusion of “safe as used” should be avoided.

ABSTRACT – page 2

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. Positive sensitization results appeared to be related to use of a penetration enhancer in formulation; additionally, sensitization that occurred with the use of a moisturizer containing Caprylhydroxamic Acid appeared to occur with use on damaged skin. Therefore, the Panel cautioned against the use of Caprylhydroxamic Acid in a manner that would result in increased penetration, such as formulations with penetration enhancers. 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 potential impurities. The Panel considered all the available data, and concluded that Caprylhydroxamic Acid is safe in cosmetics in the present practices of use and concentration described in this safety assessment.

The abstract should focus on describing/summarizing the safety data and findings that comprise the majority of the report and substantiate the conclusion, i.e. that CHA is considered, “safe in cosmetics in the present practices of use and concentration described in this safety assessment.”

As written, the abstract does not provide an accurate account of the weight of evidence used to draw a conclusion on skin sensitization. The abstract emphasizes certain confounded incidences of sensitization associated with CHA (e.g. on compromised skin, in the presence of other ingredients, and/or in shared HRIPT panels), yet fails to mention the pivotal results supporting the safe use of CHA, i.e. that results of unconfounded HRIPT testing of CHA for skin sensitization revealed a NESIL value of 1056 $\mu\text{g}/\text{cm}^2$ and that a subsequent quantitative risk assessment revealed no significant risk of skin sensitization for all reported applications and use levels, as evidenced by margins of safety (MOS) ≥ 1 .

The effects of a penetration enhancer are speculative and do not warrant mention in the abstract; such precautions, which are applicable to all ingredients in the context of QRA for skin sensitization, are more appropriately included in the Discussion section.

The comments relating to nitrosamide formation are also speculative and do not warrant inclusion in the abstract. Such speculative comments (“theoretically possible”) do not serve the purpose of substantiating the safety of CHA. See below for a more detailed discussion of this point.

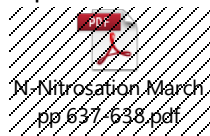
Method of Manufacture – page 3

In Figure 2, the synthesis route diagram incorrectly states “ammonium hydroxide” in step 1 above the reaction arrow. The correct reagent is “hydroxylamine”.

Nitrosation

Inclusion of this section is not recommended due to the extremely speculative nature of the formation of long-lived N-nitroso compounds upon nitrosation of alkylhydroxamic acid, such as CHA. Contrary to what is suggested in the report, the structural features of alkylhydroxamic acids are not amenable to the formation of stable N-nitroso derivatives. To suggest that there is a risk of product contamination with N-nitroso compounds due to CHA is misleading based on a lack of evidence to suggest that formation of such compounds can even occur. Furthermore, such discussion of N-nitrosoamine/N-nitroamide contamination in the report may create undue and unfounded concerns about a risk that is not present for CHA, especially if taken out of context.

Per March’s *Advanced Organic Chemistry*, N-nitrosation is a reaction that occurs when secondary amines (dialkyl-, diaryl-, or alkylarylamines) are treated with nitrosating reagents, i.e. nitrous acid. March also reports that the reaction may occur for mono N-alkyl substituted amides (RCONHR’) and tertiary amines.



It is important to note 1) that alkylhydroxamic acids, such as CHA, are not amines nor amides, and 2) that the nitrogen of the hydroxamic acid moiety does not bear the requisite N-alkyl or N-aryl substitution that would enable formation of a stable N-nitroso species, i.e. R₂N-NO.

The single reference cited in the report (Reference 11, Shirota, et al.) describes the formation of N-nitroso derivatives of alkylhydroxamic acids as transient species that undergo rapid decomposition to yield nitrogen oxides. Scheme 3 shows that the N-nitroso intermediate decays in the presence of water to yield two equivalents of nitroxyl (HNO) and one equivalent of the alcanoic acid, with the nitroxyl rapidly converting to the nitrous oxide (N₂O) that was measured in the study. Shirota et al. do not report the identification or isolation of N-nitroso derivatives in the study.



DERMAL IRRITATION AND SENSITIZATION – page 6

Paragraph 5: The confounded nature of the shared HRIPT panel should be elaborated. Refer to QRA document, which states, “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, specifically in the one individual with positive results to multiple products.”

CLINICAL STUDIES – Provocative Testing – page 7

Paragraph 1 – the functions of the individual compounds in the preservative should be specified: phenoxyethanol (preservative), caprylhydroxamic acid (chelating agent), methylpropanediol (solvent).

Due to the regulatory interpretation of the word “preservative” in certain jurisdictions, it must be clear that the function of CHA is as a chelating agent in the preservative mixture.

Page 8 – Paragraph 1 (continued from previous page) – It should be noted that Ackermann et al. failed to consider other possible root causes of sensitization or cross-sensitization in their study of the APOBASE products associated with allergic contact dermatitis in patients with compromised skin. Most notably, Ackermann et al. failed to acknowledge the possibility of (cross)sensitization due to the potential for degraded ethoxylated emulsifiers in particular lots of APOBASE product (for example, if improperly stored or expired lots of such emulsifiers were used in the manufacture of the lots of APOBASE associated with allergic contact dermatitis). The APOBASE products were formulated with Cetareth-20 and Cetareth-12; these types of ethoxylated fatty alcohols are known to generate irritating and sensitizing degradation byproducts when not properly stored to prevent oxidation (see references of Bergh, et al.)



ethoxylate
allergenicity Bergh 19



skin irritation
oxidized ethoxylates B

Case Reports – Page 8

It should be noted that the reported cases (Reference 50, Kluger) were related to the same moisturizer products (APOBASE) reported in the initial Ackermann study and not different products. This is clearly stated in the Kluger letter.

DISCUSSION – page 10

Paragraph 2 – For audiences who are unfamiliar with QRA and its applications, it would be helpful to include language that explains that MOS increases as ingredient exposure decreases, and that by decreasing the use level of an ingredient in a formulation, the MOS will consequently increase. Therefore, in applications where the MOS is approaching a value of 1 based on the reported use levels used in the present QRA, the MOS may be increased by using a lower level of CHA than the maximum reported use level used in the QRA.

Paragraph 2 – The report states that Panel determined that studies that had positive sensitization results were those in which the test substance included a penetration enhancer. The report should be clear as to which specific studies which are assumed to be clinical case reports and not the HRIPT test conducted with multiple products.

Paragraph 3 – recommend removing, as this could lead to unreasonable requests for N-nitroso analysis to be conducted, a contaminant that is only “theoretically possible” and extremely unlikely to exist at all as a stable species in products containing CHA.