Safety Assessment of Capryloyl Salicylic Acid as Used in Cosmetics

Status: Draft Final Amended Report for Panel Review
Release Date: November 15, 2019
Panel Date: December 9-10, 2019

The 2019 Cosmetic Ingredient Review Expert Panel 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 CIR Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: November 15, 2019
Subject: Draft Final Amended Report on Capryloyl Salicylic Acid

Enclosed is a Draft Final Amended Report on Capryloyl Salicylic Acid (*capryl122019rep*). A Tentative Amended Report with the following conclusion on this ingredient was issued at the September 16-17, 2019 Panel meeting: the Panel concluded that the data were insufficient to support a determination of safety for Capryloyl Salicylic Acid under intended conditions of use in cosmetic formulations. The data needs to assess the safety of this ingredient are listed below.

- Impurities
- Phototoxicity

To date, there has been no response to the above data requests. Comments on the Tentative Amended Report (*capryl092019pcpc*) were received and have been addressed.

Also included in this package for your review are the flow chart (*capryl122019flow*), literature search strategy (*capryl122019strat*), ingredient data profile (*capryl122019prof*), CIR report history (*capryl122019hist*), 2019 FDA VCRP data (*capryl122019fda*), and minutes from the June 2019 and September 2019 Panel meetings (*capryl122019min*).

After reviewing these documents, and ensuring that the Abstract, Discussion, and Conclusion are in-line with their thinking, the Panel should issue a Final Amended Report at this meeting.

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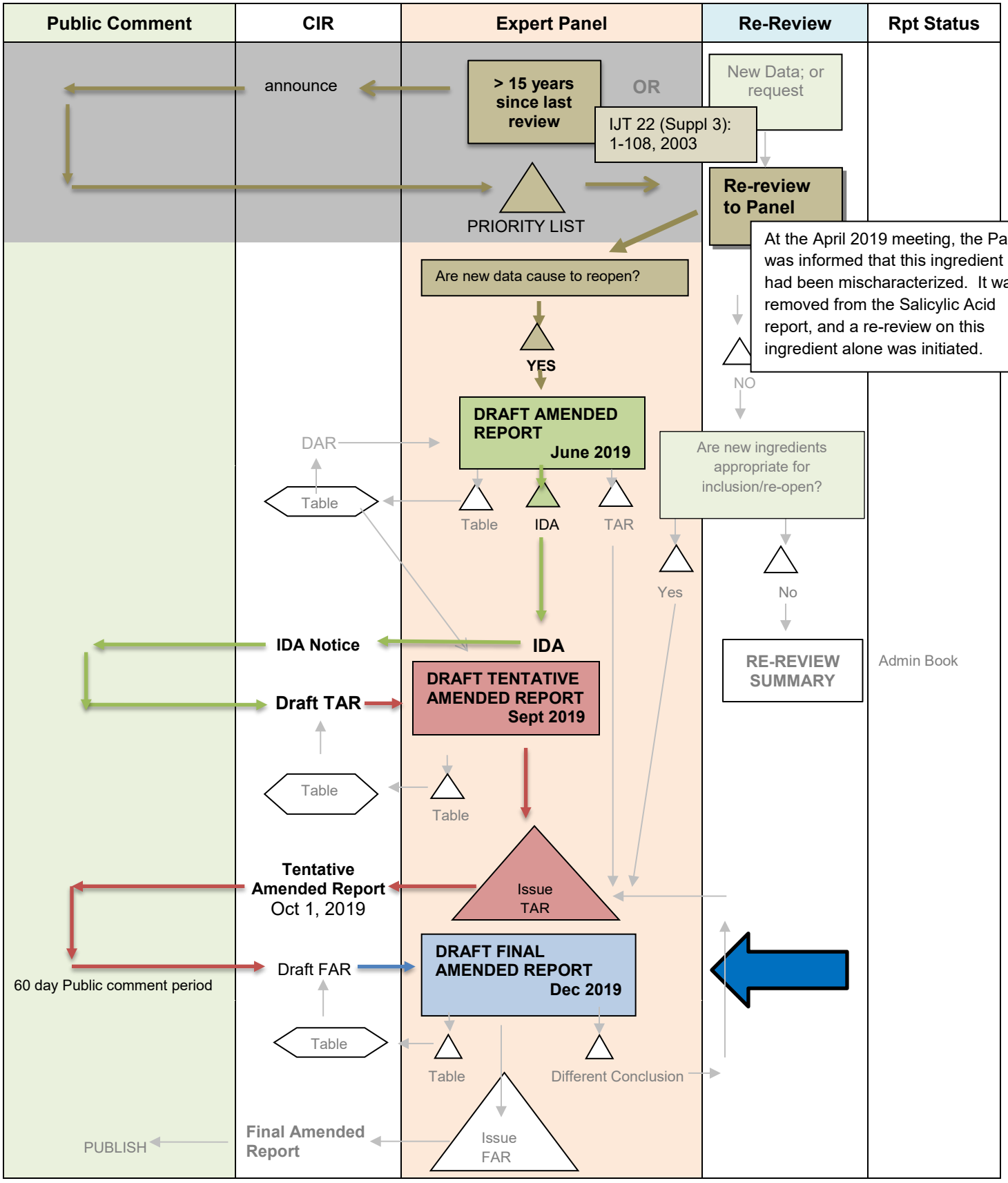
RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Capryloyl Salicylic Acid

MEETING December 2019



*If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

CIR History of:

Capryloyl Salicylic Acid

Draft Amended Report, Teams/Panel: June 20-21, 2019

Capryloyl Salicylic was removed from the Salicylic Acid and Salicylates ingredient group (i.e., because it is a ketone, and not an ester) prior to the Panel's review of the Draft Final Amended Report at the April 2019 Panel meeting. A Final Amended Report on this group (minus Capryloyl Salicylic Acid) was issued at that meeting. A Draft Amended Report on Capryloyl Salicylic Acid that contains data on this ketone (identified by CAS No. 78418-01-6 and corresponding chemical names for this ketone) has been prepared for the Panel's review at this Panel meeting.

The Panel discussed the issue of skin sensitization potential for this ingredient. Capryloyl Salicylic Acid induced skin sensitization in guinea pig maximization tests at challenge concentrations of 0.5%, 2%, and 5%, but not at 1%. However, in HRIPTs, cosmetic products containing 0.5% or 2% Capryloyl Salicylic Acid were classified as non-sensitizing. After reviewing the HRIPT results and considering that the highest reported maximum use concentration of Capryloyl Salicylic Acid is 0.5% in leave-on cosmetic products, the Panel was reassured that the sensitization potential of exposure to this ingredient via cosmetic use is not a risk.

After reviewing the available data, the Panel issued an Insufficient Data Announcement (IDA) with the following data requests:

- Impurities
- Phototoxicity

Draft Tentative Amended Report, Teams/Panel: September 16-17, 2019

Report comments that were received from the Council prior to the June Panel meeting have been addressed. To date, there has been no response to the IDA that was issued at the June Panel meeting.

A tentative amended report with the following conclusion on this ingredient was issued: The Panel concluded that the data were insufficient to support a determination of safety for Capryloyl Salicylic Acid under intended conditions of use in cosmetic formulations. The data needs on this ingredient are listed below.

- Impurities
- Phototoxicity

Draft Amended Final Report, Teams/Panel: December 9-10, 2019

To date, there has been no response to the above data requests. Comments on the tentative amended report were received and have been addressed.

Capryloyl Salicylic Acid Data Profile* –December 9-10, 2019 Panel – Wilbur Johnson, Jr.

				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	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Capryloyl Salicylic Acid	**X**	**X**	X	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

[Capryloyl Salicylic Acid – 7/31/2019;10/25/2019]

Ingredient Names (for same ingredient)	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS*	NICNAS	NTIS	NTP	WHO	FAO	ECET -OC	Web
Capryloyl Salicylic Acid	78418-01-6	Yes	76/0	6/5	1/1	No	No	No	No	No	Not Searchable	Yes	No	No	No	No	No	
5-Octanoylsalicylic acid	78418-01-6		32/0	0	1/0	No	No	No	No	No	Ditto	No	No	No	No	No	No	
2-Hydroxy-5-octanoyl benzoic acid	78418-01-6		7/0	4/4	1/1	No	No	No	No	No	Ditto	Yes	No	No	No	No	No	
2-Hydroxy-5-octanoylbenzoic acid	78418-01-6		21/0	12/9	10/10	No	No	No	No	No	Ditto	No	No	No	No	No	No	
78418-01-6 (alone)	0		202/1	0	0/0	No	No	Yes	REACH dossier	No	Ditto	No	No	No	No	No	No	

*Database not searchable due to effects of Government Shutdown

Search Strategy

[*document search strategy used for SciFinder, PubMed, and Toxnet*]

[*identify total # of hits /# hits that were useful or examined for usefulness*]

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - http://www.personalcarecouncil.org/science-safety/line-infobase
ScfFinder (usually a combined search for all ingredients in report; list # of this/# useful) - https://scifinder.cas.org/scifinder
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - http://www.ncbi.nlm.nih.gov/pubmed
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – https://toxnet.nlm.nih.gov/ (includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases – http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (CFR); then,
list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,
http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true (EAFUS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm (SCOGS database);
http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives (indirect food additives list);
http://www.fda.gov/Drugs/InformationOnDrugs/default.htm (drug approvals and database);
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf (OTC ingredient list);
http://www.accessdata.fda.gov/scripts/cder/iig/ (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/growth/tools-databases/cosing/
ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/ (FAO);
FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
Web – perform general search; may find technical data sheets, published reports, etc
ECETOC (European Center for Ecotoxicology and Toxicology Database) - http://www.ecetoc.org/

Botanical Websites, if applicable
Dr. Duke's https://phytochem.nal.usda.gov/phytochem/search
Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
Sigma Aldrich plant profiler http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html

Fragrance Websites, if applicable
IFRA (International Fragrance Association) – http://www.ifraorg.org/

RIFM (the Research Institute for Fragrance Materials) should be contacted

Qualifiers
Absorption
Acute
Allergy
Allergic
Allergenic
Cancer
Carcinogen
Chronic
Development
Developmental
Excretion
Genotoxic
Irritation
Metabolism
Mutagen
Mutagenic
Penetration
Percutaneous
Pharmacokinetic
Repeated dose
Reproduction
Reproductive
Sensitization
Skin
Subchronic
Teratogen
Teratogenic
Toxic
Toxicity
Toxicokinetic
Toxicology
Tumor

JUNE 2019 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – June 6, 2019

DR. LIEBLER: Just a second there, Don. I'm sorry. Are we doing Capryloyl Salicylic Acid?

DR. BELSITO: Oh, I skipped that. Oh, sorry.

DR. LIEBLER: Yes.

DR. BELSITO: Okay. So this is also the first time we're looking at this, sort of. It was split out from the salicylic acid report because it's a ketone and not an ester. So, all of that data has been brought over into this document. Just again, looking at the document itself, under impurities, I didn't like the phrase "highly plausible contaminant." Dan, what do you think about that? Paul?

DR. LIEBLER: I think it's either measured or detected, or it's not. So, it should be mentioned if it's been measured or detected and not mentioned otherwise. Because otherwise, the reader has no way to interpret that. Is it there or not?

DR. BELSITO: So, delete it if it's not been measured or detected?

DR. LIEBLER: Right. And then that leaves us with nothing on impurities; no characterization of degree of purity. I think we should be able to do better than that, even if it's just our usual, this ingredient has been reported to be 98 percent pure, 99 percent pure or whatever. But can we get some accompanying data sheet that might provide a little bit more info?

DR. BELSITO: So, one of our data needs for this is impurities?

DR. KLAASSEN: Yes.

DR. BELSITO: Then, on PDF page 10, the paragraph above Toxicokinetic Studies, it says, however, the baring -- I presume that's bearing, B-E, not B-A -- of these raw material particle sizes on the particle sizes of the final consumer product formulations is not clear.

I didn't really follow that. So the particle size as a raw material, and then you're saying that doesn't tell us what it is in the final consumer preparation. Do we think this will agglomerate for any reason?

MS. EISENMANN: Well, it's mixed with other things. So I'm not sure. Since it's mixed with other things in the product, I don't think that usually the -- see, I wouldn't put the particle size of the ingredient under cosmetic use.

DR. BELSITO: Right.

MS. EISENMANN: I would put it under chemistry or physical description and move it. And then you don't necessarily have to have that additional statement.

DR. BELSITO: Right. Okay.

DR. LIEBLER: Depending on the nature of the formulation, I think that this ingredient would be dissolved and fully dispersed. It's not really a particle like we would think of silica and things like that. So, I think that description is probably a misrepresentation of the form of this. Unless it was in a purely aqueous type solution, it would probably be dissolved and fully dispersed.

And as a skin conditioning agent, if it was purely aqueous, this might not be very soluble anyway. Well, it would be somewhat soluble I guess, with a carboxylate. But I don't see this forming some particle that would need to be accounted for in the way we usually worry about particles, particle sizes.

MR. JOHNSON: So, just move the first sentence in that paragraph to the chemistry section and delete the second sentence?

DR. BELSITO: Yes.

MR. JOHNSON: Okay.

DR. LIEBLER: Yep.

DR. KLAASSEN: Do you even want the first sentence kept?

DR. BELSITO: In the chemistry section.

DR. KLAASSEN: Yeah, but even that. I guess it would be my suggestion to just remove this 100 percent, but I don't feel strongly.

DR. LIEBLER: Yeah. I would have no problem with that actually, Curt.

DR. BELSITO: So, you want to delete that completely?

DR. KLAASSEN: Yeah. I don't think it helps anybody.

DR. LIEBLER: Yep.

DR. KLAASSEN: Causes more confusion than help.

DR. BELSITO: But then, do we -- I mean, we do have some information on particle size. Again, we could be criticized for not including it.

DR. LIEBLER: Well, I could honestly go either way. You could take just that particle size sentence and put it in under Chemical and Physical Properties, right before the last sentence in Chemical and Physical Properties.

DR. BELSITO: I'd be happier with that.

DR. KLAASSEN: Fine.

MS. EISENMANN: Wilbur, you also have that sentence in the paragraph above the last paragraph in the cosmetic use section, so it has to be moved from there too.

MR. JOHNSON: Where is that again?

MS. EISENMANN: In the cosmetic use section.

MR. JOHNSON: Yes, that's what I was --

MS. EISENMANN: Because it's in there twice.

MR. JOHNSON: Okay. Where's the other location at?

MS. EISENMANN: It's in the fourth and fifth paragraphs.

MR. JOHNSON: Okay. Thank you.

MS. BURNETT: It's the one about five rows up.

MR. JOHNSON: I see. Thank you.

DR. LIEBLER: Just repeated by accident, so I'd just delete it entirely from that paragraph.

DR. BELSITO: Okay. On PDF page 11, right at the top, it says, based on this method, 17.1 percent of the applied test material was found in the stratum corneum, versus 9.7 percent of salicylic acid applied.

I don't understand what you're trying to say there. Was the Capryloyl Salicylic Acid and salicylic acid both applied? I don't --

DR. KLAASSEN: I assume there was two different experiments. In one, they used this ketone compound, and the other was just plain salicylic acid.

DR. BELSITO: But it doesn't say that. It says the skin penetration of Capryloyl Salicylic Acid was assessed in the standard stripped skin method. And then it says --

DR. LIEBLER: I think you're just going to need to reconsult that reference and see if you've missed something there.

MS. FIUME: Um-hm. Because it does say the sal acid was in the same vehicle, but the details just need to be brought over.

DR. BELSITO: Right. Okay. And then in vitro, it was clastogenic with but not without metabolic activation. I always have problems with these studies. So that when you see in effect with but not without, you don't worry about it? Is that true?

DR. KLAASSEN: No.

DR. BELSITO: No?

DR. KLAASSEN: No. You're, I think, equally concerned. But I think --

DR. BELSITO: This is page 14.

DR. KLAASSEN: Yeah. I was just looking for it.

DR. LIEBLER: It was clastogenic in the Chinese hamster ovary cell in vitro with metabolic activation. But it was clean in two follow-up in vivo clastogenesis tests.

DR. BELSITO: Okay. So you're fine?

DR. LIEBLER: I am.

DR. KLAASSEN: Yes.

DR. BELSITO: Okay. Does that go in the discussion? Or we just ignore it since the in vivos were clean?

DR. LIEBLER: You can mention it in the discussion. Since there's no carcinogenicity data, we should be clear on our reasoning for why we're not asking for it. And I think we're -- it's got no structure alerts and it's fine on the in vivo clastogenicity. It was also a negative Ames, with and without metabolic activation.

MR. JOHNSON: So you're not concerned about genotoxicity or clastogenicity based upon the two negative in vivo clastogenicity assays and the negative Ames test with and without metabolic activation?

DR. LIEBLER: Correct.

MR. JOHNSON: Okay. Thank you.

DR. BELSITO: And then, the sensitization and irritation, we have two HRIPTs with 106 in one and 105 and the other at .5 percent, and they were clean. However, the guinea pig maximization study would indicate that it does have the hazard of a sensitizer.

So, while I think we probably have the information we need, we should try and calculate a NESIL from that and make sure that the use concentrations are either acceptable so we can say safe as used, or whether we need to say formulated to be non-sensitizing.

Then, on page 16 under Case Reports -- you have those two case reports of individuals with reactions to Capryloyl Salicylic Acid. Then, in the third paragraph, you say, "In a letter to the editor on the preceding two case reports, the author" -- I think the author is not the author of the case reports, so it should clarify that.

I wouldn't say the author. I would say something like, in a letter to the editor on the preceding reports, it was suggested that Capryloyl Salicylic Acid is unlikely to be significantly allergenic and cause contact allergy. The structural isomer -- so, you can include that, but I just would get rid of "the author," because it sort of makes you think that it was the author of the case reports who then came back and said, oh, well, I was wrong.

DR. LIEBLER: Wilbur, you could just begin that sentence, "A letter to the editor."

MS. FIUME: Stated.

DR. LIEBLER: Stated.

DR. BELSITO: In their letter. Yeah. Okay. So, basically, we need just impurities.

DR. LIEBLER: Yeah.

DR. BELSITO: Otherwise, safe as used when formulated to be non-sensitizing, using methods such as a QRA, and non-irritating.

DR. LIEBLER: Right.

DR. BELSITO: Or if the QRA clears all current use levels, then just safe as used.

MR. JOHNSON: Dr. Belsito, there's no concern about irritation potential?

DR. BELSITO: Yeah. Irritation.

MR. JOHNSON: Irritation and sensitization?

DR. BELSITO: Yeah. But what I'm saying is that we could say safe as used when formulated to be non-irritating, if the QRA clears all the current use concentrations. And we don't need to mention sensitization.

I mean, we have two HRIPTs which are clean, but the guinea pig maximization test would suggest that this does have a sensitization hazard. We just don't know whether the current use concentrations mitigate that hazard. Okay? So, essentially impurities and run a QRA.

Marks Team – June 6, 2019

DR. MARKS: Next is Capryloyl Salicylic Acid. This is what you were talking about. You were just one group of ingredients ahead.

DR. BERGFELD: I know. I saw that. Sorry about that.

DR. MARKS: You were anxious to get down through this list. So this is a draft amended report on Capryloyl Salicylic Acid. Is that how you say the first word there?

MR. JOHNSON: Capryloyl, I think. Some say capryl --

DR. MARKS: Thank you, Wilbur. Well, I'm going to be seconding it, so I won't have to pronounce it tomorrow morning.

Any rate, we have the one ingredient which was separated from the previous reports of the esters. That was the ketone you were talking about, so it is one less.

And why do I have tentative amended report? I have safe when formulated to be non-irritating and non-sensitizing based on a QRA. There was irritation in animals and in the HRIPT, as well as the ocular irritation. So there's no question these are irritants.

Then there was sensitization in animals in the guinea pig max. The HRIPT was non-sensitizing. But again, based now on the guinea pig max being an alert, even though the HRIPT was non-sensitizing, I think we've evolved into -- if there's any alert for sensitization, we should add in the conclusion non-sensitizing based on QRA.

DR. SLAGA: Right.

DR. MARKS: And Ron, probably in the future, we'll also add another -- that it's formulated to be non-toxic. But we haven't gotten there yet.

DR. BERGFELD: We are peeling it down to that, though, aren't we?

DR. MARKS: I know. But any rate, does that --

DR. BERGFELD: Do you think it's important to do this?

DR. MARKS: That's how I formulate it. Does that sound good to you guys?

DR. SLAGA: Yes.

DR. MARKS: Non-irritating and non-sensitizing.

DR. SHANK: The sensitization data were negative.

DR. MARKS: The HRIPT is, but the guinea pig is positive.

DR. SLAGA: There's both positive and negative on irritation, as well as sensitization.

DR. BERGFELD: Do you think in your presentation you have to say this is the third amended to this?

DR. MARKS: Oh, yeah. I don't know that we need to say it's the third amended. I don't know that we have to -- this one is based on removing -- so we have 18 ingredients -- 18 esters, minus the ketone in the past. So I can go -- what page is that, with the sensitization? But I'm sure -- what I was doing, Ron, is based on how we've been going over the last year or so, whenever we have a sensitization alert.

And Don was very specific about HRIPT is not totally predictable. It helps us. But I think Don is very -- I'll put this in quotes, "sensitized" from MCI/MI. No pun intended. So he wants to be overly cautious, and that's why he's added the QRA in these. We'll see what the other team -- I'll be seconding it. But that's the direction I would take.

I hear you. In the past, if the HRIPT was non-sensitizing, we would say, okay, it's fine. We don't have to worry about sensitization.

DR. BERGFELD: Has anybody written a paper on that?

DR. MARKS: About the QRA?

DR. BERGFELD: No, about the HRIPT and the fact it's not totally predictive.

DR. MARKS: Not that I'm aware of. That's an interesting proposal.

DR. SHANK: So if we had that plus the lymph node assay, the two together, would you be happy?

DR. MARKS: If it were negative in both?

DR. SHANK: Yes.

DR. MARKS: I guess, then, you'd say are the guinea pigs lying. You know, how do we deal with these mixed results?

DR. SHANK: Okay.

DR. MARKS: For me, if you're being ultraconservative, you take Don's tactic, which I agree with. You say formulated to be non-sensitizing. Then it really does make the formulator, I would think, think more about, "Okay. Could I sensitize people in this use?"

DR. SHANK: Okay. Put you give him an out by putting in the QRA caveat?

DR. MARKS: Right.

DR. SHANK: Okay. Dr. Hill had some other issues.

DR. MARKS: Okay.

DR. ANSELL: Before we leave the QRA, we want to make sure that the language is not obligatory. It's permissive when formulated to be non-sensitizing. And you can use QRA.

DR. MARKS: Yeah. I think the way Don has it, based on QRA or other methodologies.

DR. ANSELL: Right. Right.

DR. BERGFELD: Do you think you would put that in the discussion, or you'd put it in the line conclusion?

DR. ANSELL: Well, Jim's suggested wording was non-sensitizing based on QRA. And we just want to make sure that QRA --

DR. MARKS: Well taken.

DR. SHANK: Non-sensitizing, which can be determined by a QRA. It doesn't say "based on." It says it "can be determined."

DR. BERGFELD: I'm just wondering if that's appropriate for a conclusion -- non-sensitizing. But if you take care of it in your discussion, that you can use the QRA, it seems to me that would be more appropriate.

DR. SHANK: Okay.

DR. BERGFELD: Just my opinion.

DR. SHANK: We have used it in the past.

DR. BERGFELD: We're just recently moving it to the conclusion. It's just a couple times now. We've done it two or three times today.

DR. MARKS: Oh, yeah.

DR. BERGFELD: It seemed to me non-sensitizing would do for the conclusion.

DR. ANSELL: No, I think that's very reasonable. In fact, what staff may want to do is -- they're not called boilerplates anymore. They're called guidances or --

MS. FIUME: Guidance documents.

DR. ANSELL: To talk about how sensitization can be --

DR. BERGFELD: We ever have a chance at looking at all those?

MS. FIUME: Yes, but the ones that really need updating need a toxicologist right now.

DR. MARKS: Well taken, Wilma. I always like less is more, sometimes. And so if you just put non-irritating and non-sensitizing, then in the discussion, you clarify what you mean. I actually do like the idea of also having a boilerplate for both of those, potentially, but certainly for sensitizing.

DR. SHANK: I'm a little uneasy about putting the burden on the formulator for sensitization. To say non-irritating is pretty good because a lot of things tested date are irritant, but in formulation are not. That's not necessarily true for sensitizers.

So if you tell the formulator, "Just formulate it to be non-sensitizing," we're not doing our job, are we? Even with the QRA out --

DR. MARKS: Well, or other methodology, as Jay correctly pointed out.

DR. SHANK: Okay. But if you say safe conclusion when formulated to be non-sensitizing, period --

DR. BERGFELD: So you're voting to put the QRA into the conclusion, or thereabouts, other methods?

DR. SHANK: Correct. Or we can discuss it tomorrow.

DR. MARKS: I think Don was the first one that, I think, came up with that terminology. I'd be surprised if he changes. But then again -- one of the things it does is it makes it clear in the conclusion how you're going to deal with the issue of non-sensitizing.

MR. JOHNSON: Dr. Marks, the other team recommended calculating a NESIL based upon the positive guinea pig sensitization test data. I just thought I'd throw that in.

DR. MARKS: We'll hear that tomorrow. I think that's fine.

DR. ANSELL: I think we wanted to recognize the QRA was an acceptable method of determining sensitization. But I think what we're finding, particularly with the development of AOPs, adverse outcome pathways, we're starting to look at a molecular level of the cause of sensitization. And I think, at some point, we're going to want to start relying on those methodologies as well.

So now, we're going to say HRIPT or QRA or at least a combination of OECD 1413, 1414(a). I think we wanted to -- and that's why I liked Wilma's discussion. I think within the discussion we can say this is a method we consider to be reliable, but we're going to have more reliable methods as time goes on.

And it's not only going to be cancer. It's not only going to be cancer endpoints, but reproductive endpoints. And I think we're very far advanced in sensitization, understanding it at a molecular level and the ability to predict whether materials would be sensitizers based on omics.

DR. BERGFELD: Based on what?

DR. ANSELL: Genomics.

DR. SLAGA: Omics of any type.

DR. BERGFELD: Okay.

DR. MARKS: So thanks for giving us a little prep for tomorrow, Wilbur. But it's interesting. Do they -- and you can share this or not -- did they want to include that in the discussion and postpone issuing a tentative amended report? Because this is tentative amended, so we're going to have another look at it. They must have had a conclusion.

MR. JOHNSON: Basically, with that information, they would be able to determine whether or not the use concentrations would cause sensitization based upon that calculation. With that in mind, it may not be necessary to say formulated to be non-sensitizing -- based upon those results. So that's sort of where they left it.

DR. BERGFELD: So they would wait for that tabulation?

DR. MARKS: They have to have a conclusion if you're going to move forward to a draft final. Or are they going to, quote/unquote, "table it" until we get the NESIL?

MS. FIUME: It's the first time it's truly being reviewed, so it can go out as an insufficient data announcement, as well. Because, to clear up how it's gone through, when it was originally included in the Salicylic Acid report that was published back in 2003 or whatever it was, it was incorrectly classified. And the structure was incorrect.

So this is the first time this ingredient, as being correctly identified, is being reviewed. But because it had been in the Salicylic Acid report, it has to be an amended report because there is a conclusion out there. And it was pulled out of the Salicylic Acid document that just went through and is being reviewed by itself.

So because it needs a new conclusion, because the existing conclusion wasn't correct for what we now know this ingredient to be, it can go through the entire process. It can go out as an insufficient data announcement. It's like a new ingredient.

MR. JOHNSON: As a matter of fact, that is one of the items in the other team's insufficient data announcement.

DR. MARKS: Okay.

DR. SHANK: And Dr. Hill's? He had a fair amount of data needs. One is on phototoxicity. He says UV absorbance surely will occur. Therefore, there's a need for phototoxicity data.

His second need is a way to handle the level of 3-Capryloyl impurity in commercial supplies, and whether this is the agent that causes sensitization.

And then, he had another issue, which is not a data need. And that's their references to comedolytic activity.

MR. JOHNSON: What kind of activity?

DR. SHANK: Comedolytic.

DR. BERGFELD: Acne.

DR. SHANK: Comedolytic?

DR. MARKS: But he says lytic, so if anything --

DR. BERGFELD: It clears it out.

DR. MARKS: Yeah. It does and proves it. But that's not surprising.

DR. BERGFELD: All acids.

DR. SHANK: Okay. He thought there needed to be more information on that captured in the report.

MR. JOHNSON: Comedolytic activity?

DR. SHANK: Yes.

MR. JOHNSON: Okay.

DR. MARKS: What was the second one, which he thinks may be the sensitizer? He wants more phototoxic.

DR. SHANK: I'll quote. "We need better handle on the level of 3-Capryloyl impurity in commercial supplies and a better sense of whether the conjecture about that impurity as a cause of sensitization and not the named ingredient has any merit."

I didn't see that. So I don't know what we say in the -- I'm looking in the discussion to see if they mention anything about impurities.

MR. JOHNSON: No, we don't.

DR. SHANK: I don't see it.

DR. BERGFELD: Because we don't have a discussion.

DR. SHANK: So I guess we can discuss that tomorrow.

DR. MARKS: Yes. Okay.

DR. BERGFELD: So are you going to go along with the insufficient?

DR. MARKS: Oh, I think so.

DR. SHANK: Yes.

MR. JOHNSON: Actually, I just want to make sure that I have all the data needs. You said the phototoxicity data?

DR. SHANK: Yes. He said we need phototoxicity data, and we need -- I'll just summarize this. I guess we need a discussion on is 3-Capryloyl, which is an impurity, the real cause of sensitization and not the ingredient in itself.

MR. JOHNSON: Okay.

DR. MARKS: I think that's, perhaps, speculation. And once we have the NESIL, it really doesn't matter.

DR. SHANK: Okay. That's good.

DR. MARKS: That's how I would approach it.

MR. JOHNSON: So just one item, the phototoxicity?

DR. SHANK: Yes, the phototox.

MR. JOHNSON: And that is on -- okay.

DR. MARKS: So, Tom and Ron, you like the idea of an insufficient data announcement tomorrow, rather than moving on to a conclusion with safe when formulated to be non-irritating and non-sensitizing?

DR. SLAGA: We'll see how one more time -- we can give it a try.

DR. MARKS: Yeah. Okay. We'll see what the motion is tomorrow. You're giving us a window into what the motion probably is going to be, Wilbur. Thank you.

MR. JOHNSON: You're welcome.

DR. MARKS: I still may present it as the alternative, and then just let Don react to that and see what he says.

DR. BERGFELD: Well, he'll be proposing the motion, so you were not going to second it? Is that correct?

DR. MARKS: I probably will second it and then, when we do the discussion, just mention it. We'll see. Obviously, I think, to give a little bit more time and thought, the insufficient data announcement is the safer way to go. If the NESIL answers and makes the conclusion crisper, I like that. Okay. Any other comments about these ingredients?

DR. SHANK: No, not here.

Full Panel – June 7, 2019

DR. BELSITO: Okay, so, this came about because we discovered that this was not a salicylic acid ester but was rather a ketone. So it was split out of the salicylic acid group that we had looked at previously. And, there was quite a bit of data here, but not all of it sufficient. So, it is insufficient for impurities, and we need to run a QRA off the HRIPTs because there is sensitizing capacity. There's also an irritating capacity. So, that we can go with by saying formulated to be nonirritating, but we need some sense of the QRA on this based off of the HRIPTs that we have. And we need more information on impurities.

DR. BERGFELD: And that is a conclusion, or that is an insufficient --

DR. BELSITO: Insufficient announcement.

DR. BERGFELD: -- right, a motion.

DR. BELSITO: It's the first time we're looking at it.

DR. BERGFELD: Okay.

DR. MARKS: We second that. And then, Ron Hill brought up the issue of phototoxicity data. Do we need that or not? And if we're unsure, we could just list that as one of the insufficiencies and then address it at the next time we see this ingredient.

DR. BERGFELD: Is that agreeable?

DR. BELSITO: No, I mean, I'm not sure why he's bringing that up.

DR. MARKS: He felt the structure, I'm sure it potentially could be a --

DR. LIEBLER: Yeah. It looks like an alkyl phenome structure. But the thing is it's got the carboxyl and phenyl substituents on it. I think both of those would mitigate against photo activation. I mean, at first glance with one eye close it looks like acetophenone, I understand what he's reacting to. But I don't think it's necessary.

DR. MARKS: Okay. Fine

DR. BELSITO: I mean, we could, rather than ask for phototoxic, if there's any concern, why not ask for a UV spectrum? If it doesn't absorb then there's no issue.

DR. LIEBLER: Oh, it'll absorb, for sure.

DR. BELSITO: Okay.

DR. BERGFELD: So are we adding the phototox request, or not?

DR. BELSITO: Dan?

DR. MARKS: I'd suggest we could add it and then come back to it again. And if you still feel that it's unlikely a phototoxic reaction would occur, based on the chemical structure, then we can just delete that insufficiency the next time.

DR. LIEBLER: Sure, I'm okay with that. I think we could add that, and we'll see what they come back with.

DR. MARKS: Okay.

DR. BERGFELD: Ron Shank?

DR. SHANK: You want me to read Dr. Hill's comment? Not necessary.

DR. MARKS: I don't think so, since that was the main -- he also mentioned about impurities, it possibly being a sensitizer. But that really isn't relevant to the IDA; we're already asking about that as you said through the QRA. So, I think we can add the phototox and we'll address it again at the -- see if we get a --

DR. BELSITO: We're also asking for impurities.

DR. MARKS: Right.

DR. BERGFELD: So, may we read the list of what is needed?

DR. SHANK: May I make a comment?

DR. MARKS: Okay.

DR. SHANK: Why do you need impurities? We have genotoxicity data, it's negative. We have DART data, negative, human sensitization, negative. Why do you need to know what the impurities are? Other than being complete?

DR. BELSITO: I'll let Dan answer that. We have negative data in humans at certain concentrations. However, it is a sensitizer because it was positive in a guinea pig maximization test. So it has the capability to sensitize, so we need to look at what that capability is.

DR. SHANK: Just say, when formulated to be non-sensitizing. Do that all the time. Why do you have to have impurities?

DR. LIEBLER: So we always ask for impurities.

DR. SHANK: Okay, checking the box.

DR. LIEBLER: Yeah, it's more checking the box then anything. And I would be satisfied with something a little bit better than what it is. Currently, it's reported that the structural isomer, blah, blah, blah is a highly plausible contaminant. In other words, I'll bet you a beer that this might be an impurity. And you just tell us is this 99 percent, and if you have other information on impurities, put it in there, a sentence or so, we're good.

DR. SHANK: Thank you.

DR. BELSITO: I just want to hold on here one second.

DR. BERGFELD: So we have a motion -- I'm just going to talk over you a little bit while you look -- motion to go as an IDA, Insufficient Data Announcement.

DR. BELSITO: Right.

DR. BERGFELD: We have, we believe, I think Wilbur's written them down, the needs that have been requested. Would you repeat these?

MR. JOHNSON: Yes, the impurities data, QRA based upon the positive for guinea pig sensitization test data, and phototoxicity data.

DR. BERGFELD: Okay.

DR. MARKS: Yes.

DR. BERGFELD: And we have the proposal motion by Don. Are you --?

DR. MARKS: Oh, I seconded that.

DR. BERGFELD: -- second that?

DR. MARKS: I think I heard Don say a little bit differently the QRA based on the human sensitization, not on the guinea pig.

DR. BELSITO: I'm just looking here; it may not be needed. Two percent non-sensitizing HRIPT and 102, and 106 at .5, and the max leave-on concentration is .5. Is that correct?

DR. SNYDER: .5 in leave-on.

DR. BELSITO: .5 in leave-on. So then, yes. Just safe as used? Because its use is below what the HRIPT and the human HRIPT was.

DR. BERGFELD: So are we retracting the motion?

DR. BELSITO: We're retracting the motion for a QRA.

DR. BERGFELD: Are we retracting anything else in this list?

DR. BELSITO: No impurities and phototox.

DR. BERGFELD: Okay. Ron Shank, you want to make a comment on that? I see you smiling.

DR. SHANK: No more comments from me.

DR. BERGFELD: All right. So there's an agreement about an insufficient data announcement. We have the needs and they've been recounted several times, and one being removed. I call the question of going forward, all those in favor? Thank you. Moving on --

DR. MARKS: In anticipation, once we -- on the next time we review this, issue a tentative amended report, are we going to still put in there, since the guinea pig max was positive, meaning sensitization, that we're going to have a non-sensitizing part of the conclusion?

DR. BELSITO: No, I mean, I think what we need to do in the discussion is say that, you know, the guinea pig maximization test indicated the potential for sensitization; however, two well-conducted HRIPTs, one at .5 and one at two percent and humans were negative. And, therefore, as currently used, max .5 in a leave-on, it's safe as used.

DR. MARKS: And I might also add, Don, in there that our clinical experience supports that conclusion in the discussion. Because, if I recall correctly, in the past you've said the HRIPT is not adequate enough when you have a sensitization alert, depending on where it's used and how it's used. Ala the MCI/MI or MI in wipes was a significant sensitizer. So, I think I'd put in the discussion at least that we're reassured with the HRIPT results and the clinical, which would indicate that it's not a significant sensitizer.

DR. BELSITO: Particularly since one of the HRIPT was at four times what is the reported max leave-on.

DR. MARKS: Yeah, I think that all could be captured in the discussion. Okay?

DR. BERGFELD: Any other comments? All right, moving on to the next ingredient, which is the third ingredient in this group, the citrates.

[MONTH YEAR] MEETING – SECOND REVIEW/DRAFT TENTATIVE AMENDED REPORT

Belsito Team – September 16, 2019

DR. BELSITO: Okay, yeah. Capryloyl salicylic acid. We've got a Wave 2.

DR. SNYDER: In vitro prototypes.

DR. BELSITO: Which was wrong. I mean, it's a probable phototoxin, so it doesn't help us. Because it's not less than 2. You have to have a PFI of less than 2. PIF greater than 5, it's phototoxic. PIF less than 2, it's not phototoxic. PIF between 2 and 5, it's a probable phototoxin.

We need other studies. So, this study that we got doesn't clear it. So we asked for impurities which we didn't get, right?

MS. EISENMANN: They told me they're working on it.

DR. BELSITO: Okay. We didn't get impurities, and the phototoxicity data we have doesn't clear phototoxicity in Wave 2. So, it's still insufficient for those two reasons as far as I'm concerned.

MR. JOHNSON: Dr. Belsito, will you say again why the in vitro phototoxicity data are not --

DR. BELSITO: Because the PIFs. Let me go to Wave 2. What page is this on?

DR. SNYDER: It's on PDF 30. Wave 2.

DR. BELSITO: Yeah, I know. But you can't look at the wave and do --

DR. SNYDER: Yeah, the reports.

DR. BELSITO: It's on 30, Dan?

DR. LIEBLER: Oh, the Wave 2?

DR. BELSITO: Yeah.

DR. LIEBLER: Yeah. That's the PIF table and the studies.

DR. BELSITO: Okay. So, if you look at the PIF value for test article one, the PIF value is 4. And for test value two, the PIF value ranges from 1.7 to 2.6, whatever that means -- why they got a range? And as Wilbur correctly states in the prior page, the OECD Guideline for this 3T3 Neutral Red assay is the PIF has to be less than 2 to be negative, greater than 5 to be definite and between 2 and 5 is probable phototoxic.

So, if you look at PIF -- Wilbur's memorandum on page 20, he defines what the phototoxicity is. That's the OECD Guideline. PIF of greater than 2 and less than 5 -- which is what these have -- or an MPE of greater than 0.1 and less than 0.15 predict probable phototoxicity.

The data we have predict probable phototoxicity, so we haven't cleared that endpoint. It's still insufficient for the same reasons.

DR. SNYDER: It's even worse, because if it is phototoxic --

DR. BELSITO: In fact, even more insufficient because this data suggests that it could in vitro. So then where do you go? Because there is -- I'm trying to think. I don't think that it's been ECVAM validated. There is a 3D in vitro phototox model using in vitros EpiDerm, but I don't know -- do you know if it's had any kind of -- I definitely don't think there's an OECD guideline for it. But I'm not sure whether it's been validated by ECVAM or the Japanese society.

The Japanese have been working a lot on reactive oxygen species for phototoxicity too. Let me just do a search. Because if this is the only data you have, it's not going to work. It's going to be classified as a probable phototoxin.

DR. LIEBLER: There's the phototoxin in the report, I can't find it.

DR. SNYDER: In the report?

DR. LIEBLER: Yeah.

DR. BELSITO: It's in Wave 2.

DR. SNYDER: I don't think it's been put into the report.

DR. LIEBLER: Oh, it's not in the report?

DR. BELSITO: No, it's in Wave 2.

DR. SNYDER: No. Wave 2.

DR. LIEBLER: It is out of the blue --

DR. SNYDER: Yeah.

DR. LIEBLER: I see.

DR. SNYDER: It's too new. Did they mis-concluded it? Because it says it was concluded that under the condition employed in this study --

DR. BELSITO: They mis-concluded because they don't know the OECD Guidelines.

DR. SNYDER: They said according to the proposed OECD guideline criteria.

DR. BELSITO: They're misquoting that.

MS. EISENMANN: The study was done in 2000; so maybe it was done under different -- I don't know when the OECD's --

DR. BELSITO: I don't know that the OECD Guidelines have ever changed for that.

DR. LIEBLER: The thing about this report is that it's opaque with respect to phototox, with respect to what was actually tested. It's a formulation that is reported from Carol that contains capryloyl salicylic acid. But if you look through the narratives the only compound that's actually mentioned by name in that is the positive control chlorpromazine. And the tested material product, I guess, is blacked out at every mention.

MS. EISENMANN: Because there probably using a trade name.

DR. LIEBLER: But it raises the possibility that there's something else in this product that is phototoxic in the 3T3 cell assay. I'm not saying we ignore this, but it needs to be explained. We either need more better data, something that clears it, you know, an in vivo phototox. Because this opens a can of worms for us.

DR. SNYDER: What ping us to phototox in the first place?

DR. BELSITO: UV absorption, I think. Right?

DR. SNYDER: Why did we ask for phototox?

DR. BELSITO: The UV absorption, no?

MS. EISENMANN: We did.

DR. SNYDER: But why? I want to know why.

DR. BELSITO: Physical and chemical properties.

MR. JOHNSON: That's a chromophore.

DR. SNYDER: Is it a chromophore?

DR. LIEBLER: Yeah, that's a chromophore that can absorb UV, that's for sure.

DR. SNYDER: Okay.

DR. LIEBLER: You know what, I seem to remember Ron Hill mentioning it. I'll have to go pour through the minutes to see if that's correct. Maybe this came up. The thing is, this study's been around for a while and it just got pulled out. Somebody pulled it out.

DR. BELSITO: Yeah. The in vitro skin models, the 3D skin models, have not yet been validated. So, the only validated model still is the 3T3, at least OECD. But let me see if I can see what ECVAM has for photo testing. Let me search that.

DR. LIEBLER: The thing is, if the test material contained anything in addition to capryloyl salicylic acid and some obviously inert vehicle, then we have an ambiguity that we can't resolve without more data.

DR. SNYDER: It looks like in the minutes Ron Hill says UV absorbent surely will occur. We don't have UV data, but he says it surely will occur.

DR. LIEBLER: Right? It's true?

DR. KLAASSEN: Yeah. Yeah.

DR. SNYDER: Okay.

DR. LIEBLER: But there are a lot of UV-absorbing molecules that we've looked at that do not produce phototoxicity. The majority of them don't. And the point I'm making is it might still be that capryloyl salicylic acid per se does not, but something else in this tested product did. And we're not in the position to know what happened. So, it's insufficient for phototox.

DR. KLAASSEN: Yeah.

DR. BELSITO: And impurities.

DR. LIEBLER: And impurities. Right. Yeah. So, it's insufficient.

DR. BELSITO: So, it's back to where we were.

DR. LIEBLER: Right. But we added a new insufficiency.

DR. SNYDER: Except for if that phototox study is correct, it's phototoxic. So, we don't need phototoxicity data, we have it.

MS. EISENMANN: Well, it's not in the clear phototoxic, it's probable.

DR. BELSITO: Probable. The EpiSkin phototoxicity assay -- this is L'Oreal. This is just methodology, but it doesn't say whether it's been validated. The reason everyone's looking at other models is that 3T3 assay overpredicts phototoxins. So, it's not a great model.

False positives are very high. The false negatives are very low. So, that's obviously what you would want as the first cut if that's all you have. But I don't see that the EpiSkin models have been improved.

DR. LIEBLER: See these values are kind of borderline compared to the positive control.

DR. BELSITO: Yeah. But they used chlorpromazine which is a huge phototoxin.

DR. LIEBLER: Right. Yeah. Well, that's a problem. I don't know if it can be resolved without an in vivo test.

DR. BELSITO: No, I think that in vitro EpiSkin testing is so far along now that someone could do that and convince us.

DR. LIEBLER: Yeah. We could accept it even if it's not OECD.

DR. BELSITO: Yeah.

DR. LIEBLER: But we definitely need more data in light of this.

DR. BELSITO: Okay. Here, I got something from using Google. It's not giving me the latest results. Validated and accepted alternative methods. Phototoxicity is still the only one. Actually, the Japanese have, in 2013, a reactive species assay photosafety test that JaCVAM has at least approved.

So, there's that. But this is an old paper. I think that ECVAM has accepted the 3D skin model for phototoxicity. But whoever's responsible for this chemical search can find out if that, in fact, is true. Because I don't think another 3T3 study is going to -- you know, we need two to break this tie.

So, I think you need to use an alternative method. And I think it could be a 3D skin model. That's been very well studied. Or the Japanese reactive oxygen species. In Wave 2, it doesn't really even say -- did it say the purity of the material? It didn't tell us anything.

DR. SNYDER: No.

DR. LIEBLER: Nope.

MS. EISENMANN: Like I said, they told me they're working on an analytical method. They did have one comment that -- where is it? Based on preliminary studies. So their 3-capryloyl salicylic acid was not detected. There's limited detection of less than 500 ppm.

I think that was a material that someone was speculating was the sensitizer. But they haven't finalized anything, so I didn't give you anything in writing yet. They said they're still working on it.

DR. BELSITO: Well, it's insufficient for impurities and phototoxicity. Whoever sells this has to come up with that data.

DR. SNYDER: Right.

DR. BELSITO: Okay. Palm.

MR. JOHNSON: One question about that, Dr. Belsito. I noticed that a slight skin irritation was observed in the guinea pig maximization test as well as in the human studies. Should skin irritation be addressed in any way in the discussion? It's slight skin irritation that was observed.

DR. BELSITO: No, when formulated to be non-irritating, if we ever get to the point where it's safe based on the other endpoints. But at this time I don't think the irritation needs to enter into the discussion because we have insufficiencies. And I think we've all become convinced that irritation is a matter of formulation. We can't control it based upon defining a limit. Okay.

Marks Team – September 16, 2019

DR. MARKS: Okay. The next is Capryloyl Salicylic Acid. A chemist in the room can correct my pronunciation. Ron or Tom, how would you -- Capryloyl? That's how I'm saying it. Is there a better way to pronounce that? Okay.

We have before us Wilbur in his August 22nd memo presented the draft tentative amended report on Capryloyl Salicylic Acid. As you may recall, this ingredient was removed by the Salicylic Acid and Salicylates ingredient group because it's a ketone and not an acid.

The June meeting this year, the panel requested impurities and phototoxicity. Dan commented on the phototoxicity on page 53. Wave 2 phototox study was okay, and Dan even wondered whether we really needed that. And then Ron and Tom, your comments concerning the impurities. Ron, I know you had comment that we really didn't need the impurities.

DR. SHANK: Correct.

DR. SLAGA: I agree. I think it's safe now.

DR. SHANK: If impurities were present at toxicologically significant concentrations, their presence would have been evident in the toxicology studies. I think we can eliminate the request for impurities. So, safe.

DR. MARKS: Right. Do you want to put safe when formulated to be non-irritating? There was some alert to irritation, so safe when formulated to be non-irritating.

DR. SHANK: Okay.

DR. SLAGA: That's fine.

DR. BERGFELD: Also, your eye study. I'm not sure what page but just above your discussion they quote an eyelid study which was irritant.

DR. MARKS: Right. That's why I felt we should include that into it. Any other comments?

MR. JOHNSON: The issue of sensitization. I know that in the maximization test, you had positive results at the use concentrations. But I recognized that the human data indicated no concern about sensitization. So, with that in mind, are there any concerns about the sensitization that would warrant including that caveat in the conclusion?

DR. MARKS: I think, to me, the question there was the case report of sensitization in the discussion, Page 67, the 3-cap impurity may be an allergen in two case reports. That was the only question I had. But no, I think the sensitization, we didn't pick that out when we reviewed it in June. So, I think that's not an issue.

MR. GERMILLION: Could I ask, for impurities data that's just on a case-by-case basis that you ask for the impurities data?

DR. MARKS: We had that discussion, actually, at the last meeting and decided to include the impurities as a request. But that was based on the other team's requests. Ron had made the point that there were no toxicologic concerns so therefore, we really didn't need the impurities. Our team will go with that again, and then let's see what the Belsito team feels tomorrow.

Okay, tomorrow I will be moving for our team that we have a tentative amended report, safe when formulated to be non-irritating. Any other comments?

Okay. Again, I'll mention that for me to save any changes in the document, it takes about five clicks and at least a few seconds for the computer to save them.

Full Panel – September 17, 2019

DR. MARKS: So at the June meeting in 2019, an insufficient data notice was issued and a data request for impurities and phototoxicity. As you recall capryloyl salicylic acid was removed from the salicylic acid and salicylates because it was a ketone and not an ester in that other grouping of salicylates.

Our team moves that we issue a tentative amended report with a conclusion, safe when formulated to be non-irritating. And, Ron can comment on the impurities. There were comments from Dan on phototoxicity from the previous meeting in which he didn't think this would be a concern, and Wave 2 data phototox study confirmed that.

DR. BERGFELD: Is there a second, or a comment from the Belsito Team?

DR. BELSITO: Phototox did not confirm it. For a negative phototox you have to have a PIF of less than 2, and this did not. And the conclusion of the investigators is not correct; it's not according to OECD guidelines.

If it's five or greater, it's phototoxic. If it's less than two it's not phototoxic. If it ranges between two and five, it is probably phototoxic. So, we felt that it was still insufficient for impurities and phototoxicity.

And, the issue is as far as I'm aware there are no other test that currently has OECD guidelines and approvals for phototoxicity. But JacVAM, the Japanese Society, has a reactive oxygen species test that they've approved, and perhaps this can be looked at.

In that test since the 3T3 is prone -- the good thing about the 3T3 is if it passes, it's almost certainly not phototoxic; but there are a lot of issues where you get false positives. So I think phototoxicity is still out there for this material, and it's insufficient for that potential impurities.

DR. BERGFELD: Dr. Marks?

DR. MARKS: I assume Dan obviously concurs.

DR. LIEBLER: Yeah, I have to concur. I mean, they provided data with that test. It was marginally in excess of the threshold Don mentioned.

DR. BELSITO: In one, in the other it was 4.

DR. LIEBLER: Right, so with the scale of that sort of the dynamic response range for that test with chlorpromazine being the positive control, presumably representing somewhere near the max -- I think it was like about 15, or so -- the PIF parameter that was calculated, whereas the capryloyl salicylic acid was 4. So twice the threshold as opposed to more than a dozen. You know, not being calibrated for the assay, I don't know how significant that is, but a threshold is a threshold, if you're not going to use it the test is worthless.

So, I think unfortunately we need other data to support it because the one piece of data that they provided us does not allows us to clear it. I wouldn't have thought that this would be phototoxic. That was my hunch, but sometimes that's why we do experiments.

DR. MARKS: and then, Ron Shank, do you want to comment on impurities? I know we're back to that.

DR. SHANK: No, I will not comment on impurities.

DR. MARKS: So, I'll withdraw the motion I made and, Don, if you want to state your motion again we'll second that.

DR. BELSITO: Insufficient for impurities and additional data looking at phototoxic potential.

DR. MARKS: So that would be a tentative amended report.

DR. BERGFELD: And you're seconding that?

DR. MARKS: Yes.

DR. BERGFELD: Any further discussion?

DR. SHANK: How about UV absorption, would that help?

DR. BELSITO: Well, if it were negative, yeah, certainly.

DR. LIEBLER: The problem is it's going to absorb. So, I mean, if you just look at the structure you're going to have UV-Vis absorption for this molecule.

And we already have a positive phototox result in a test. Admittedly, it's prone to false positives, but we already have that. We would use a UV negative data to exclude any further consideration of phototox, but the horse is already out of the barn on this one.

DR. BERGFELD: Is Carol going to speak?

MS. EISENMANN: My question is would the photo data on salicylic acid itself be useful to look at? Because isn't that part of the part that is absorbent?

DR. LIEBLER: It's part of it but not enough of it. And the salicylic acid isn't the same molecule, unfortunately.

DR. BELSITO: Which is why we threw this out of the salicylate report.

MS. EISENMANN: Right, but I just thought maybe for that one specific endpoint, especially if there's a 3T3 assay on it to see how it responded in that assay.

DR. LIEBLER: No, the salicylic acid would be like this molecule minus the side chain with the ketone. It's an alkyl phenome, which is that structure could explain phototoxicity. It could be responsible for phototoxicity. So the salicylic acid doesn't capture that feature and wouldn't be relevant even if it had negative data.

DR. BERGFELD: All right. Any other comments? So, we're going to go tentative insufficient, but we'll need a vote on that, we've had it seconded.

All those in favor of this conclusion please indicate by raising your hand. Unanimous. Any other comments? Okay, you're just voting.

The next one is Dr. Belsito, and the ingredient called Palm.

Safety Assessment of Capryloyl Salicylic Acid as Used in Cosmetics

Status: Draft Final Amended Report for Panel Review
Release Date: November 15, 2019
Panel Date: December 9-10, 2019

The 2019 Cosmetic Ingredient Review Expert Panel 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 CIR Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst.

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ABSTRACT: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reassessed the safety of Capryloyl Salicylic Acid in cosmetic products; this ingredient is reported to function as a skin conditioning agent. The Panel reviewed relevant data relating to the safety of this ingredient in cosmetic formulations, and concluded that the available data are insufficient to make a determination that Capryloyl Salicylic Acid is safe under intended conditions of use in cosmetic formulations.

INTRODUCTION

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) published a safety assessment of Salicylic Acid and 16 salicylates in 2003.[1] That safety assessment included Capryloyl Salicylic Acid, which was included in the grouping because of structural similarity. However, it is now known that this ingredient is a ketone, and it does not belong in that family of ingredients; therefore, this separate report was prepared. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), Capryloyl Salicylic Acid is reported to function as a skin conditioning agent.[2]

The published data in this document were identified by conducting an exhaustive search of the world's literature. A list of the typical search engines and websites used, sources explored, and endpoints that CIR evaluates, is available on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties. Much of the data included in this safety assessment was found at the European Chemicals Agency (ECHA) and National Industrial Chemicals Notification and Assessment Scheme (NICNAS) websites.[3,4] Please note that these websites provide summaries of information from other studies, and it is those summary data that are reported in this safety assessment when ECHA or NICNAS is cited.

CHEMISTRY

Definition and General Characterization

Capryloyl Salicylic Acid (CAS No. 78418-01-6) was previously, erroneously, defined as the ester of salicylic acid and caprylic acid. However, it has become apparent that Capryloyl Salicylic Acid is instead the 5-capryl ketone of salicylic acid. As such, this chemical is structurally distinct from the salicylate carboxyl esters. It is now defined as the organic compound that conforms to Figure 1.[2]

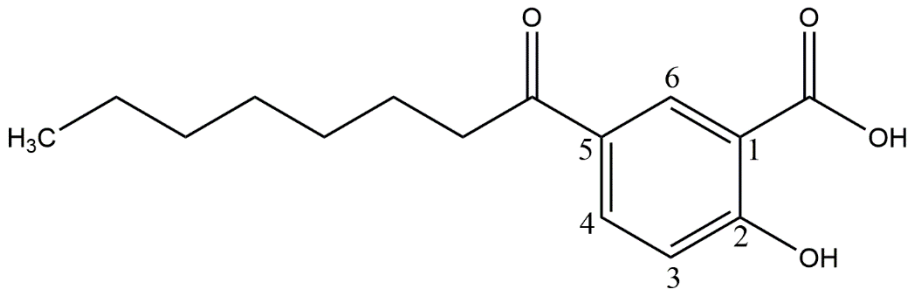

Figure 1. Capryloyl Salicylic Acid

Chemical and Physical Properties

Capryloyl Salicylic Acid has a molecular weight of 264 Da and has an 8-carbon acyl fatty chain linked to the fifth carbon of the benzene ring.[5] This white powder is water soluble (29.7 mg/mL) and acidic (estimated pKa of 2.68). According to information submitted for the ECHA dossier, the particle size distribution of this ingredient as a raw material includes 13.23 – 26.71% of particles < 100 μm;[3] however, the bearing of these raw material particles sizes on the particle sizes of final consumer product formulations is not clear. Further chemical and physical properties of Capryloyl Salicylic Acid are presented in Table 1.[3,6]

Method of Manufacture

The synthetic method of manufacture for Capryloyl Salicylic Acid is based on Friedel-Crafts acylation of methyl salicylate by capryloyl chloride and aluminum trichloride to yield the methyl ester of Capryloyl Salicylic Acid.[7] This ester is hydrolyzed with sodium hydroxide, after which acidification yields Capryloyl Salicylic Acid.

Impurities

It has been reported that the structural isomer, 3-capryloyl salicylic acid, is a highly plausible contaminant of Capryloyl Salicylic Acid.[7]

USE

Cosmetic

The safety of this cosmetic ingredient is evaluated based, in part, on data received from the United States (US) Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics.[8] Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.[9]

According to 2019 VCRP data, Capryloyl Salicylic Acid is reported to be used in 104 cosmetic products (93 leave-on and 11 rinse-off).[8] The results of a concentration of use survey conducted in 2018 indicate that Capryloyl Salicylic Acid is used at concentrations up to 0.5% (in moisturizing products, not spray), which is the highest reported maximum use concentration for leave-on formulations.[9] In rinse-off products, Capryloyl Salicylic Acid is reported to be used at concentrations up to 0.4% (in paste masks and mud packs), which is the highest reported maximum use concentration for rinse-off formulations. Further use frequency and concentration of use data are presented in Table 2.

Cosmetic products containing Capryloyl Salicylic Acid may be applied to the skin at concentrations up to 0.5% (moisturizing products, not spray) and may come in contact with the eyes during use of eye lotions and other eye makeup preparations (use concentrations were not reported by industry). Capryloyl Salicylic Acid also could be incidentally ingested during product use (e.g., use concentrations up to 0.1% in lipsticks). Products containing Capryloyl Salicylic Acid may be applied as frequently as several times per day and may come in contact with the skin for variable periods following application. Daily or occasional use may extend over many years.

Capryloyl Salicylic Acid is reported to be used in deodorant sprays (aerosolized) at concentrations up to 0.3%. 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 below 10 µm, compared with pump sprays.[10-13] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[14,15] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[15] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. Capryloyl Salicylic Acid is being used in face powders at concentrations up to 0.3%. 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.[16-18]

TOXICOKINETIC STUDIES

Dermal Penetration

In Vitro

The penetration of Capryloyl Salicylic Acid through human skin was assessed using a Franz diffusion chamber and skin samples.[5] The amount of Capryloyl Salicylic Acid that penetrated deeper than the stratum corneum after a 16-h contact time was significantly lower than its parent acid, salicylic acid, in the same vehicle. Thus, only approximately 6% of Capryloyl Salicylic Acid was found to penetrate deeper than the stratum corneum, after 16 h, versus 58% for salicylic acid.

Human

The skin penetration of Capryloyl Salicylic Acid was also assessed using a standard stripped skin method.[5] Capryloyl Salicylic Acid was applied to the skin (number of subjects involved not stated), followed by rinsing with water/alcohol 30 min later. Strips of stratum corneum were then harvested, using adhesive tape, and analyzed for test material content. An estimation of the level of penetration through the skin over a 4-day period was determined using the stored concentration method. Based on this method, 17.1% of the applied test material was found in the stratum corneum, versus 9.7% of salicylic acid applied.

Absorption, Distribution, Metabolism, and Excretion

Data on the absorption, distribution, metabolism, and excretion of Capryloyl Salicylic Acid were neither found in the published literature, nor were these data submitted.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

The acute dermal toxicity of Capryloyl Salicylic Acid was studied using Sprague-Dawley rats (5 males, 5 females).[3] The study was performed according to Organization for Economic Co-operation and Development (OECD) Test Guideline (TG) 402. A semi-occlusive patch (7 cm x 4 cm) containing the test substance (in peanut oil) was applied for 24 h to an area defined as 10% of the total body area. This amounted to a single dose exposure of 2000 mg/kg. Dosing was followed by a 14-day observation period, after which the animals were killed. Necropsy was performed, but tissues were not retained. None of the animals died during the observation period, but the following signs of toxicity were observed: hunched posture, lethargy, and piloerection during the first day. With the exception of 1 male rat, body weight gain was not affected by treatment. The following adverse dermal reactions were observed: edema and blanching and hard, light brown colored scabs at the application site. These findings were accompanied by loss of the upper layers of skin and fur, resulting in purple/pink areas. The distribution of toxicity signs/adverse dermal reactions in the dosed group was not reported. The LD_{50} was > 2000 mg/kg.

Oral

The acute oral toxicity of Capryloyl Salicylic Acid (in peanut oil) was evaluated using groups of 10 Sprague-Dawley rats (5 males, 5 females/group).[3] The four dose groups received single oral doses (by gavage) of 2530, 3000, 3557, or 4217 mg/kg. The study was performed according to OECD TG 401. A control group was not included in the study. Dosing was followed by a 14-day observation period. All animals were subjected to gross necropsy. The following major signs of toxicity were observed in all dose groups: hunched posture, piloerection, lethargy, ptosis, decreased or gasping respiration, red/brown staining around the snout or mouth, and ataxia and/or increased salivation. Incidences of reduced body weight gain or body weight loss also occurred in all dose groups. Distended abdomen and/or emaciation were observed in animals of the 3 higher dose groups. Pallor of the extremities, with an isolated incidence of tiptoe gait, was observed in animals of the 3557 mg/kg dose group. Mortalities in all dose groups were reported as follows: 2530 mg/kg (1 female); 3000 mg/kg (4 males and 2 females); 3557 mg/kg (3 males, 3 females), and 4217 mg/kg (4 males, 4 females). The following abnormalities were observed at necropsy of animals that died during the study: hemorrhagic or abnormally red lungs; dark liver or patchy pallor of the liver; pale spleen; pale or dark kidneys; hemorrhage or sloughing of the glandular gastric epithelium; and hemorrhage of the small and/or large intestines. Abnormalities observed at necropsy of animals (2530 g/kg group) that were killed at the end of the study were described as occasional white foci (~1 mm x 1 mm covering 75% of the non-glandular gastric epithelium). At necropsy, there were no abnormalities in animals that received a dose of 3000 mg/kg or higher and were killed at the end of the study. The combined oral LD_{50} (males + females) for the test material was 3354 mg/kg (95% confidence limit between 2834 and 3970 mg/kg).

Results relating to acute oral toxicity are included in a micronucleus test on Capryloyl Salicylic Acid (in 0.5% carboxymethylcellulose aqueous vehicle).[4] The micronucleus test (described later in this report), performed in accordance with OECD TG 474, used groups of 10 (5 males, 5 females per group) Swiss CD-1 mice. A single dose of the test substance (500, 1000, or 2000 mg/kg) was administered by gavage to 3 groups. Two female mice and 1 male mouse dosed with 2000 mg/kg were found dead 24 h after dosing. Piloerection was observed in all animals on the same day of dosing with 1000 mg/kg. Piloerection and swollen abdomen were observed in the 2000 mg/kg dose group.

Results relating to acute oral toxicity are also included in an unscheduled DNA synthesis test on Capryloyl Salicylic Acid (in 0.5% in carboxymethylcellulose aqueous vehicle).[4] The assay was performed in accordance with OECD TG 486 using groups of 4 Sprague-Dawley rats. In 2 tests, single doses of 500, 1000, or 2000 mg/kg were administered by gavage. The animals were killed at 14 h in one test and at 2 h in the other test. No mortalities or clinical signs were observed. (Results relating to genotoxicity are included in that section of this report.)

Short-Term Toxicity Studies

Dermal

A short-term dermal toxicity study (10-day study) on Capryloyl Salicylic Acid (in hexaethylene glycol (PEG-6)) was performed using groups of 5 female rats of the Crl:CD(SD)BR (VAF plus) strain.[3] The test substance was applied for 6 h directly to the back (not less than 10% of body area; constant volume of 2 mL/kg) once daily at concentrations of 2% and 5%. A third group was treated with vehicle only. The test protocol was similar to OECD TG 410. None of the animals died during the study. The animals were killed at the end of the 10-day dosing period and subjected to gross necropsy. Tissues were examined microscopically. There were no treatment-related changes in food consumption or body weight gain. The authors noted that occasional transient weight losses were observed which, because of the small group sizes, skewed the means. Other than the scabbing that was observed at necropsy, there were no other necropsy findings. The no-observed-effect-levels (NOEL) for local and systemic effects of Capryloyl Salicylic Acid were 2% and > 5%, respectively. Additional results from this study are included in the Skin Irritation section of this report.

In a guinea pig maximization test of Capryloyl Salicylic Acid (in 0.5% aqueous methylcellulose) , performed according to OECD TG 406, clinical observations were made.[4] Twenty Dunkin-Hartley guinea pigs (10 males, 10 females) were tested with this ingredient in this study. During topical induction, Capryloyl Salicylic Acid was applied at a concentration of 1%. One animal was found dead on day 18, but microscopic examination revealed no apparent abnormalities. None of the other animals had clinical signs; body weight gains were comparable to the control animals. Results relating to skin sensitization potential are included in that section of this report.

Oral

A short-term oral toxicity study on Capryloyl Salicylic Acid (in PEG-6) was performed using groups of 10 or 20 rats of the CRL:CD(SD)BR strain.[3] The control group and highest dose group (initially, 300 mg/kg/day) each consisted of 20 rats (10 males, 10 females per group). Each of the remaining dose groups (10, 30, and 100 mg/kg/day) consisted of 10 rats (5 males, 5 females per group). The animals were dosed orally (by gavage) daily for 28 days in accordance with OECD TG 407. Two recovery groups (5 males, 5 females per group; for control and highest dose groups) were maintained un-dosed for an additional 14 days after the last day of dosing (day 28). The dose level in the highest dose group was reduced from 300 to 200 mg/kg/day on day 13 due to adverse clinical signs, including death. The animals were subjected to gross necropsy and microscopic examination of tissues at the end of the study. Five rats from the highest dose group died during the study, and the following clinical signs were observed: rough coat, piloerection, post-dose salivation. A slight reduction in body weight gain (13 to 14%) was also noted in males of the highest dose group during treatment and non-treatment periods, and in females of the 100 mg/kg dose group during treatment only. Hematology and blood chemistry evaluations did not reveal any adverse effects. At necropsy, a dose-related increase in the incidence of stomach abnormalities was observed (at the end of both the treatment and the treatment-free period) for animals dosed with 100 mg/kg/day and 300/200 mg/kg/day. Microscopic findings included hyperplasia of the non-glandular stomach in animals of the 300/200 mg/kg/day group. This finding was accompanied by chronic inflammation and ulceration. Hyperplasia was also observed in 1 male in the 100 mg/kg/day dose group. Similar, but less severe, hyperplastic lesions were also observed in recovery animals that were previously dosed with 300/200 mg/kg/day. Hyperplasia of the non-glandular mucosa of the stomach was less severe at the end of the treatment-free period, which indicates that some recovery had taken place. Additionally, reversibility was observed and the effects were limited to the non-glandular stomach, and, thus, were considered to be of doubtful relevance to humans. The NOEL for local effects was 30 mg/kg/day, and the NOEL for systemic effects was > 100 mg/kg/day.

Subchronic Toxicity Studies

Data on the subchronic toxicity of Capryloyl Salicylic Acid were neither found in the published literature, nor were these data submitted.

Chronic Toxicity Studies

Data on the chronic toxicity of Capryloyl Salicylic Acid were neither found in the published literature, nor were these data submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Dermal

The developmental toxicity of Capryloyl Salicylic Acid (in PEG-6) was evaluated using groups of 24 pregnant female Sprague-Dawley rats.[3] The 2 test groups received doses of 40 mg/kg/day and 100 mg/kg/day, respectively, on gestation days 6 to 15. The vehicle control group was dosed with PEG-6. The test substance and vehicle control were each applied for 6 h directly to skin on the back (not less than 10% of the body area). The rats wore Elizabethan collars during the 6-h exposure period, and the application collars were rinsed after 6 h. On gestation day 20, all females were killed and subjected to necropsy. Numbers of corpora lutea and live and dead implantations were recorded. Live fetuses were examined for external and visceral abnormalities. One-half of the fetuses were subsequently examined for skeletal abnormalities. No premature deaths or treatment-related clinical signs were recorded during the study. There was no treatment-related effect on mean maternal food consumption and body weight. However, when compared to the control group, a statistically significant reduction in body weight gain values was reported for the 40 mg/kg/day dose group (gestation days 9 - 12) and for the 100 mg/kg/day dose group (gestation days 6 - 15). There were no treatment-related effects on pregnancy parameters, mean fetal weight, and incidences of major external, visceral, or skeletal abnormalities.

When compared to the background range, a higher (but not statistically significant) increase in the incidence of minor skeletal abnormalities and variants (including incomplete ossification of the sacral neural arch) was observed in the vehicle control group and both dose groups. The historical control range was from 0% to 9%, compared to a value of 18.3% for the incidence of sacral neural arch incomplete ossification in the vehicle control group. Therefore, the authors noted the likelihood that the incidence of the skeletal minor abnormalities observed in both dose groups was also overestimated. Furthermore, they noted that these statistically non-significant skeletal findings in both dose groups were likely related to the transient, but statistically significant, decrease in body weight gain observed in dams (gestation days 9 - 12). This decrease was attributed to the moderate or severe skin lesions that led to pain and stress in the animals. Therefore, it was determined that the increase in the incidence of skeletal variations reported for fetuses from both groups were likely secondary to maternal toxicity (induced by local effects leading to pain and stress) and not indicative of a teratogenic effect. (Results relating to maternal skin irritation potential are included in the Skin Irritation section of this report.) A no-observed-adverse-effect-level (NOAEL) was not reported in this study summary. However, the following conclusion is reported in a summary of this study from a different source, "The NOAEL for developmental toxicity was established as 40 mg/kg/day, based on an increase in the incidence of fetuses with incomplete ossification of the sacral neural arch at 100 mg/kg/day."[4] The NOAEL was not established for maternal toxicity, as treatment-related effects (local reaction at the site of administration and reductions in body weight gain) were observed at both doses tested.

Oral

The reproductive and developmental toxicity of Capryloyl Salicylic Acid (in PEG-6) was evaluated using groups of 20 (10 males, 10 females per group) Wistar Hannover rats.[3] The animals were dosed orally (by gavage) with the test substance once daily in accordance with OECD TG 421. The 3 dose groups received 10 mg/kg/day, 30 mg/kg/day, and 100 mg/kg/day, respectively (dose volume of 4 mL/kg/day). Male rats were dosed 2 weeks prior to mating, during the mating period, and up to 5 weeks post-mating (50 days total). Female rats were dosed 2 weeks prior to mating, during the mating period (up to 14 days), during gestation, and at least 4 additional days during the lactation period (40 to 49 days total). The vehicle control group was dosed with PEG-6. At the end of the dosing period, all parental animals were killed and subjected to gross necropsy. Histopathological examination of tissues was performed. There were no mortalities or clinical signs that were attributed to treatment with the test substance, and there were no effects on body weight and food consumption. The following parameters in treated animals were similar to those of the vehicle control group: reproductive performance of males and females, mating, fertility, gestation, and live birth indices. There were no treatment-related effects on weights of testes, epididymides, ovaries, uterus, and cervix. Furthermore, there were no treatment-related findings at necropsy or microscopic examination. There also were no effects on the clinical condition of pups, body weight, or sex ratio. No macroscopic findings were noted in pups that were killed on day 4 post-partum. The NOEL of Capryloyl Salicylic Acid was considered to be 100 mg/kg/day for the following: parental toxicity, embryo-fetal developmental toxicity, and pup development until day 4 post-partum.

GENOTOXICITY STUDIES

The genotoxicity studies on Capryloyl Salicylic Acid that are summarized below are also described in Table 3.

In Vitro

The genotoxicity of Capryloyl Salicylic Acid (in ethanol) was evaluated in the Ames test using the following bacterial strains, with and without metabolic activation: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvr A.[3] Doses up to 1000 µg/plate were tested, and the test material was classified as non-genotoxic. The mammalian chromosome aberration test involving Chinese hamster ovary cells (with and without metabolic activation) was used to evaluate the genotoxicity of Capryloyl Salicylic Acid (in ethanol) at concentrations of 50 µg/mL and 80 µg/mL.[4] The test material was classified as clastogenic with, but not without, metabolic activation.

In Vivo

The genotoxicity of Capryloyl Salicylic Acid (in 0.5% carboxymethylcellulose aqueous vehicle) was evaluated in the micronucleus test using groups of 10 (5 males, 5 females per group) mice of the CD-1 strain.[3] A single dose of the test substance (250, 500, or 1000 mg/kg) was administered by gavage to the 3 groups. The test material was classified as non-clastogenic. In a second micronucleus test, Capryloyl Salicylic Acid (in 0.5% aqueous carboxymethylcellulose) was administered to groups of 10 (5 males, 5 females per group) Swiss CD-1 mice.[4] A single dose of the test material (500, 1000, or 2000 mg/kg) was administered by gavage to the 3 groups. A slight increase in the polychromatic erythrocytes (PCEs)/normochromatic erythrocytes (NCEs) ratio was observed in males of the 2000 mg/kg dose group, only at the 24-h sampling time. This finding was indicative of an inhibitory effect on erythropoietic cell division. Results indicated that the test material was non-clastogenic in this assay. (Results relating to the acute oral toxicity of this test material are included in that section of this report.) The unscheduled DNA synthesis test was also used to evaluate the genotoxicity of Capryloyl Salicylic Acid (in 0.5% aqueous carboxymethylcellulose), using groups of 4 Sprague-Dawley rats.[4] In 2 tests, single doses of 500, 1000, or 2000 mg/kg were administered by gavage, and the test material was classified as non-clastogenic in both. (Results relating to acute oral toxicity are included in that section of this report.)

CARCINOGENICITY STUDIES

Data on the carcinogenicity of Capryloyl Salicylic Acid were neither found in the published literature, nor were these data submitted.

DERMAL IRRITATION AND SENSITIZATION STUDIES

The skin irritation and sensitization studies summarized below are presented in detail in Table 4.

The skin irritation potential of Capryloyl Salicylic Acid was evaluated in a 4-h occlusive patch test using 3 male New Zealand White rabbits.[3] The animals were patch tested with 0.5 g (62.5 mm^2 patch) of the test material, and results were negative. In a study involving groups of 5 female rats of the Crl:CD(SD)BR (VAF plus) strain, Capryloyl Salicylic Acid (in PEG-6) was applied to the back (constant volume of 2 mL/kg) once daily for 10 days. The test material was applied at concentrations of 2% and 5%; only the 5% concentration caused very slight erythema (in 2 to 5 rats) and edema (3 or 4 rats). Minimal/moderate scabbing at the application site was also observed. (Additional results from this study are included in the Short-Term Dermal Toxicity section of this report.) Skin irritation data are reported in a developmental toxicity study (described previously) on Capryloyl Salicylic Acid (in PEG-6) involving 2 groups of 24 pregnant female Sprague-Dawley rats.[3] The test material was applied to skin of the back (2 groups) at doses of 40 mg/kg/day and 100 mg/kg/day, respectively, on gestation days 6 to 15. Erythema and eschar formation were observed in both groups (number of animals not stated), the severity of which was dose-related. Slight edema was also reported, and scabbing and/or reddening at test sites was observed at necropsy.

Reactions described as cutaneous signs of slight intensity were observed in 5 of 49 subjects after application of a face product containing 0.3% Capryloyl Salicylic Acid to the face and eye contour twice daily for 4 weeks.[4]

The skin sensitization potential of Capryloyl Salicylic Acid (in arachis oil) was evaluated in the guinea pig maximization test, using 20 female Dunkin-Hartley guinea pigs.[3] Induction involved intradermal injection and topical application of 1% and 0.5% concentrations, respectively. This was followed by challenge with 2% (occlusive patch). The test material was classified as a skin sensitizer. In another maximization test, 20 guinea pigs were tested with Capryloyl Salicylic Acid (in ethanol).[4] Induction involved intradermal injection and topical application of 0.5% and 10% concentrations, respectively. There were no signs of skin irritation during induction. The animals were challenged with 2%. Sensitization reactions were observed (at 24 h and 48 h) at the application sites of 5 guinea pigs. However, these findings were classified as limited evidence of skin sensitization. The skin sensitization potential of Capryloyl Salicylic Acid (in PEG-300) was also evaluated in the maximization test, using 20 guinea pigs.[4] The induction phase involved concentrations of 25%, 15%, and 10%. When a concentration of 25% was applied, several test animals (number not stated) had erythema scores of 2 or more at the application site after the first induction application. The concentration was decreased during

induction because of skin irritation, and induction was followed by topical challenge with 5%. At 24 h, but not 48 h, sensitization reactions were observed at the application sites of 2 animals. These findings were classified as limited evidence of skin sensitization. Capryloyl Salicylic Acid (in 0.5% aqueous methylcellulose) was evaluated for sensitization potential in the guinea pig maximization test, using 20 Dunkin-Hartley guinea pigs.[4] A test concentration of 1% was used for topical induction and challenge. Skin reactions were not observed in any of the test animals during induction or the challenge phase, and the test material was classified as a non-sensitizer. Results relating to short-term dermal toxicity reported in this maximization test are included in that section of this report.

In 2 human repeated insult patch tests (HRIPTs), involving 106 subjects in one study and 105 subjects in the other, a face serum product containing 0.5% Capryloyl Salicylic Acid was classified as a non-sensitizer.[4] In the study involving 106 subjects, slight skin irritation was observed in a few subjects (number not stated) during the induction phase and at the first challenge reading. A cream product and a fluid cream product (each containing 0.5% Capryloyl Salicylic Acid) were also classified as non-sensitizers in HRIPTs involving 104 subjects and 106 subjects, respectively. A cosmetic product containing 2% Capryloyl Salicylic Acid was classified as a non-sensitizer in an HRIPT involving 102 subjects.[4] Slight skin irritation was observed in a few subjects (number not stated) during the induction phase and at the first challenge reading. A face powder containing 2% Capryloyl Salicylic Acid and a deodorant aerosol product containing 2% Capryloyl Salicylic Acid were also classified as non-sensitizers in HRIPTs involving 105 subjects and 103 subjects, respectively.[4]

Photosensitization/Phototoxicity

In Vitro

The phototoxicity of Capryloyl Salicylic Acid (100% pure, in dimethyl sulfoxide (DMSO)) was evaluated using the in vitro 3T3 neutral red uptake (NRU) phototoxicity test.[19] The study was performed in accordance with the OECD Guideline for Testing of Chemicals Draft Proposal for a New Guideline, issued in 2000. Balb/c 3T3 mouse fibroblasts (in microtiter plates) were treated with a range of test substance concentrations in 2 independent experiments. In the first experiment, Capryloyl Salicylic Acid was tested at concentrations ranging from 0.316 to 1000 µg/mL in the absence of ultraviolet (UV) light, and at concentrations ranging from 0.316 to 100 µg/mL in the presence of UV light. In the second experiment, Capryloyl Salicylic Acid was tested at concentrations ranging from 5 to 100 µg/mL in the absence of UV light, and at concentrations ranging from 1.25 to 30 µg/mL in the presence of UV light. Chlorpromazine (in phosphate-buffered saline (PBS)) and 1% v/v DMSO (in PBS) served as positive and negative controls, respectively. Both experiments involved the exposure of cells to the test substance, negative control, or positive control at a volume of 100 µL. For UV exposure of test plates, the long-wavelength ultraviolet (UVA) light source was described as a solar lamp fitted with a filter against mid-wavelength ultraviolet (UVB) emission. After a 1-h incubation period in the dark, test cultures were exposed to UVA for ~40 min in order to achieve a UVA dose of 5 J/cm^2.

At the end of the incubation period, the cells were examined microscopically for evidence of cytotoxicity. Optical densities (OD) of test plates were read at a wavelength of 540 nm, and mean ODs were calculated. IC_{50} (half maximal inhibitory concentration) values were calculated for the test substance and positive control using a curve fitting program. Photo-irritation factors (PIF = (IC_{50} in the absence of UVA) ÷ (IC_{50} in the presence of UVA)) for the test substance and positive control were also calculated. According to the evaluation criteria that were used, a test article was considered to be phototoxic in this assay if a marked decrease in cell viability (as measured by OD_{540} in the NRU) was observed in the presence of UVA (by comparison with the viability seen in the absence of UVA), such that PIF values of ≥ 5 were obtained. A test article was considered to be non-phototoxic in this assay if there was no marked decrease in cell viability when cells were exposed to the test article in the absence and presence of UVA, or if similar toxic profiles were observed in the absence and presence of UVA (PIF < 5). The test yielded PIFs of 4 (experiment 1) and 2.6 - 1.7 (experiment 2). Based on these PIF values, the author concluded that, according to the proposed OECD guideline evaluation criteria, Capryloyl Salicylic Acid was not phototoxic in the in vitro 3T3 NRU phototoxicity test. The negative and positive controls yielded acceptable responses, and the study was considered valid. In light of the author's conclusion, it should be noted that, according to the current OECD Guideline for the in vitro 3T3 NRU phototoxicity test (OECD Guideline 432), PIF values are to be interpreted based on the following criteria: a test substance with a PIF of < 2 predicts "no phototoxicity", a PIF of > 2 and < 5 predicts "probable phototoxicity", and a PIF of > 5 predicts "phototoxicity."[20] Therefore, using these criteria, Capryloyl Salicylic Acid would have been classified as probably phototoxic.

OCULAR IRRITATION STUDIES

Animal

The ocular irritation potential of Capryloyl Salicylic Acid was evaluated using 3 New Zealand White rabbits, according to OECD TG 405.[3] The test substance (~ 65 mg) was instilled into the eye, and exposure was not followed by

ocular rinsing. Reactions were scored at 24 h, 48 h, and 72 h after instillation, and the animals were observed for a total of 14 days after exposure. Diffuse corneal opacity, iridial inflammation, and moderate or severe conjunctivitis were observed in all treated eyes at 1 h post-instillation and in 2 treated eyes at 24 h, 48 h, and 72 h post-instillation. In the eye of 1 treated animal, corneal opacity increased and areas of opalescent corneal opacity with iridial inflammation and moderate to severe conjunctival irritation were observed at 48 h and 72 h post-instillation. Adverse effects observed on the nictitating and/or conjunctival membranes in the eye of this animal were described as pale appearance, small green-colored or white areas, and areas of hemorrhage. In another rabbit, diffuse corneal opacity, iridial inflammation, and minimal conjunctival irritation persisted in the treated eye on day 7; these effects were resolved by day 14. Circumcorneal vascularization and convoluted eyelids were also noted in this animal, and the nictitating membrane was also pale in appearance. In the third rabbit, corneal opacity increased and opalescent corneal opacity with pannus formation (indicative of irreversible ocular damage) had developed on day 14. It was not possible to assess iridial inflammation at this time, and minimal conjunctival irritation with convoluted eyelids were also observed. Capryloyl Salicylic Acid was classified as a severe irritant to the rabbit eye.

Human

A face product containing 0.3% Capryloyl Salicylic Acid was applied to the face and eye contour of 49 subjects twice a day for 4 weeks.[4] The group included subjects with sensitive skin, sensitive eyes, non-sensitive eyes, and contact lenses wearers. According to the authors, "observations were recorded before application and at least 10 min after the first application and the last application respectively." Microscopic examinations of ocular and periocular structures revealed no appearance of ocular physical signs or palpebral signs. Colorimetric examinations of the cornea and the conjunctiva revealed a maximal corneal index of 0.50% and a maximal conjunctival index of 0%, indicating an absence of toxicity to the conjunctiva and a very slight toxicity to the cornea. Clinical examinations revealed an ocular irritation rate of 0.03% and an ocular comfort rate of 99.83%. Additionally, the product did not induce any pathology that was specific to contact lenses wearers.

An eye contour product containing 0.3% Capryloyl Salicylic Acid was applied to the face and eye contour of 50 subjects twice a day for 4 weeks.[4] The group included subjects with sensitive eyes, non-sensitive eyes, and contact lenses wearers. Observations were recorded before application and at least 10 min after the first application and the last application, respectively. The product induced moderate ocular burning in 1 subject with sensitive eyes, and slight ocular stinging in 1 contact lenses wearer. Biomicroscopic examinations of ocular and periocular structures revealed 2 bilateral occurrences of bulbar conjunctival redness in 2 subjects. Colorimetric examinations of the cornea and the conjunctiva revealed a maximal corneal index of 0% and a maximal conjunctival index of 0%, indicating an absence of toxicity to the conjunctiva and very slight toxicity to the cornea. Clinical examinations revealed an ocular irritation rate of 0.04% and an ocular comfort rate of 99.88%. Additionally, the product did not induce any pathology that was specific to contact lenses wearers.

CLINICAL STUDIES

Case Reports

A female patient who used day and night creams containing Capryloyl Salicylic Acid presented with dermatitis of the face, which was first observed 3 months earlier.[21] Positive patch test reactions (+) to both products and to Capryloyl Salicylic Acid (1% in alcohol) were reported. Another female patient who used the same night cream containing Capryloyl Salicylic Acid also presented with facial dermatitis and had a positive patch test reaction to this ingredient (1% in alcohol).

A female patient presented with a pruritic erythematous rash that arose on her face 10 days after application of a cream containing Capryloyl Salicylic Acid (concentration not stated). A positive allergic reaction (++) to 1% Capryloyl Salicylic Acid in alcohol was observed in the patient (at 48 h and 96 h), but not in 15 healthy control subjects.

In a letter to the editor on the preceding 2 case reports, the author stated that Capryloyl Salicylic Acid is unlikely to be significantly allergenic, and is therefore unlikely to be the cause of the contact allergy reported.[7] However, the structural isomer, 3-capryloyl salicylic acid, is a highly plausible contaminant of Capryloyl Salicylic Acid and is likely to be sufficiently allergenic to account for the observed contact allergy.

Other Clinical Reports

In a split-face study, 44 female volunteers with mild to moderate facial hyperpigmentation and fine lines/wrinkles were randomized, and a Capryloyl Salicylic Acid containing peel was applied to one side of the face.[22] Increasing peel concentrations were applied (5 - 10% Capryloyl Salicylic Acid) based on the tolerance level of the subjects and clinical observations of an expert dermatologist for 12 weeks at biweekly intervals. Results indicated that there were no significant changes in erythema for Capryloyl Salicylic Acid from baseline values when compared with pre-peel to pre-peel and post-peel to post-peel at different weeks.

SUMMARY

Capryloyl Salicylic Acid was previously, erroneously, defined as the ester of salicylic acid and caprylic acid. However, is has become apparent that Capryloyl Salicylic Acid is, instead, the 5-capryl ketone of salicylic acid. Capryloyl Salicylic Acid can be manufactured via Friedel-Crafts acylation of methyl salicylate with capryloyl chloride and aluminum trichloride, to yield the methyl ester of Capryloyl Salicylic Acid, which is then hydrolyzed with sodium hydroxide, after which acidification yields this ketone, Capryloyl Salicylic Acid.

Capryloyl Salicylic Acid is reported to be used in 104 cosmetic products (93 leave-on and 11 rinse-off). The results of a concentration of use survey conducted in 2018 indicate that Capryloyl Salicylic Acid is used at concentrations up to 0.5% (in moisturizing products, not spray), which is the highest reported maximum use concentration for leave-on formulations. In rinse-off products, Capryloyl Salicylic Acid is used at concentrations up to 0.4% (in paste masks and mud packs), which is the highest reported maximum use concentration for rinse-off formulations.

In vitro skin penetration data (human skin samples) indicate that, after 16 h of contact, ~ 6% of the applied Capryloyl Salicylic Acid was found to "penetrate deeper than the stratum corneum." Using a standard tape stripping method for determining skin penetration (number of subjects not stated), it was determined that 17.1% of Capryloyl Salicylic Acid applied to the skin of human subjects was found in the stratum corneum over a 4-day period.

The acute dermal toxicity of Capryloyl Salicylic Acid was studied using Sprague-Dawley rats (5 males, 5 females). An LD_{50} of > 2000 mg/kg was reported. The following adverse dermal reactions were observed after a single dermal dose of 2000 mg/kg: edema and blanching and hard, light brown colored scabs at the application site.

The acute oral toxicity of Capryloyl Salicylic Acid (in peanut oil) was evaluated using groups of 10 Sprague-Dawley rats (5 males, 5 females/group). The highest dose administered was 4217 mg/kg. The combined oral LD_{50} (males + females) was 3354 mg/kg (95% confidence limit between 2834 and 3970 mg/kg). Abnormalities observed at necropsy of animals (2530 g/kg group) that were killed at the end of the study were described as occasional white foci (~1 mm x 1 mm covering 75% of the non-glandular gastric epithelium). At necropsy, there were no abnormalities in animals that received a dose of 3000 mg/kg or higher and were killed at the end of the study.

Results relating to the acute oral toxicity of Capryloyl Salicylic Acid (in 0.5% carboxymethylcellulose aqueous vehicle) are reported in a micronucleus test involving groups of 10 (5 males, 5 females per group) Swiss CD-1 mice. A single dose of the test substance (500, 1000, or 2000 mg/kg) was administered by gavage to the 3 groups. Two female mice and 1 male mouse dosed with 2000 mg/kg died. Results relating to acute oral toxicity of Capryloyl Salicylic Acid (in 0.5% carboxymethyl-cellulose aqueous vehicle) were also reported in an unscheduled DNA synthesis test using groups of 4 Sprague-Dawley rats. Single doses of 500, 1000, or 2000 mg/kg were administered by gavage, and no mortalities or clinical signs were observed.

A short-term (10-day) dermal toxicity study on Capryloyl Salicylic Acid (in PEG-6) was performed using groups of 5 female rats of the Crl:CD(SD)BR (VAF plus) strain. The test substance was applied for 6 h directly to the back once daily at concentrations of 2% and 5%. The NOEL for local and systemic effects was considered to be 2% and > 5%, respectively. Results relating to short-term dermal toxicity of Capryloyl Salicylic Acid (in 0.5% aqueous methylcellulose) are reported in a guinea pig maximization test involving 20 Dunkin-Hartley guinea pigs. One animal was found dead on day 18, but microscopic examination revealed no apparent abnormalities.

A short-term (28 day) oral toxicity study on Capryloyl Salicylic Acid (PEG-6) was performed using groups of 10 or 20 rats of the CRL:CD(SD)BR strain. The highest dose group (initially 300 mg/kg/day) consisted of 20 rats (10 males, 10 females per group). Each of the remaining dose groups (10, 30, and 100 mg/kg/day) consisted of 10 rats (5 males, 5 females per group). The NOEL for local effects was 30 mg/kg/day, and the NOEL for systemic effects was > 100 mg/kg/day.

The developmental toxicity of Capryloyl Salicylic Acid (in PEG-6) was evaluated using groups of 24 pregnant female Sprague-Dawley rats. The test material was applied for 6 h directly to skin on the back (not less than 10% of the body area). One group was dosed with 40 mg/kg/day and the other group was dosed with 100 mg/kg/day on gestation days 6 to 15. The NOAEL for developmental toxicity was established as 40 mg/kg/day, based on an increase in the incidence of fetuses with incomplete ossification of the sacral neural arch at 100 mg/kg/day. The NOAEL was not established for maternal toxicity, as treatment-related effects (local reaction at the site of administration and reductions in body weight gain) were observed at both doses tested. The reproductive and developmental toxicity of Capryloyl Salicylic Acid (in PEG-6) was evaluated using groups of 10 male and 10 female Wistar Hannover rats. The animals were dosed orally (by gavage) with the test substance once daily. The 3 dose groups received 10 mg/kg/day, 30 mg/kg/day, and 100 mg/kg/day, respectively (dose volume of 4 mL/kg/day). Males were dosed for 50 days total and females were dosed for 40 to 49 days total. The

NOEL was considered to be 100 mg/kg/day for the following: parental toxicity, embryo-fetal developmental toxicity, and pup development until day 4 post-partum.

In the Ames test, Capryloyl Salicylic Acid (in ethanol) was non-genotoxic in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2 uvr A when evaluated at doses up to 1000 µg/plate with and without metabolic activation. Capryloyl Salicylic Acid (in ethanol) was classified as clastogenic with, but not without, metabolic activation, in the mammalian chromosome aberration test involving Chinese hamster ovary cells. The test material was evaluated at concentrations of 50 µg/mL and 80 µg/mL in this assay.

Capryloyl Salicylic Acid (in 0.5% aqueous carboxymethylcellulose) was classified as non-clastogenic when evaluated in in vivo micronucleus tests using groups of 5 male and 5 female mice of the CD-1 strain. Single doses of the test substance up to 2000 mg/kg were administered by gavage. The in vivo unscheduled DNA synthesis test was also used to evaluate the genotoxicity of Capryloyl Salicylic Acid (in 0.5% aqueous carboxymethylcellulose) using groups of 4 Sprague-Dawley rats. Single doses of 500, 1000, or 2000 mg/kg were administered by gavage, and the test material was classified as non-clastogenic.

When 3 male New Zealand White rabbits were patch tested with 0.5 g of Capryloyl Salicylic Acid, skin irritation was not observed. However, skin irritation was reported in other types of toxicity tests. In a short-term dermal toxicity study, daily (for 10 days) applications of Capryloyl Salicylic Acid (in PEG-6) at a concentration of 5% caused very slight erythema and edema in a group of 5 female rats of the Crl:CD(SD)BR (VAF plus) strain. Scabbing was observed in all 5 rats at necropsy. Very slight erythema was observed in 2 animals and well-defined erythema in 1, and very slight edema was observed in 2 or 4 animals.

In a developmental toxicity study, Capryloyl Salicylic Acid (in PEG-6) was applied to the backs of pregnant female Sprague-Dawley rats (2 groups of 24) at doses of 40 mg/kg/day and 100 mg/kg/day, respectively, on gestation days 6 to 15. Erythema and eschar formation, dose-related in severity, were observed (number of animals not stated).

Reactions described as cutaneous signs of slight intensity were observed in 5 of 49 subjects after application of a face product containing 0.3% Capryloyl Salicylic Acid to the face and eye contour twice daily for 4 weeks.

Three maximization tests involved groups of 20 Dunkin-Hartley guinea pigs tested with Capryloyl Salicylic Acid (different vehicles used). A challenge concentration of 2% was sensitizing to 5 of 20 guinea pigs, and a challenge concentration of 5% was sensitizing to 2 of 20 guinea pigs. The absence of skin sensitization was noted in a group of 20 guinea pigs challenged with a concentration of 1%. Additionally, findings relating to skin irritation (number of animals with reactions not stated) during induction were reported in the 3 maximization tests. A test concentration of 25% applied topically was irritating, whereas, 0.5% (injected intradermally) and 10% (topical application) were not. In a fourth guinea pig maximization test, the following results reported after challenge with 2% Capryloyl Salicylic Acid: Positive reactions were observed in 14 of 20 guinea pigs at 24 h after challenge. At 48 h, 4 guinea pigs had positive reactions. The test material was classified as skin sensitizer because more than 30% of total number of guinea pigs tested (i.e. 70%) had a positive response. Positive reactions were observed at the 24-h challenge reading, but not at the 48-h reading.

In 2 HRIPTs involving 106 subjects and 105 subjects, respectively, face serum products containing 0.5% Capryloyl Salicylic Acid was classified as a non-sensitizer. In the HRIPT involving 106 subjects, slight skin irritation was observed in a few subjects (number not stated) during the induction phase and at the first challenge reading. A cream product and a fluid cream product (each containing 0.5% Capryloyl Salicylic Acid) were also classified as non-sensitizers in HRIPTs involving 104 subjects and 106 subjects, respectively. A cosmetic product containing 2% Capryloyl Salicylic Acid was classified as a non-sensitizer in an HRIPT involving 102 subjects. Slight skin irritation was observed in a few subjects (number not stated) during the induction phase and at the first challenge reading. A face powder containing 2% Capryloyl Salicylic Acid and a deodorant aerosol product containing 2% Capryloyl Salicylic Acid were also classified as non-sensitizers in HRIPTs involving 105 subjects and 103 subjects, respectively.

The phototoxicity of Capryloyl Salicylic Acid (100%, in DMSO) was evaluated using the in vitro 3T3 NRU phototoxicity test. The study was performed in accordance with the OECD Guideline for Testing of Chemicals Draft Proposal for a New Guideline, issued in 2000. In the first experiment, Capryloyl Salicylic Acid was tested at concentrations ranging from 0.316 to 100 µg/mL in the presence of UVA light. The second experiment involved test concentrations ranging from 1.25 to 30 µg/mL in the presence of UVA light. The test yielded PIFs of 4 (experiment 1) and 2.6 - 1.7 (experiment 2), and Capryloyl Salicylic Acid was classified as non-phototoxic. However, retroactive application of the current OECD test guideline, would probably have classified Capryloyl Salicylic Acid as phototoxic.

Capryloyl Salicylic Acid was classified as being a severe ocular irritant in a test involving 3 New Zealand White rabbits. The test substance (~ 65 mg) was instilled into the eye, and exposure was not followed by ocular rinsing.

A face product containing 0.3% Capryloyl Salicylic Acid was applied to the face and eye contour of 49 subjects twice a day for 4 weeks. Clinical examinations revealed an ocular irritation rate of 0.03%. In another test, an eye contour product containing 0.3% Capryloyl Salicylic Acid was applied to the face and eye contour of 50 subjects twice a day for 4 weeks, and clinical examinations revealed an ocular irritation rate of 0.04%

Positive patch test reactions to 1% Capryloyl Salicylic Acid have been reported in case reports, one of which reported no reactions in a control group of 15 subjects.

DISCUSSION

The Panel discussed the issue of skin sensitization potential for this ingredient. Capryloyl Salicylic Acid induced skin sensitization in guinea pig maximization tests at challenge concentrations of 2% (after induction with up to 10%) and 5% (after induction with up to 25%), but not at 1% (after induction with 1%). However, in HRIPTs, cosmetic products containing 0.5% or 2% Capryloyl Salicylic Acid were classified as non-sensitizing. After reviewing the HRIPT results and considering that the highest reported maximum use concentration of Capryloyl Salicylic Acid is 0.5% in leave-on cosmetic products, the Panel was reassured that the sensitization potential of exposure to this ingredient via cosmetic use is not a risk. Furthermore, dermatologists on the Panel stated that, based on their clinical experience, Capryloyl Salicylic Acid is not a sensitizer.

The Panel noted the absence of carcinogenicity data from this safety assessment. However, it was agreed that due to the predominance of negative genotoxicity data on Capryloyl Salicylic Acid and the absence of structural alerts in the chemical structure, the carcinogenic potential of this ingredient is not a concern.

The Panel also discussed the issue of incidental inhalation exposure from powders and hair sprays. The Council's survey results indicate that Capryloyl Salicylic Acid is being used in deodorant sprays (aerosolized) at concentrations up to 0.3%. Also, Capryloyl Salicylic Acid is being used in face powders at concentrations up to 0.3%. The Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable. However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. 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 ingredients are 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.

In response to the Panel's prior request for phototoxicity data, the results of an in vitro 3T3 NRU phototoxicity test were provided by the Council. The study was performed in accordance with the OECD Guideline for Testing of Chemicals Draft Proposal for a New Guideline (2000). According to the evaluation criteria that were used, a test article was considered to be phototoxic in this assay if a marked decrease in cell viability (as measured by OD340 in the NRU) was observed in the presence of UVA (by comparison with the viability seen in the absence of UVA) such that PIF values of ≥ 5 were obtained. A test article was considered to be non-phototoxic in this assay if there was no marked decrease in cell viability when cells were exposed to the test article in the absence and presence of UVA, or if similar toxic profiles were observed in the absence and presence of UVA (PIF < 5). The test yielded PIFs of 4 and 2.6 - 1.7 in separate experiments that were performed. Based on these PIF values, the author concluded that, according to the proposed OECD guideline evaluation criteria at that time, Capryloyl Salicylic Acid was not phototoxic in the in vitro 3T3 NRU phototoxicity test. However, the Panel noted that, according to the current OECD Guideline for the in vitro 3T3 NRU phototoxicity test, the results of this test are to be interpreted based on the following criteria: a test substance with a PIF of < 2 predicts "no phototoxicity," a PIF of > 2 and < 5 predicts "probable phototoxicity," and a PIF of > 5 predicts "phototoxicity." Thus, the Panel agreed that Capryloyl Salicylic Acid (PIFs of 4 and 2.6 - 1.7) should have been as probably phototoxic in the in vitro 3T3 NRU phototoxicity test. Furthermore, the Panel agreed that because this test is prone to false positives, additional data would be needed in order to evaluate the phototoxicity potential of Capryloyl Salicylic Acid.

Impurities data were also previously requested by the Panel. Data on impurities were not provided, and the request for these data remains. Thus, the Panel determined that the available data are insufficient, and the data needs include:

- Impurities
- Phototoxicity

CONCLUSION

The Panel concluded that the data were insufficient to support a determination of safety for Capryloyl Salicylic Acid under intended conditions of use in cosmetic formulations.

TABLES

Table 1. Chemical and Physical properties of Capryloyl Salicylic Acid

Property	Value/Results	Reference
Form (at 20 ºC and 1013 hPa)	White powder	[3]
Molecular weight	264.32	[6]
Specific Gravity (at 23 ºC)	0.35	[3]
Boiling point (ºC)	thermal decomposition occurs (at 264ºC) before boiling	[3]
Melting/Freezing point (ºC) (at 101,325 Pa)	115	[3]
Water solubility (mg/L at 20 ºC)	29.7	[3]
Vapor pressure (Pa at 21 ºC)	97.3	[3]
log P_{ow} (at 20 ºC)	0.32 (non-ionized form)	[3]
pK_a (at 25 ºC)	2.68 ± 0.10 (estimated)	[6]

Table 2. Frequency (2019) and Concentration (2018) of Use According to Duration and Exposure.

	# of Uses	*Max Conc of Use (%)*
	Capryloyl Salicylic Acid	
	2019[8]	**2018[9]**
Totals*	**104**	**0.1 -0.5**
Duration of Use		
Leave-On	***93***	***0.1-0.5***
Rinse-Off	***11***	***0.1-0.4***
Diluted for (Bath) Use	***NR***	***NR***
Exposure Type		
Eye Area	9	NR
Incidental Ingestion	NR	0.1
Incidental Inhalation-Spray	35[a];28[b]	0.1
Incidental Inhalation-Powder	28[b]	0.3; 0.3-0.5[c]
Dermal Contact	104	0.1-0.5
Deodorant (underarm)	NR	not spray: 0.3 aerosol: 0.3
Hair - Non-Coloring	NR	0.1
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	NR	0.1-0.3
Baby Products	NR	NR

*Because this ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

NR – not reported

[a]It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.

[b] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

[c]It is possible that these products may be powders, but it is not specified whether the reported uses are powders.

Table 3. Genotoxicity Studies on Capryloyl Salicylic Acid.

Ingredient	Strain/cell type	Assay	Dose/Concentration	Results
		In Vitro		
Capryloyl Salicylic Acid (in ethanol)	*Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvr A.	Ames test, with and without metabolic activation. Test protocol equivalent or similar to OECD TG 471. Controls: vehicle (ethanol); positive, without metabolic activation (2-aminoacridine, 2-nitrofluorene, and sodium azide); and positive, with metabolic activation (2-aminoanthracene and 4-nitroquinoline-1-oxide)	1st experiment: doses up to 1000 µg/plate (with and without metabolic activation). 2nd experiment: doses up to 100 and 200 µg/plate (without metabolic activation)	No substantial increases in revertant colony numbers over vehicle control count in any bacterial strain. Non-genotoxic.[3]
Capryloyl Salicylic Acid (in ethanol)	Chinese hamster ovary cells	Mammalian chromosome aberration test, with and without metabolic activation. Controls: vehicle (ethanol) and positive (mitomycin C and cyclophosphamide). Exposure and harvest times not reported.	Two experiments performed at concentrations up to 50 mg/mL and 80 mg/mL, respectively.	1st test (with metabolic activation): statistically significant increases in chromosome aberrations at 1st harvest observed at 50 µg/mL. (actual frequency was within background for this cell line). 2nd test (with metabolic activation): statistically significant increases in chromosome aberrations at 1st harvest observed at 80 µg/mL (actual frequency was above background for this cell line). No statistically significant increases in chromosome aberrations without metabolic activation. Results for positive controls confirmed validity of the test system. Clastogenic to Chinese hamster ovary cells.[4]
		In Vivo		
Capryloyl Salicylic Acid (0.5% in carboxymethyl-cellulose)	Groups of 10 (5 males, 5 females per group) mice of the CD-1 strain	Micronucleus test. Protocol similar to OECD TG 474, with minor deviations. Vehicle control group dosed with carboxymethylcellulose, and positive control group dosed with mitomycin C (injected intraperitoneally). Animals killed at 24 h, 48 h, and 72 h post-dosing. Bone marrow cells obtained and analyzed for micronuclei. Minimum of 1000 polychromatic erythrocytes (PCE) counted per animal.	3 groups received single oral doses (by gavage) of 250, 500, and 1000 mg/kg, respectively.	Micronuclei not induced at any administered dose of test material, despite decrease in PCE/normochromatic erythrocytes at dose of 1000 mg/kg at 24 h. Test material was non-clastogenic. Positive control induced appropriate increase in number of PCE.[3]
Capryloyl Salicylic Acid (in 0.5% aqueous carboxymethylcellulose)	Groups of 10 (5 males, 5 females per group) Swiss CD-1 mice	Micronucleus test. Performed in accordance with OECD TG 474. Vehicle control group dosed with carboxymethyl-cellulose, and positive control group dosed with mitomycin C.	3 groups received single oral doses (by gavage) of 500, 1000, and 2000 mg/kg), respectively.	A slight increase in the polychromatic erythrocytes (PCEs)/normochromatic erythrocytes (NCEs) ratio was observed in males of the 2000 mg/kg dose group, only at the 24-h sampling time. No statistically significant increases in frequency of micronucleated PCEs. Test material was non-clastogenic. Positive and negative controls yielded satisfactory response, confirming validity of test system.[4]

Table 3. Genotoxicity Studies on Capryloyl Salicylic Acid.

Ingredient	Strain/cell type	Assay	Dose/Concentration	Results
Capryloyl Salicylic Acid (in 0.5% aqueous carboxymethylcellulose)	Groups of 4 Sprague-Dawley rats	Unscheduled DNA synthesis test. Performed in accordance with OECD TG 486. Vehicle control group dosed with carboxymethylcellulose, and 2-acetamidofluorene and methylnitrosourea served as positive controls.	In 2 tests, single doses of 500, 1000, or 2000 mg/kg were administered by gavage. In the 2 tests, animals were killed at 14 h and 2 h, respectively.	Treatment with the test material did not produce group mean net grain value that was greater than -0.88, and no more than 6% of the cells were found in repair. Test material was non-clastogenic. Positive and negative controls yielded satis-factory response, confirming validity of test system.[4]

Table 4. Skin Irritation and Sanitization Studies on Capryloyl Salicylic Acid.

Test Substance	Animals/Subjects	Test Protocol	Results
Irritation (Animal)			
Capryloyl Salicylic Acid	3 male New Zealand White rabbits	OECD TG 404. Occlusive patch containing test material (0.5 g moistened with distilled water (0.5 ml)) applied for 4 h to 62.5 cm^2 area on dorsal flank. Skin irritation evaluated according to Draize scale at 24 h, 48 h, and 72 h after patch application.	No skin irritation at any time after patch application. Test material classified as non-irritant.[3]
Capryloyl Salicylic Acid (in PEG-6) tested at concentrations of 2% and 5%.	5 female rats of the Crl:CD(SD)BR (VAF plus) strain	Test protocol similar to OECD TG 410. Applied for 6 h directly to the back (not less than 10% of body area; constant volume of 2 ml/kg) once daily (for 10 days) at each concentration	In group that received 5% concentration, very slight erythema observed in 2 to 5 animals throughout dosing period (beginning at day 6), and well-defined erythema observed in 1 female between days 8 and 10 of dosing period. (It is not clear from the study whether the animal with well-defined erythema initially had slight erythema.) Very slight edema observed in 3 or 4 animals treated with 5%, beginning at day 7, and scabbing (minimal/moderate; observed at necropsy) at application site observed in all animals treated with 5%.[3]
Capryloyl Salicylic Acid (in PEG-6)	2 groups of 24 pregnant female Sprague-Dawley rats	Developmental toxicity study in which skin irritation results are included. Test material applied to skin of the back (2 groups) at doses of 40 mg/kg/day and 100 mg/kg/day, respectively, on gestation days 6 to 15.	Erythema and eschar formation observed in both groups (number of animals not stated), the severity of which was dose-related. Slight edema also reported, and scabbing and/or reddening at test sites observed at necropsy.[3]
Irritation (Human)			
Face product containing a 0.3% Capryloyl Salicylic Acid	49 subjects	Product applied to face and eye contour twice a day for 4 weeks.	Cutaneous signs of slight intensity were observed in 5 subjects.[4]

Table 4. Skin Irritation and Sanitization Studies on Capryloyl Salicylic Acid.

Test Substance	Animals/Subjects	Test Protocol	Results
Sensitization (Animal)			
Capryloyl Salicylic Acid (in arachis oil), tested during induction (1% and 0.5%) and challenge (2%)	30 female Dunkin-Hartley guinea pigs (20 test and 10 controls)	OECD TG 406. Guinea pig maximization test. Initially, following 3 pairs of intradermal induction injections (0.1 ml per injection) made in group of 20animals: 1:1 mixture of Freund's complete Adjuvant in distilled water; 1% (w/v) dilution of test material in arachis oil; and 1% (w/v) dilution of test material in a 1:1 preparation of Freund's complete Adjuvant and arachis oil. These intradermal injections comprise 2 induction exposures during an exposure period of 7 days + 48 h. One week later, a 48-h topical application (induction) of 0.2 to 0.3 ml of 0.5% (w/w) test material in arachis oil over injection sites (shoulder region). At 2 weeks post-topical induction, a 24-h epicutaneous challenge with 2% (w/w) test material in arachis oil (occlusive patch) involved the left flank. Dose per cm^2 for induction and challenge applications not stated. Challenge reactions scored at 24 h and 48 h. Positive and vehicle controls were 2,4-dinitrochlorobenzene and arachis oil, respectively.	Positive reactions observed in 14 of 20 guinea pigs at 24 h after challenge. At 48 h, 4 guinea pigs had positive reactions. Test material classified as skin sensitizer because more than 30% of total number of guinea pigs tested (i.e., 70%) had positive response. Control animals treated with arachis oil did not have positive reactions. Positive control (2,4-dinitrochlorobenzene) induced sensitization.[3]
Capryloyl Salicylic Acid (in ethanol), tested during induction (0.5% 10%) and challenge (2%)	30 female Dunkin-Hartley guinea pigs (20 test and 10 controls)	Method similar to OECD TG 406. Guinea pig maximization test. During induction, animals injected intradermally with concentration of 0.5%, and received topical applications at a concentration of 10%. Challenged with a concentration of 2%. The dose per cm^2 for induction and challenge applications was not stated. Challenge reactions were scored at 24 h and 48 h.	No signs of skin irritation during induction at concentrations of 0.5% (injected intradermally) and 10% (topical application). Positive (sensitization) reactions observed (at 24 h and 48 h) at the application sites of 5 guinea pigs. Classified as limited evidence of reactions indicative of skin sensitization. Adverse skin reactions not observed in control animals.[4]
Capryloyl Salicylic Acid (in PEG 300), tested during induction (25%, 15%, and 10%) and challenge (5%)	30 female Dunkin-Hartley guinea pigs (20 test and 10 controls)	OECD TG 406 (no significant protocol deviations). Guinea pig maximization test. During induction, test material applied topically at concentration of 25%. Due to severity of skin reactions after first induction application, concentration reduced to 15% for 2^{nd} induction, and to 10% for last induction. Animals challenged topically with a test substance concentration of 5%. Dose per cm^2 for induction and challenge applications not stated. Challenge reactions scored at 24 h and 48 h.	When a concentration of 25% was applied, several test animals (number not stated) had erythema scores of 2 or more at the application site after the first induction application. At the 24 h challenge reading, positive (sensitization) reactions observed at application sites of 2 animals. Positive reactions not observed in any animals at 48 h. Reactions classified as limited evidence of reactions indicative of skin sensitization. Adverse skin reactions not observed in control animals.[4]
Capryloyl Salicylic Acid (in 0.5% aqueous methylcellulose), tested at 1% (induction and challenge)	Dunkin-Hartley guinea pigs (test: 10 males, 10 females; controls: 5 males, 5 females)	OECD TG 406. Guinea pig maximization test. Topical application during induction, followed by topical challenge. Dose per cm^2 for induction and challenge applications not stated. Challenge reactions scored at 24 h and 48 h. Ten positive control animals tested with 2,4-dinitrochlorobenzene.	Skin reactions not observed in any test animals during induction or challenge. No evidence of adverse skin reactions in negative control animals. Test material classified as non-sensitizer. Sensitization in 3 of 10 positive control animals.[4] [Results relating to short-term dermal toxicity in that section of this report.]

Table 4. Skin Irritation and Sanitization Studies on Capryloyl Salicylic Acid.

Test Substance	Animals/Subjects	Test Protocol	Results
		Sensitization (Human)	
Face serum product containing a 0.5% Capryloyl Salicylic Acid	106 subjects	HRIPT. During induction, occlusive patches containing 0.02 mL of product applied (50 mm^2 area; application site not stated) 3 times per week (Tuesdays, Thursdays, and Saturdays) for total of 9 applications. Patches removed after 48 h (or 72 h for patches applied on Saturday). Sites graded 15 to 20 min after patch removal. Challenge phase initiated after 13-day non-treatment period. Challenge patch containing 0.02 mL of product applied to previously treated site and to new site for 48 h. Patch alone applied to new site served as negative control. Reactions scored at least 30 min and ~ 48 h after patch removal.	Slight skin irritation observed in a few subjects (number not stated) during induction phase and at first challenge reading. Sensitization not observed at 1st challenge reading, and no adverse responses observed at final challenge reading. Product classified as non-sensitizer.[4]
Face serum product containing a 0.5% Capryloyl Salicylic Acid	105 subjects.	HRIPT. During induction, occlusive patches containing 0.02 mL of product applied (50 mm^2 area; application site not stated) 3 times per week (Mondays, Wednesdays, and Fridays) for total of 9 applications. Patches removed after 48 h, and reactions scored prior to next patch application. Challenge phase initiated after 10 to 14-day non-treatment period. Challenge patch containing 0.02 ml of product applied to previously treated site and to new site for 48 h, after which reactions were scored. Reactions also scored at 72 h and 96 h post-application.	No evidence of adverse responses during induction or challenge. Product classified as non-sensitizer.[4]
Cream product containing a 0.5% Capryloyl Salicylic Acid	104 subjects	HRIPT. Occlusive patches containing 0.02 mL of product applied to 50 mm^2 area. Details relating to test protocol not included.	No evidence of adverse responses during induction or challenge. Product classified as non-sensitizer.[4]
Fluid cream product containing a 0.5% Capryloyl Salicylic Acid	106 subjects	HRIPT. Occlusive patches containing 0.02 mL of product applied to 50 mm^2 area. Details relating to test protocol not included.	No evidence of adverse responses during induction or challenge. Product classified as non-sensitizer.[4]
Cosmetic product containing a 2% Capryloyl Salicylic Acid	102 subjects	HRIPT. During induction, semi-occlusive patches containing 0.2 mL of product applied (40 mm^2 area; application site not stated) 3 times per week (Tuesdays, Thursdays, and Saturdays) for total of 9 applications. Patches removed after 48 ± 4 h (or 72 ± 4 h for patches applied on Saturday). Sites graded 15 to 30 min after patch removal. Challenge phase initiated after 13-day non-treatment period. Challenge patch containing 0.2 ml of product applied to previously treated site and to a new site for 48 ± 4 h. Patch alone applied to new site served as negative control. Reactions scored 30 to 35 min and ~ 48 ± 4 h after patch removal.	Slight skin irritation observed in a few subjects (number not stated) during induction phase and at first challenge reading. Sensitization not observed at 1st challenge reading, and no adverse responses observed at final challenge reading. Product classified as non-sensitizer.[4]

Table 4. Skin Irritation and Sanitization Studies on Capryloyl Salicylic Acid.

Test Substance	Animals/Subjects	Test Protocol	Results
Face powder containing a 2 % Capryloyl Salicylic Acid	105 subjects	During induction, occlusive patches containing 0.02 mL of product applied (50 mm^2 area; application site not stated) 3 times per week (Mondays, Wednesdays, and Fridays) for total of 9 applications. Patches removed after 48 h, and reactions scored prior to next patch application. Challenge phase initiated after 10- to 14-day non-treatment period. Challenge patch containing 0.02 ml of product applied to previously treated site and to new site for 48 h, after which reactions scored. Reactions also scored at 72 h and 96 h post-application.	No evidence of adverse responses during induction or challenge phases. Product classified as non-sensitizer.[4]
Deodorant aerosol product containing a 2% Capryloyl Salicylic Acid	103 subjects	HRIPT. During induction, occlusive patches containing 0.02 mL of product applied (50 mm^2 area; application site not stated) 9 times over period of 3 consecutive weeks. Patches removed after 48 h, and reactions scored prior to next patch application. Challenge phase initiated after 2-week non-treatment period. Challenge patch containing 0.02 ml of product applied to previously treated site and to new site for 48 h, after which reactions scored. Reactions also scored at 72 h and 96 h post-application. Patch alone applied to new site served as negative control.	No evidence of adverse responses during induction or challenge. Product classified as non-sensitizer.[4]

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2019 VCRP Data

Capryloyl Salicylic Acid

03D - Eye Lotion	5
03G - Other Eye Makeup Preparations	4
07I - Other Makeup Preparations	1
11G - Other Shaving Preparation Products	2
12A - Cleansing	9
12C - Face and Neck (exc shave)	24
12D - Body and Hand (exc shave)	4
12F - Moisturizing	24
12G - Night	10
12J - Other Skin Care Preps	20
13C - Other Suntan Preparations	1
Total	**104**

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: October 25, 2019

SUBJECT: Tentative Amended Report: Safety Assessment of Capryloyl Salicylic Acid as Used in Cosmetics (release date: October 1, 2019)

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

Abstract - As the material reviewed in this safety assessment (Capryloyl Salicylic Acid, a ketone) is not the same material reviewed in the Salicylic Acid report (capryloyl salicylic acid, an ester), it is not necessary to say that this report "reassessed" safety. This is essentially a new review.

Abstract; Conclusion - What are the "intended conditions of use" for Capryloyl Salicylic Acid? The conclusion should be revised to indicate that "the available data are insufficient to make a determination that Capryloyl Salicylic Acid is safe in cosmetic formulations under the intended conditions of use." "Intended conditions of use" refers to the use of the cosmetic products, e.g., a lipstick is used on the lips, not the hands, rather than the use of the ingredient.

DART, Dermal; Summary - In the description of the dermal developmental toxicity study (reference 3), it should be made clear that the rats wore Elizabethan collars during the 6-hour exposure periods and that the application sites were rinsed after 6 hours.

Summary - In the paragraph regarding acute dermal toxicity, it says: "adverse dermal reactions were observed after a single oral dose..."; "oral dose" needs to be corrected to "dermal dose".

Summary; Discussion - The induction concentrations used in the guinea pig maximization tests should also be noted.

Table 4, 105 subject HRIPT - Please complete: "after which reactions"

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