Safety Assessment of Alkanoyl Lactyl Lactate Salts as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: May 10, 2019
Panel Date: June 6-7, 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.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst.

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Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons

From: Wilbur Johnson, Jr.
Senior Scientific Analyst

Date: May 10, 2019

Subject: Draft Final Report on Alkanoyl Lactyl Lactate Salts

Enclosed is a draft final report on 10 alkanoyl lactyl lactate salts (*alkylL062019rep*). This ingredient family comprises the carboxylic acid salts of diesters that are formed between a fatty acid group and two equivalents of lactic acid. A tentative report was issued at the December 2018 meeting, and the Panel's conclusion therein states that the 10 alkanoyl lactyl lactate salts are safe in cosmetics in the present practices of use and concentration described in the safety assessment, when formulated to be non-irritating and non-sensitizing, which may be based on a QRA.

The attached draft final report has been revised to include the Council's comments (*alkylL062019pcpc2*) on the tentative report that was announced. These comments, as well as those that were received from the Council prior to the December 2018 Panel meeting (*alkylL062019pcpc1*), are also attached for the Panel's review. All comments have been addressed.

The draft final report has also been revised to include 2019 FDA VCRP data (*alkylL062019fda).* When compared to 2018 FDA VCRP data, it should be noted that the new data indicate that Sodium Lauroyl Lactylate is now being used in 34 additional bath soaps and detergents (40 + 34 = 74 products), and that Sodium Stearoyl Lactylate is now being used in 32 additional moisturizing skin care preparations (151 + 32 = 183 products). New product categories relating to ingredient use include 1 reported use of Sodium Caproyl/Lauroyl Lactylate in a moisturizing skin care preparation, and 1 reported use of Sodium Stearoyl Lactylate in the suntan gels, creams, and liquids product category.

Also included in this package for your review are the CIR report history (*alkylL062019hist*), flow chart (*alkylL062019flow*), literature search strategy (*alkylL062019strat*), the ingredient data profile (*alkylL062019prof*), and minutes from the December 2018 Panel meeting (*alkylL062019min*).

The Panel should carefully review the Abstract, Discussion, and Conclusion of this safety assessment. If these are satisfactory, the Panel should issue a Final Report.

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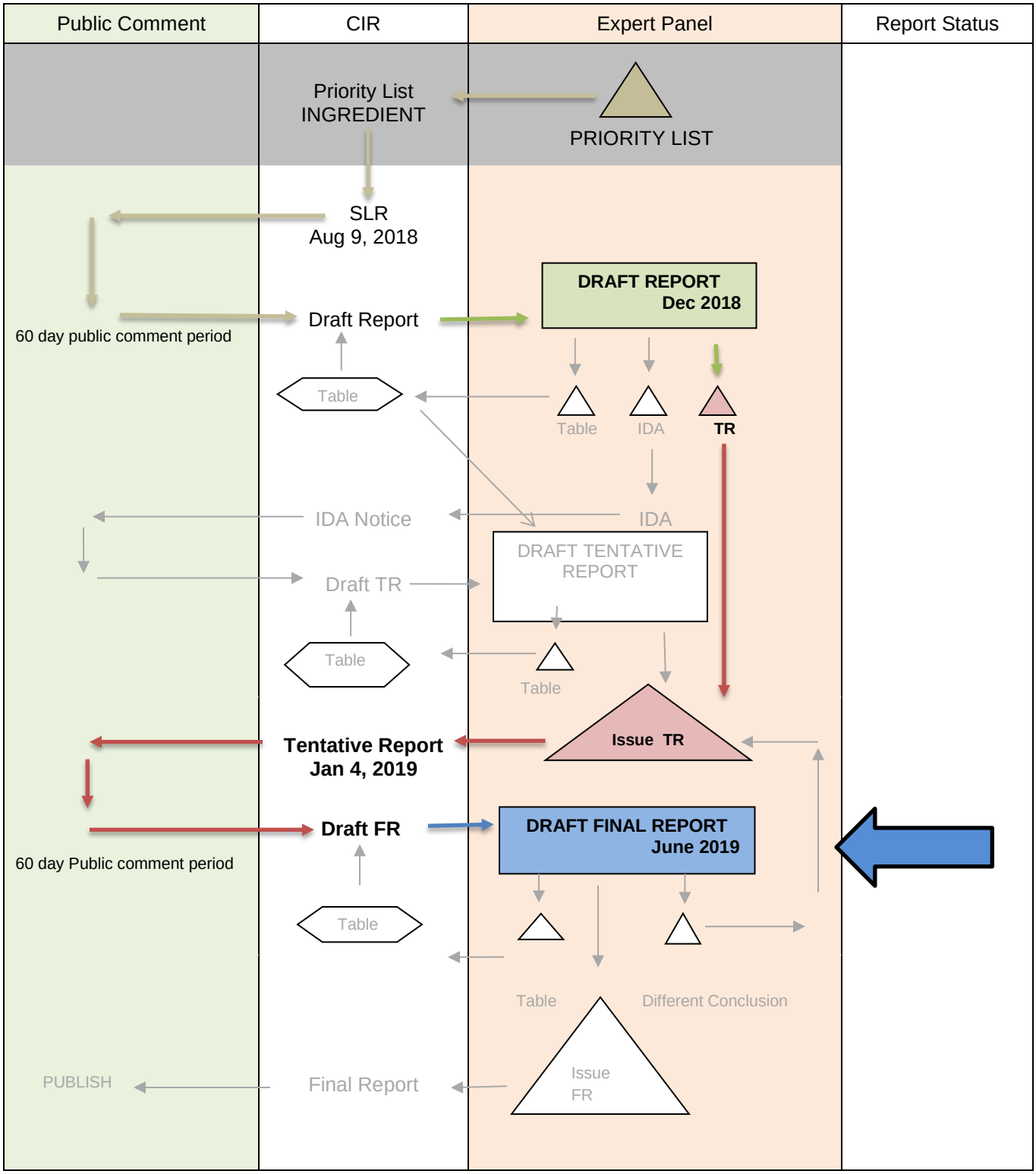
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Alkanoyl Lactyl Lactate Salts

MEETING June 2019



CIR History of:

Alkanoyl Lactyl Lactate Salts

A Scientific Literature Review (SLR) on Alkyl Lactyl Lactate Salts was issued on August 9, 2018. Comments and unpublished data were received from the Council before/after announcement of the SLR.

Draft Report, Teams/Panel: December 3-4, 2018

The draft report has been revised to include the following unpublished data that were received from the Council before/after announcement of the SLR: (1) use concentration data, (2) primary skin and acute eye irritation studies (rabbits) on undiluted Sodium Lauroyl Lactylate, (3) delayed guinea pig dermal sensitization study on a silicone antifoam emulsion with 2% Sodium Stearoyl Lactylate (75% dilution; effective test concentration = 1.13% Sodium Stearoyl Lactylate), (4) human skin irritation test on a hair styling product containing 5% Calcium Stearoyl Lactylate,, and (5) four human skin irritation tests on a moulding cream containing 7% Calcium Stearoyl Lactylate Additionally, comments on the SLR that were received from the Council have been addressed.

The Panel issued a tentative report for public comment with the conclusion that the 10 alkyl lactyl lactate salts listed below are safe in cosmetics in the present practices of use and concentration described in the safety assessment, when formulated to be non-irritating and non-sensitizing, which may be based on a QRA.

Calcium Stearoyl Lactylate
Sodium Behenoyl Lactylate
Sodium Caproyl Lactylate
Sodium Caproyl/Lauroyl Lactylate
Sodium Cocoyl Lactylate*
Sodium Cupheoyl Lactylate*
Sodium Isostearoyl Lactylate
Sodium Lauroyl Lactylate
Sodium Oleoyl Lactylate*
Sodium Stearoyl Lactylate

*Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.

Acknowledging positive sensitization data on alkyl lactyl lactate salts, the Panel noted that the potential for induction of skin sensitization varies depending on a number of factors, including the area of product application; thus, formulators should assess the potential for final formulations to induce sensitization using a QRA or other accepted methodologies. The Panel was also concerned that the potential exists for dermal irritation with the use of products formulated using alkyl lactyl lactate salts. The Panel also specified that products containing alkyl lactyl lactate salts must be formulated to be nonirritating.

Draft Final Report, Teams/Panel: June 6-7, 2019

The draft final report has been revised to include comments that were received from the Council and 2019 FDA VCRP data. When compared to 2018 FDA VCRP data, it should be noted that the new data indicate that Sodium Lauroyl Lactylate is now being used in 34 additional bath soaps and detergents (40 + 34 = 74 products), and that Sodium Stearoyl Lactylate is now being used in 32 additional moisturizing skin care preparations (151 + 32 = 183 products). New product categories relating to ingredient use include 1 reported use of Sodium Caproyl/Lauroyl Lactylate in a moisturizing skin care preparation, and 1 reported use of Sodium Stearoyl Lactylate in the suntan gels, creams, and liquids product category.

Alkyl Lactyl Lactate Salts Data Profile for June 6-7, 2019 Panel – Wilbur Johnson

			Dermal Penetration			Nail Penetration	Penetration Enhancement	ADME					Acute Toxicity			Short-Term Toxicity	Sub-Chronic Toxicity	Chronic Toxicity	DART		Genotoxicity	Carcinogenicity	Other Relevant Studies		Dermal Irritation*	Dermal Sensitization*/ Phototoxicity*		Ocular Irritation *		Clinical Studies	Case Reports		Epidemiology Studies
			In Vivo -Animal	In Vitro-Human	In Vivo-Human	In Vitro-Human	In Vitro-Animal	In Vitro-Animal and human	Animal-Dermal	Animal-Oral	Animal-IV	Human-Oral	Animal-Dermal	Animal-Oral	Animal-Inhalation	Animal	Animal	Animal	In Vitro	In Vivo	In Vitro/In Vivo	In Vivo/In Vivo	In Vitro	In Vivo-Animal	Animal/Human/In Vitro	Animal/In vitro	Human	In Vitro	Animal/Human	Human-Dermal/Oral	Human-Dermal	Human-Oral	Human
Calcium Stearoyl Lactylate								X		X				X		X	X	X			X				X				X				
Sodium Behenoyl Lactylate																																	
Sodium Caproyl Lactylate																																	
Sodium Caproyl/Lauroyl Lactylate																X					X				X	X		X					
Sodium Cocoyl Lactylate																																	
Sodium Cupheoyl Lactylate																																	
Sodium Isostearoyl Lactylate														X											X				X				
Sodium Lauroyl Lactylate														X											X	X			X				
Sodium Oleoyl Lactylate																																	
Sodium Stearoyl Lactylate														X		X	X	X				X	X		X	X			X		X		

[Alkyl Lactyl Lactate Salts –6/30/2018; 10/17/18 update]

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECET -OC	Web
Sodium Stearoyl Lactylate	18200-72-1; 25383-99-7	1	409/12	34/1	1/1	Yes	No	No	No	No	No	No	No	No	Property, 2nd CAS	Yes	No	Yes
Calcium Stearoyl Lactylate	5793-94-2	1	540/4	16/0	4/0	Yes	No	No	No	No	No	No	No	No	Yes	Yes	No	Yes
Sodium Behenoyl Lactylate		1	5/0	0/0	1/1	No	No	No	No	No	No	No	No	No	No	No	No	Yes
Sodium Caproyl Lactylate	42566-88-1	1	12/1	0/0	1/1	No	No	No	No	No	No	No	No	No	No	No	No	Yes
Sodium Caproyl/Lauroyl Lactylate	1312021-45-6	1	0/0	0/0	1/1	No	No	Yes CAS	Yes	No	No	No	No	No	No	No	No	Yes
Sodium Cocoyl Lactylate		1	6/0	0/0	1/1	No	No	No	No	No	No	No	No	No	No	No	No	Yes
Sodium Cupheoyl Lactylate		1	0/0	47/0	0/0	No	No	No	No	No	No	No	No	No	No	No	No	Yes
Sodium Isostearoyl Lactylate	66988-04-3	1	83/3	0/0	1/1	No	No	No	No	No	No	No	No	No	No	No	No	Yes
Sodium Lauroyl Lactylate	13557-75-0; 1312021-45-6	1	125/6	0/0	1/1	Yes	No	Yes CAS2	Yes CAS2	No	No	No	No	Yes LLNA	No	No	No	Yes
Sodium Oleoyl Lactylate		1	1/1	0/0	0/0	Yes	No	No	No	No	No	No	No	No	No	No	No	Yes

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

December 3-4, 2018 CIR Expert Panel Meeting – Dr. Belsito's Team

Alkanoyl Lactyl Lactyl Lactate Salts

DR. BELSITO: Okay. Alkyl lactyl lactate salts. Wilber sent an email with updated concentrations earlier this morning. Did other people get that? It came through at 10:34. Does it substantively change what's in our current report?

MR. JOHNSON: It's just that the data were inadvertently missing from the build, so that's why I sent it to. We discovered that this morning. That's why I sent the data to all panel members.

DR. HELDRETH: You're just talking about the raw survey data?

MR. JOHNSON: Yeah, from industry, the use concentration data.

DR. BELSITO: Okay. So again, I was wondering, to my tox colleagues, whether it was insufficient for dermal absorption, and if absorbed DART studies were needed.

DR. LIEBLER: We don't have absorption data I don't think. Dermal.

DR. BELSITO: No.

DR. LIEBLER: Go ahead, Carol.

DR. EISENMANN: For fatty acids and lactates, if they were metabolized, would you be concerned?

DR. LIEBLER: No, I'm just talking -- I was just strictly referring to the fact that we don't have absorption data.

DR. EISENMANN: Right. So if they were absorbed, would you be concerned?

DR. LIEBLER: Right. I'm looking down, scrolling down to refresh my memory on what do we have in vivo tox?

DR. BELSITO: Genotox is negative.

DR. LIEBLER: Right. No repro developmental, but we do have chronic/subchronic short term. Those are all clean, right, Paul?

DR. BELSITO: Mm-hmm.

DR. LIEBLER: Because I had a note on the head of this that basically said I thought the data needs were met.

DR. SNYDER: Yeah, I'm looking too, because I did not flag the repro/developmental.

DR. BELSITO: Okay. We just didn't have dermal absorption, and we have no DART data on this.

DR. LIEBLER: Right.

DR. EISENMANN: But they are used in food.

DR. BELSITO: Yeah. Okay.

DR. KLAASSEN: That's the part that --

DR. SNYDER: It's only like .5 percent, and so we have a leave-on at 7 percent, with no absorption data.

DR. KLAASSEN: Our muscles make this, et cetera. It's not a --

MR. JOHNSON: One question that I have in the short-term toxicity section, whereby an increase in liver weight is observed, and also the lipogranulomata and the subchronic high toxicity study.

DR. SNYDER: That's nothing.

MR. JOHNSON: No concern?

DR. SNYDER: No.

DR. BELSITO: We'll need the heavy metal and the respiratory boilerplates for this. Also, Wilber, in the cosmetic use section, it's used in aerosols and you didn't put the aerosol boilerplate in. I flagged that, too, but it's the subchronic toxicity. I think if you're concerned at all, the mucous membrane use is extremely low, if you wanted to put that in the discussion. On PDF page 16, the second paragraph, the skin toxicity of Sodium Stearoyl Lactylate was investigated so that is the, I think, it's called the Luke (phonetic) assay. That's actually sensitization, not irritation; so that should be moved down to sensitization. You see what I'm talking about?

MR. JOHNSON: What page, Dr. Belsito?

DR. BELSITO: PDF page 16. The skin toxicity of Sodium Stearoyl Lactylate was investigated using RHE, and detection of the inflammation markers (IL)-1 alpha and IL-8. It was predicted to be an allergen-based upon the results of this study. That should be moved out of irritation down into sensitization.

DR. LIEBLER: So, Don, are you concerned that we don't have human studies?

DR. BELSITO: Pardon?

DR. LIEBLER: Are you concerned we don't have human studies for sensitization?

DR. BELSITO: No, I actually -- we have an LLNA that it can be a weak sensitizer, so mine was safe as used when formulated to be non-sensitizing.

DR. LIEBLER: Okay.

DR. BELSITO: With a heavy metal and respiratory boilerplates and aerosol boilerplate.

DR. SNYDER: Did you mean -- you said formulated to be non-sensitizing. Did you mean irritating?

DR. BELSITO: I mean sensitizing, but I don't know about irritation as well. What is the irritation data?

DR. KLAASSEN: It's a weak irritator.

DR. BELSITO: It was considered non-corrosive when the irritation/corrosive potential of this ingredient was evaluated, in EpiDerm. Non-irritating, non-irritating.

DR. LIEBLER: But Sodium Isostearyl Lactylate in rabbits, severe irritant?

DR. BELSITO: Where was this?

DR. LIEBLER: The last sentence of the paragraph.

DR. BELSITO: Undiluted ingredient. I mean, we can add it when formulated to be non-irritating and non-sensitizing. Anything else on this?

Okay. So respiratory, heavy metal, and boilerplates. If you're concerned, at all, about the lipogranulomata, you can put in the discussion the mucous membrane use is extremely low.

MR. JOHNSON: What were we saying about the lipogranulomata?

DR. BELSITO: We didn't think we needed to discuss it at all, right, Paul.

DR. SNYDER: Yeah.

MR. JOHNSON: What about the increase in liver weight in the short-term study? In the absence of histopathology?

DR. KLAASSEN: That, basically, doesn't need to be addressed.

MR. JOHNSON: Don't need to address that?

DR. SNYDER: No. No.

DR. BELSITO: Okay. Anything else here?

MR. JOHNSON: Can you just repeat what you said about mucous membranes, so I can get it?

DR. BELSITO: We're not even putting that in the discussion, because we didn't feel it needed to be addressed.

MR. JOHNSON: Okay.

December 3-4, 2018 CIR Expert Panel Meeting – Dr. Marks' Team

Alkanoyl Lactyl Lactyl Lactate Salts

DR. MARKS: Wilbur gives us a draft for four of these ten ingredients. This is the first review, and the first thing I always for Ron, Ron, and Tom is, do you like the ingredients in this group? I know, Ron Hill, you often don't like that grouping.

DR. HILL: That's not true.

DR. SLAGA: And you like this one, don't you?

DR. HILL: This one is fine.

DR. MARKS: Then I'll retract that statement, Ron Hill. First, do you like these ten ingredients?

DR. HILL: Yes, sure.

DR. MARKS: Okay, great.

DR. SHANK: Well, one --

DR. MARKS: Oh, there we go. That's why I ask the question. Well, there's no reason to move on. Yeah, which one?

DR. SHANK: I don't like it, I can't pronounce it. Sodium Cupheoyl -- or something like that -- Lactylate. We have no information on it, on the fatty acids in that plant, Cuphea viscosissima or something like that. Did I miss something? It's spelled C-U-P-H-E --

DR. MARKS: H-E-O-Y-L, yeah.

MR. JOHNSON: This information will be in the next draft, but Council provided a reference that indicates the fatty acid concentrations. And the oil typically contains around 70 percent Capric acid, 9 percent Oleic acid, 6 percent Palmitic acid, 5 percent Linoleic acid, 4 percent Myristic acid, and 3 percent Lauric acids.

DR. SHANK: And this will be added to the report?

MR. JOHNSON: That will be added.

DR. SHANK: Okay.

DR. MARKS: Okay, good. So all the ingredients that's listed are okay, the ten ingredients. What needs do we have, Ron, Tom?

DR. SLAGA: I have no needs.

DR. HILL: I had a lot.

DR. MARKS: Okay. And I had a sensitization need. Okay, go ahead, Ron Hill. And then, Ron Shank, did you have needs?

DR. SHANK: No. I was using two of the ingredients for read across. And the lead ingredients are approved food additives, so we don't require systemic toxicology data. There is irritation potential, so we would say formulated to be non-irritating. There's weak sensitization potential, and we'll have to discuss that; highest concentration, use concentration 7 percent.

DR. MARKS: Yeah. That's what I had on the Sodium Stearoyl Lactylate at 7 percent; I'd like to see a sensitization study since this is the first time we've looked at this. I wasn't as convinced with the irritation. I saw there was mild, but it was a little bit of a mix.

DR. SLAGA: There were others that were non-irritating and so --

DR. MARKS: Exactly.

DR. SLAGA: You know, it was non-genotoxic. We had carcinogenicity data. Sensitivity, I agree with Ron, it was just weak or mild, and I don't have a problem with it. There were others that's non-sensitizing, so.

DR. MARKS: You don't feel we need the Sodium Stearoyl Lactylate?

DR. SLAGA: I don't -- I couldn't think -- but it's the first time. So, if you want on sensitization, I --

DR. MARKS: Yeah. I'd like -- that's the highest concentration. It has a lot of uses. It has over 300 uses, so it's got a lot of uses, and 7 percent. And the Sodium Lauroyl Lactylate also had a 7 percent concentration. So, I thought we could ask for that to begin with.

Repeat again, Ron Shank, use. And, Ron Hill, I'm going to call on you in a minute here, your concerns. You used two ingredients?

DR. SHANK: Calcium Stearoyl Lactylate, and Sodium Stearoyl Lactylate' so the Calcium Stearoyl derivatives.

DR. MARKS: I'm sorry, Calcium Stearoyl --

DR. SHANK: Calcium Stearoyl Lactylate. These are food additives.

DR. MARKS: And the second?

DR. SHANK: And the same thing, Sodium.

DR. MARKS: Sodium, okay.

DR. SHANK: And then use those as read across for the rest.

DR. MARKS: Are food additives?

DR. SHANK: Those two, yes. No systemic toxicology needs.

DR. HILL: So, while you're on that, talk about the adipose lipogranulomata that were observed with Calcium Stearoyl Lactylate.

DR. SHANK: Where are you?

DR. HILL: In the sub-chronic study. I've got Page 14, in my notes, if it's accurate.

MR. JOHNSON: Yes, it's 14.

DR. HILL: And part of my concern relates to, really, do we know there's -- the chemistry in this report, at the moment, is a disaster. And part of it is not knowing what the nature of the substance actually are, in some cases, that were tested. And it's not clear if that's better known, and understood, in the food additives uses or not.

But there was one place where it was discussed, the discrepancy between what might be there in food, based on the way, I believe, the Federal Register is written, versus what these substances actually are in practicality. I even question why did we name them as Alkyl Lactyl Lactate as opposed to just Alkyl Lactylate? Because lactylate is specific with a dimer of lactic acid to monomers; except that in production, they're doing production from lactate itself and getting in (inaudible) that has who knows exactly what distribution of lactate.

Maybe they're pulling out -- because we don't have but sketchy information, maybe they're pulling out, in some way, the dimeric. I think that was the sense that I got, is that the isolation process they're getting, actually, lactyl lactate, which is lactylate.

But it's clear that in some cases, these are being supplied as mixtures, so then the read across from dietary use.

Anyway. So, in terms of things that we observe systemically, these adipose granulomata were observed. And what I had was -- what did I have pertaining to that? I had, "which suggests that despite the rodent high gut biotransformation, something perhaps the entire order lactate polymers might be getting in." Those should probably bypass first-pass metabolism in the liver and go through chylomicron uptake, in which case they go straight into the bloodstream.

And in human blood, we don't hydrolyze the Stearoyl Lactylate, it seems; whereas, in rodent blood they hydrolyze quickly. Then we have a two-year dog study, but we don't know that the test substance in Reference 13 and 14 were the same. And I don't know where the dog study came from. It doesn't appear in Reference 13 or 14. So was that from a robust summary somewhere?

DR. MARKS: Ron Hill, you don't feel we could move on to -- I'm going to move an insufficient data announcement. I'd like to see sensitization data on the Sodium Stearyl Lactylate at 7 percent use concentration in leave-on. There was a guinea pig at like 1.5 percent, so there's a significant gap. Do you feel there are other needs besides the sensitization?

DR. HILL: I've got a list, so I'll just read them down. A lot of them relate to the chemistry and knowing what the substances are, number one, that are being tested for read across purposes. And number two, just because we don't know, necessarily, what they are and whether they do, in fact, relate to food.

We need to, first of all, clarify the Caproyl thing, because Caproyl should be C6, but it seems that they've got C10, in the dictionary; and the structure that's drawn has got a C10.

So C-A-P-R-O-Y-L is C6, not C10; that's a Hexanoyl. And even one of the ingredient supplier lists it as a C6. They say explicitly Hexanoyl. So, we need to get that cleaned up. If the dictionary is incorrect it needs to be fixed; but then that creates kind of a labeling nightmare, so who knows. That's an industry question.

Do we have a detailed concentration of use table, because I didn't find it in the packet? I'm not talking about the distilled version, I'm talking about the actual survey data. I didn't find it. Is it there and I missed it?

MR. JOHNSON: It should be there.

DR. MARKS: Page 23? I have on my --

DR. HILL: That's a table, isn't it, in the report? I'm not talking about the report table, I'm talking about the actual, this concentration in shampoo, this concentration in lipstick, this concentration -- you get what I'm saying.

DR. MARK: I mean, we usually have it at --

DR. HILL: I see the VCRP but it looks like there might be missing pages between 33 and 34,

where there's no table, but I'm not sure. Or did the survey data come back?

MR. JOHNSON: We do have the survey data.

DR. HILL: Okay, it's not in here. That was one of the things I was looking for in considering how much needs do we actually have. But what I wrote is -- we got for chemistry, back to the chemistry, Calcium Stearyl Lactylate, defined as a mixture of the calcium salts of Stearyl Lactylic acids, and its polymers, and minor amounts of calcium salts of other related acids. Manufactured by base catalyzed esterification of lactic acid and commercial stearic acid.

So, if you do the esterification with lactic acid, we would expect stearoyl esters of lactic acid, lactylic acid, and undoubtedly some higher order lactic acid polymers. Similarly, for the others. So, what's the composition of the commercial ingredients?

It's got, note under composition, the typical composition of the product of the neutralization process is approximately 50 percent stearoyl-mono-lactylate, 20 percent stearoyl di-lactylate, which means four lactate monomers, I presume. And 5 percent stearoyl tri-lactylate. Which would suggest, if that's correctly written, six lactate polymers, and trace amounts of the tetra. So, I'm not sure if it's written correctly in the first place, not necessarily by Wilbur, but by wherever the source is.

And the reason I ask about all this is, in terms of the chronic toxicology we don't have any skin ADME information. We don't know if we have a lactylate in the first place; does that get hydrolyzed in our skin? And the reason I concern myself with that is, does this thing become a membrane lipid? Because we've got a polar head group and a fatty acid tail. Because the more and more we know, again, about lipid grafts and membrane substructure, the more we have to worry about what happens if we accumulate strange looking lipids into our cell membranes in skin. And what does that do?

DR. MARKS: Bart do you have any comments about the chemistry?

DR. HELDRETH: I do.

DR. MARKS: I mean, Ron Hill, you bring up a lot of issues, but Ron Shank was reassured, as a read across, for these two food additives --

DR. HILL: And I would agree.

DR. MARKS: -- with calcium and sodium. So, I hear your concerns. And, obviously, tomorrow when we discuss it, you can bring it up. But Bart, the chemistry issue?

DR. HELDRETH: In consideration of the way the International Nomenclature folks look at the chain links, when they're talking about C10 they say Caproyl, for C8, they say Capryloyl. There's an extra Y --

DR. HILL: Capryloyl is C8, but Capryl, C-A-P-R-Y-L should be C10, Capryl. As in Capric Acid, as in C10.

DR. HELDRETH: The way that's it's commonly used in the dictionary, it's Capryloyl.

DR. HILL: That should refer to C6. And if that's not the case, then the dictionary is screwed up. I'll just be blunt about it.

DR. HELDRETH: Okay. So, what we're talking about are chemicals that are C10. That's the way that the dictionary have named it.

DR. HILL: Well, that's really problematic because, again, Capryloyl -- you can search in chemical abstracts and you'll see what I mean. It's always Hexanoyl. But Capryl, C-A-P-R-Y-L is C10, and Capryloyl is C8. We had somewhere in here where I found -- when I googled my way back, or went to one of the chemical registries, I believe, was that there was actually a supplier sheet that said Hexanoyl for the Capryloyl. Capryloyl/Hexanoyl. And that they were selling them for cosmetic use. So, there seems to be confusion that might relate to the dictionary.

DR. HELDRETH: Yeah, there may be some confusion in there.

DR. HILL: It doesn't matter that much except that if we have a C6 attached to a lactylate dimer -- and again, I have no information about skin penetration. And at some point I would have said, well, we've got a sort of a soap here. It's going to hang in the upper layers of skin, no worries mate. But then we've seen some things that are short chain linked with the polar group, and it's a carboxylic acid. If we can get salicylate across the skin, we can get this across the skin.

I'm concerned, not about systemic toxicology, although the Federal Register says the foodstuffs are supposed to be lactylate; which means two lactic acids tied together to make lactylic acid, and then you can make salts with that. The cosmetic situation seems to be disparate from that.

DR. MARKS: Well, I have a feeling this discussion is going to continue tomorrow, and perhaps the next time we see it. I'm going to move for insufficient data announcement tomorrow. That the need is sensitization data on the Sodium Stearoyl Lactylate at the highest use concentration, 7 percent. And then, the ingredients are okay, we agreed on that. Ron Shank, I'll mention how you use the two ingredients that are food

additives as read across, and we're not concerned about systemic toxicity. But Ron Hill, I'll also mention you're concerned about the chemistry and clarify that.

DR. HILL: And which one was it, that you want it for? Because I had sensitization flagged here. Was it the Capryloyl/Lauroyl?

DR. MARKS: No, I had the Sodium Stearoyl Lactylate. That's the one with the highest number of uses, 315; and it's the highest concentration at 7 percent. And I could use that for the others; there are two other ingredients with the highest concentration of 7 percent.

DR. HILL: The reason I ask question is because they list an EC3 for Sodium Caproyl/Lauroyl as 9.3 percent, and it's used up to 7 percent. So 7 percent is not 9.3 percent. So you would assume maybe 1 percent sensitization, at 7 percent, if it's an EC3 of 9.3 percent, if that LLNA translated to human data.

MR. JOHNSON: Dr. Marks, Sodium Stearoyl Lactylate is used at concentration up to 10 percent in rinse-off products, but up to 7 percent in leave-on.

DR. MARKS: And I always use the leave-on assay.

MR. JOHNSON: Leave on, okay.

DR. MARKS: Yeah. That's what I use as the high concentration. There is, with two of the other ingredients, some weak sensitization with a local lymph node assay, but those I wasn't as concerned as the one that I mentioned. And if we get it for the Sodium Lauroyl Lactylate, that would be fine. And if we get it for the Calcium Stearoyl Lactylate, that would be fine too. They're all 7 percent use concentration on leave-ons. But, I picked that one as the prototype. Any other comments?

MR. JOHNSON: Well, I think, Dr. Hill, you had a comment about a use concentration in a particular category, is that right?

DR. HILL: Well, what I was just saying was there -- for the sensitivity was -- no, my bigger question was we've got your table -- what I call the distilled table in the report. But not the original table where it shows, actually, what formulations -- our survey data is not in here.

MR. JOHNSON: I think a mistake was made, because the cover memo is there but the data are missing for it.

DR. HILL: Yeah, that was my point. And I'd use that if I wanted to drill down and see, well, all right this is used in this, or is it used in that. If it's lipstick, it's one thing; if it's hand cream, it might be another.

DR. HELDRETH: So, we'll make sure that data is patched in the next iteration.

DR. HILL: That would be great.

DR. MARKS: Okay. If no other comments, we'll move on to the next ingredient.

DR. HILL: I did have just a general comment; which is, on the search strategy you didn't list further details in this particular case. And that's one of the things I feel is my responsibility to look at, when I review this report, as much as anything else in there, is the details of the search strategy. That's just a general comment, while we have multiple people here; to make sure that that does get captured in the same manner, in the report -- or in the document we see.

MR. JOHNSON: Okay.

DR. MARKS: The next ingredient I have is the Polyaminopropyl Biguanide.

December 3-4, 2018 CIR Expert Panel Meeting – Full Panel

Alkanoyl Lactyl Lactyl Lactate Salts

DR. MARKS: So this is the first time we've seen these ten alkyl lactyl lactate salts, so it's a first review. We felt the ingredients were fine. And in this report, Ron Shank used the Calcium Stearoyl Lactylate and the Sodium Stearoyl Lactylate, which are food additives or feed additives, as I read across. There were no systemic toxicity needs. The irritation was mild, so we felt that was fine.

The question we had was, what's the sensitization? And I felt that we should see some sensitization data on the sodium stearoyl lactylate at 7 percent, which is the highest use concentration. There were some local lymph node assay alerts that this is a weak sensitizer. So, we would move that we had an insufficient data announcement for the sensitization data; and we can use sodium stearoyl lactylate at 7 percent as the need.

Then Ron Hill, when we get into the discussion, also wanted to clarify the chemistry of these ingredients. So, that's a motion, insufficient data announcement.

DR. BERGFELD: Belsito team?

DR. BELSITO: Not seconded.

DR. BERGFELD: You're not seconding? No. You want to make some comments?

DR. BELSITO: Yeah, again, what we've learned over the last 2008, ten years, is that you can't just do an HRIPT on the back and say, okay, it clears the back. Because then, if it's used in a dial, it'll sensitize. That's exactly what happened with methylisothiazolinone now, in wipes.

So, we know there's some evidence of weak sensitization; and I think, again, as with the salicylates, we need to say formulated to be non-sensitizing based upon a QRA, or another methodology. Because it's going to depend upon where this product is used. If it's used anogenital, it's going to be much more sensitizing than if it's used on the back. If it's used on shaved skin, it will be more sensitizing. So, methodologies like QRA look specifically where it is.

We've gotten into trouble with sensitizers by just looking at HRIPTs on backs, and saying, okay, it clears the back and so it's fine at 7 percent. Fine at seven percent on the back, but it may not be fine in a deodorant or in other cosmetic uses. I think, when we get these type of sensitization signals, we need to be aware that that level, that will sensitize, will vary depending upon where the product is used.

So, companies have to look at qualitative risk assessments or other methodologies as to where they're putting it, to determine what level is non-sensitizing. Our conclusion was safe for using cosmetics when formulated to be non-irritating and non-sensitizing, using a QRA or other methodologies.

DR. MARKS: I withdraw my motion and, Don, I like your reasoning. It's going to be interesting how often we now use that sort of conclusion, formulate to be non-irritating and non-sensitizing. But the reasoning's good, it needs to be captured in the discussions so we know the why, as with a number of the ingredients, we use sensitization data whether it was the HRIPT or a guinea pig max or that sort of thing. Okay.

DR. BERGFELD: Is that a motion?

DR. BELSITO: Yeah.

DR. BERGFELD: Did you make a motion?

DR. MARKS: Yeah. I withdraw my --

DR. BERGFELD: Excuse me. And are you seconding, Don's motion?

DR. MARKS: Second.

DR. BERGFELD: Thank you. Go ahead.

DR. HILL: Well, I still had other issues.

DR. MARKS: Yeah.

DR. BERGFELD: Okay.

DR. BELSITO: Yeah, I mean, there a few other issues in the discussion. But, I think that if something clears in LLNA at a hundred percent, if it clears a guinea pig maximization at huge levels, then there's no concern of sensitization, and then you're fine with that. But when you get signals of weak sensitizers, again, I think, the issue becomes where it's going to be used, and that will change the levels. And it's quite clear, and we've experienced many epidemics of allergic reactions, because we didn't realize that before. So, it's something that -- it's the newest evolution in evaluating sensitization for products that are put on the skin.

DR. BERGFELD: Ron Hill, did you have a comment?

DR. HILL: Did you have other things?

DR. BELSITO: Just in terms of we needed to have heavy metal boilerplate in there. Also, the aerosol boilerplate and the cosmetic use section needed to be inserted. In regard to your fact about food, the

presence of food, also in the discussion, you can point out that the mucous membrane use is extraordinarily low; so the amount that would be absorbed by applications in mucous membranes would be low as well. That would be another supporting argument.

DR. BERGFELD: Are you through, then, so I could call on Ron Hill?

DR. BELSITO: Yep, I'm through.

DR. BERGFELD: Ron Hill?

DR. HILL: We need some significant clarification of the chemistry here. Also, I would personally like to see what additional information we have about the biotransformation, the biohandling, of these substances. Because some of them are in the molecular weight range and the lipophilicity range. Grant you, they're carbocyclic acids, but in the free acid form, the LogP would allow dermal penetration and we've got -- I don't know that humans do, in fact, biotransform these lactyl lactylates, in particular, in skin. I've never encountered in biochemistry lactate dimers. And then we know that we have, based on the way these are made, in some cases, we have higher order. In fact, it's not even clear when we say -- where is it -- calcium stearoyl lactate is a mixture that includes the dimer but also tetramer, trimers.

Anyway, because it appears that the esterification is done with the lactate, where it's actually lactate itself under conditions where we get lactate esterifying itself.

There's a serious lack of chemistry, and we also have information that the stearoyl lactylate, which is a lactate dimer, is not significantly transformed as it persists in human blood, whereas in rodents that's not the case. Rodent blood, we see hydrolysis; in humans, we don't. So, that begs the question, if this stuff is in skin, we have a lipid tail and a polar head group, what happens if it accumulates in the lipid structures of the skin? Is this problematic or not?

For me, there were some serious unknowns. But I didn't have any structural hits for sensitization. Honestly, I wasn't worried about sensitization, because I rather doubted that that would likely happen with this set of ingredients.

Anyway, right now my concern is the clarification of the chemistry. What do we actually really have? And there was the whole capryloyl thing, which capryloyl is clearly C6, by chemical nomenclature, but apparently there's some concern in the dictionary. So, we might actually have -- and I found one cosmetic ingredient vendor that specifically said capryloyl, hexanoyl, which means C6. So, this two different chemicals, at least, maybe being sold under the same name, based on this confusion in the dictionary.

In getting to the bottom of, what do we actually have in this stuff? I mean, one of my roles on the panel, I think, is to try to answer the question whatever possible, what is this stuff? There's no reason to, then, necessarily assume that this stuff that's in the cosmetic formulations is the same as the stuff that's in foodstuffs. Plus, when you give something orally, our gut is made to process things that have lipids and polar things attached to it. That isn't necessarily the case in our skin, or our bloodstream, or anywhere else.

DR. BERGFELD: Thank you. Any more comments? Dan?

DR. LIEBLER: One point that Ron raised was about a metabolism. And so, the esterases are -- there are diverse esterases, and they have pretty liberal substrate specificities in some cases.

If you look at PDF, Page 13, under toxicokinetic study ADME, Calcium Stearoyl Lactylate, Ron mentioned the evidence of hydrolysis of the Calcium Stearoyl Lactylate and in vitro homogenates from rats, mice and guinea pigs. And that hydrolysis was also demonstrated using whole blood. I interpreted that as squirting the ingredient into blood and then looking at hydrolysis over time.

They said they didn't see it in human blood, no hydrolysis, but the next sentence is, "in a single sample of human duodenal mucosa, C14 Calcium Stearoyl Lactylate was rapidly hydrolyzed to stearic acid and lactic acid." I think it's how you do the experiment. It's a one-off, I admit. But that's constant with what, I think, we could reasonably expect in terms of hydrolysis and molecules like this.

DR. HILL: I noted that except, what does that mean in terms of higher order lactate esters, where we have more than two lactates strung together; which is clearly the case in very significant amounts in at least some of the sources of the ingredients, based on what was written?

DR. LIEBLER: Well, this is the ingredient, Calcium Stearoyl Lactylate.

DR. HILL: If you read the definition of that ingredient, it does not -- I agree with you, except that clearly stuff is being sold that is not that. And based on the method of manufacture, we're going to get things that are not that in there. They're not just trivial amounts or minor impurities in some cases, there's a significant amount of them.

So, if at least we get clarification about the chemistry, we still probably won't get them with the ADME data that's related to those higher molecular weight. But we could at least make commentary, intelligently, in the discussion based on what information we do have. We have concern about these as being other substances

that are not consistent with the structure of the title and ingredient; and then people can figure out what to do with that.

DR. LIEBLER: So, just to clarify what Ron's talking about here, is under the composition description it indicates that the Sodium Stearoyl Lactylate and Calcium Stearoyl Lactylate, are a mixture of the monolactic acid, the dilactic acid, and a little bit of the tri and a trace of the tetra.

DR. HILL: Let me interrupt for just a second. That's not even clear because lactylate is two lactates strung together. So, if you say, monolactylate, if that's accurate, then there are two lactates. If you say dilactylate, that should be four lactates strung together. If you say trilactates, six, and tetra are eight. I want to know, is that what we're looking at or not?

DR. LIEBLER: I agree there's ambiguity here. And in fact, the ambiguity goes back to the INCI names for these. Because INCI names used the lactylate, L-A-C-T-Y-L-A-T-E, and actually is the lactoyl lactate ester, so that's a double lactate. So, lactylate is the double lactate. So, what Ron's talking about, raising the question, are they counting by ones or twos?

DR. HILL: Exactly.

DR. LIEBLER: So, clarification of the composition would be good here; especially, because of the ambiguity between the INCI name and the actual chemical descriptive name. It would be easy to be mixed up seeing lactylate thinking that's, o-lactate.

DR. HILL: Yeah, it's based on what they did in the skin study; if it is in fact lactylate, then all should be well. Although, we could still make the comment that in human skin we know that there are long-chain esterases, and then other esterase that handle things smaller than C12. And so, I guess, Lauroyl, though, is the smallest one in here that we're dealing with, so that should still be okay.

DR. BERGFELD: Bart's going to make a comment here.

DR. BELSITO: I just wanted to mention that between now and the next iteration of this report, we can contact the folks over at the nomenclature committee, and see if they can provide some clarification on what was submitted to them, and what they feel these ingredients actually are.

DR. HILL: Because the other aspect of it is, when we are making inferences -- what we typically call read across -- we not only need to know what the ingredient is, but also what was tested and cleared for safety. If we're relying on use in foodstuff, where it seems pretty sure that lactylate is lactylate, monomer, more or less pure lactylate, seems pretty sure, then well and good. But that doesn't necessarily clear the chemicals, that are mixtures, that have other things in there.

DR. BERGFELD: Well, thank you for bringing that to our attention, and we'll get clarification. Any comments from Tom or Ron? Paul? Curt? Wilber? Come around.

MR. JOHNSON: Yes, I know Dr. Mark's team discussed the findings in the short term and a sub-chronic oral toxicity study, specifically, the increased liver weight and the lipogranulomata. So, should anything relating to that be included in the discussion?

DR. HILL: See if they picked that up in the other team. I don't remember that we came to any firm conclusion. We definitely did discuss it.

DR. BERGFELD: Paul?

DR. SNYDER: We briefly discussed it. It's only related to the high-dietary intake, and long-chain fatty acids. And so, it's not relative to cosmetic use.

DR. BERGFELD: Okay.

DR. BELSITO: And, again, we have very low use in the mucous membranes.

DR. BERGFELD: Jim.

DR. MARKS: Don, just sort of projecting ahead, for the future of the quantitative risk assessment to become now part of the conclusions. We're seeing it come up. If we had the sensitization data, on the highest concentration on a leave-on -- in this case, I mention the Sodium Stearoyl Lactylate -- is the panel going to do what we do with margin of safety?

Are we actually going to do a quantitative risk assessment, since you're concerned with body location; so that, ultimately, we could say, okay, it's safe? Or are we going to just have the conclusion based on a quantitative risk assessment and allow the formulators to calculate that? I'm just thinking ahead. Are we going to do the quantitative risk assessment when we have enough data on sensitization? This one I don't think we do, but if we did?

DR. BELSITO: I mean, personally, I think that's up to the formulators to be doing it. Our job is to alert them to the fact that it can be sensitizing, and to point them in the direction of means of assessing where their product is going to be used. A lot of that is really dependent upon other factors that we can't envision or control.

I think it also opens up the possibility that, for instance, if this were four years ago we would be doing quantitative risk assessment, which is now called QRA1. We've now realized that we need to consider cumulative exposure. It's not just your underarm deodorant, it's the soap you use before you put on the deodorant, it's the moisturizer you use.

So, there's now QRA2 that looks at cumulative exposure to a specific product, or a specific material chemical, and multiple different products that a consumer may use. There may be a QRA3, in another three years, and we've now set limits based on old methodologies. So, I don't think we should be setting limits. We should just be just pointing out that they need to be assessing, based upon the current state of the art for assessing sensitization for a specific potential sensitizer in different body areas.

DR. HILL: The other thing that I would point out is that Lauroyl also used in leave-ons, up to 7 percent, and that would be the more dermally penetrable molecule. So, if you had stearoyl, you might not still get the strongest signal.

DR. MARKS: Both are at seven.

DR. BERGFELD: All right. Monice?

MS. FIUME: Can I ask a question to help inform the discussion, as we go into the QRA path. Looking at the use table, it looks like one ingredient is used in one deodorant without a concentration of use. Is that the concern, as Wilber tries to craft language for the discussion, or is the concern that it's a potential sensitizer and it's a cumulative use? Because he's going to need some type of language to understand why the QRA is part of the conclusion, because we do state as given in this safety assessment.

DR. BELSITO: I think he can point out that we don't have a concentration of use in an underarm deodorant, and that's an area that's particularly prone to sensitization. We don't have the capability, since we don't have access to the Crème data, to look at cumulative exposures to calculate these. The critical thing, when you're calculating it, is not only the area of the body that it's applied to, but also the expected cumulative exposure based upon consumer use. We don't have that data. We don't have cumulative data. Bart looked into it, and it was prohibitively expensive to purchase the Crème data.

DR. BERGFELD: It sounds to me like this is going to be a continued discussion on all ingredients in the future. And we might want to develop some language around this for our discussions.

DR. BELSITO: Yeah. I think after -- we all learned from methylisothiazolinone. It looked great when it was used on the back.

DR. BERGFELD: Right. Okay. Wilber?

MR. JOHNSON: Given the panel's conclusion relating to irritation and sensitization potential, what information relating to irritation and sensitization should be included in the discussion?

DR. BELSITO: Well, the fact that there were positive LLNAs. There were some positive animal data. And the fact that there's evidence of irritation that was noted. As we know, it really depends upon, with irritation, what else it's formulated in. It's very difficult for us to predict irritation.

If you take Salicylic Acid, and you make a salt of it, it's not irritating. If there's not a salt, it is irritating. Irritation is formulation specific. When we start seeing irritant signals, I think we need to be saying when formulated to be non-irritating.

MR. JOHNSON: What are we going to say about sensitization?

DR. BELSITO: Again, there are positive LLNA data. There's some positive animal data, so there's evidence of -- based on just the LLNA data, there's evidence of weak sensitization. And we realize that sensitization, and the induction of sensitization, can vary depending upon where the product is applied. Whether it's applied to the anogenital area, to the shaved underarm, to a shaved face; that all has different factors, that are put into the QRA to assess for those areas, that reduce the concentrations that should be used there.

DR. BERGFELD: It sounds like we have a beginning.

DR. MARKS: Also the product. Because with methylisothiazolinone, it was baby wipes that were really -- so it's the product.

DR. BELSITO: But you know, it's the area. It's anogenital; so it's where the product is used. It also created some issues with suntan lotions. Interestingly, again, probably because it was applied not just to the back, but to multiple other areas like the neck and the face.

DR. BERGFELD: So, if we can come back to the question; if we've decided the discussion is over, and the editorial changes in the discussion points, you're clear on those, Wilber?

MR. JOHNSON: Yes.

DR. BERGFELD: Okay. I need to call the question. All those hand in favor. Unanimous. So, this is going out as a safe.

DR. SNYDER: I want to ask Don a question I just thought of. So, in requesting, by methodology, QRA, do we need to specify QRA1 or QRA2?

DR. BELSITO: I don't think we should specify the methodology. My language was using QRA or other accepted methodologies. We're not going to force the QRA on people who don't want to use it; it's what the fragrance industry is using. But, if there are other methodologies that they want to use, that's fine too.

DR. HELDRETH: Yeah, our conclusion thus far, in these types of instances, is safe and formulated to be non-sensitizing, which may be determined by a QRA.

DR. BERGFELD: Any other additive comments? Ron Hill?

DR. HILL: I want to go back to that biotransformation thing, for just a minute, because it just re-registered on me what we saw. It didn't stun me that we had biotransformation, in the gastric mucosa system, because our gut is made to digest things that have lipids attached to polar substances. The fact that we saw that in the gut, but not in blood in humans, actually makes matters worse for if we have something dermally absorbed; because if we don't do something with that substance in the skin, that means that the oral toxicology data might be irrelevant; assuming that rodents do the same thing, and that we can only make inferences from dermal.

So, I wasn't concerned with systemic toxicity, though, in this case, but just what would happen if this stuff builds up in the skin and there's no way for the skin to hydrolyze that ester over time. If there were sensitization, that would be a sentinel, but I'm not sure these things have a good mechanism to sensitize. I'm not sure it's a good sentinel, even, in that case.

So, if there is further information, while we're out on insufficiency, this is after the vote, so it’s sort of informal. If we get further information about anything that's known about the biohandling of these substances, besides in the gut, that would be great.

DR. BERGFELD: I think this will be reflected in the minutes and perhaps and in the public announcement, that there was some concern and discussion over this. We also did vote on a safe conclusion.

DR. HILL: We did vote, yeah.

DR. BERGFELD: And we also are going to clarification on the chemistry. Is that correct? Anything else? All right. We're going to move on, after that hardy discussion, to the next report, which is fatty acids, fatty acid salts. Dr. Belsito.

Safety Assessment of Alkanoyl Lactyl Lactate Salts as Used in Cosmetics

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The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This 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) reviewed the safety of 10 alkanoyl lactyl lactate salts. These ingredients have the surfactant function in cosmetics in common. The Panel reviewed data relevant to the safety of these ingredients, and concluded that these 10 ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-irritating and non-sensitizing, which may be based on a quantitative risk assessment (QRA).

INTRODUCTION

The safety of the following ten alkanoyl lactyl lactate salts as used in cosmetics is reviewed in this Cosmetic Ingredient Review (CIR) safety assessment.

Calcium Stearoyl Lactylate
Sodium Behenoyl Lactylate
Sodium Caproyl Lactylate
Sodium Caproyl/Lauroyl Lactylate
Sodium Cocoyl Lactylate
Sodium Cupheoyl Lactylate
Sodium Isostearoyl Lactylate
Sodium Lauroyl Lactylate
Sodium Oleoyl Lactylate
Sodium Stearoyl Lactylate

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), all of these ingredients are surfactants, while other functions are reported for some of the ingredients, as indicated in Table 1.[1] Functioning as an antifungal or antidandruff agent, as some of these ingredients are reported to do, is not considered a cosmetic function in the United States (US) and, therefore, the CIR Expert Panel (Panel) does not evaluate safety in relation to either of those uses.

This safety assessment includes relevant published and unpublished data for each endpoint that is evaluated. Published data are 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.

CHEMISTRY

Definition and General Characterization

Alkanoyl lactyl lactates (i.e., alkanoyl lactylates) are the carboxylic acid salts of diesters that are formed between a fatty acid group and two equivalents of lactic acid.[2] The generic structure of alkanoyl lactyl lactates is presented below. Like other anionic emulsifiers/surfactants, the properties of these ingredients result from the diametrically opposed lipophilic (fatty acid) tail and the hydrophilic (lactylate) head. The definitions and structures of the alkanoyl lactyl lactate salts are presented in Table 1.[1]

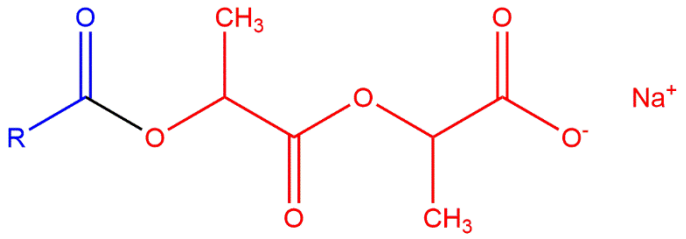


Figure 1. Generic structure of alkanoyl lactyl lactates

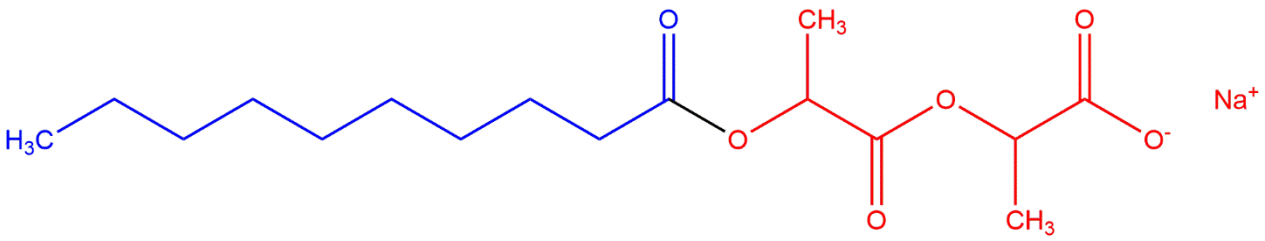


Figure 2. Example structure of an alkanoyl lactyl lactate, Sodium Caproyl Lactylate

Chemical and Physical Properties

Alkanoyl lactyl lactates hydrate readily in water at ambient temperature.[3] Compositions comprising a greater proportion of free acids are more soluble in fatty products, and have a slower rate of hydration. Conversely, compositions comprising a greater proportion of fully deprotonated salt forms are less soluble in fatty products, and have a faster rate of hydration. Furthermore, the calcium salt, Calcium Stearoyl Lactylate, hydrates more slowly than the respective sodium salt, Sodium Stearoyl Lactylate. These ingredients vary in formula weights from as small as 338 Da for Sodium Caproyl Lactylate (315 Da without the sodium cation) to as large as 507 Da for Sodium Behenoyl Lactylate (484 Da without the sodium cation). Calcium Stearoyl Lactylate technically has the highest formula weight (895 Da; 855 Da without the calcium cation), but this is an artifact of the $^{2+}$ oxidation state of calcium and 2 equivalents of stearoyl lactylate needed to balance this salt formula (i.e. each stearoyl lactylate is only 428 Da). Properties of alkanoyl lactyl lactate salts are presented in Table 2.

Method of Manufacture

Calcium Stearoyl Lactylate

According to one food additive supplier, Calcium Stearoyl Lactylate (defined as a mixture of the calcium salts of stearoyl lactylic acids and its polymers and minor amounts of calcium salts of other related acids) is manufactured by base-catalyzed esterification of lactylic acid and commercial stearic acid.[4] However, the *Dictionary* describes Calcium Stearoyl Lactylate as the calcium salt of the stearic acid ester of lactyl lactate (i.e., no indication of polymers or other acids provided).

Sodium Isostearoyl Lactylate

According to one method, Sodium Isostearoyl Lactylate is the reaction product of isostearic acid with lactic acid in the presence of sodium hydroxide.[5]

Sodium Stearoyl Lactylate

According to one food additive supplier, Sodium Stearoyl Lactylate (defined as a mixture of the sodium salts of stearoyl lactylic acids and its polymers and minor amounts of sodium salts of other related acids) is manufactured by base-catalyzed esterification of lactic acid and commercial stearic acid.[4] However, the *Dictionary* describes Sodium Stearoyl Lactylate as the sodium salt of the stearic acid ester of lactyl lactate (i.e., no indication of polymers or other acids).

Composition

Sodium Stearoyl Lactylate and Calcium Stearoyl Lactylate

As noted above, when used as food additives, Sodium Stearoyl Lactylate and Calcium Stearoyl Lactylate are manufactured using the same process.[4] The distribution of the components in each is dependent upon the relative proportion of lactylic acid, fatty acid and the amount of sodium/calcium salt that is used in the neutralization process. The typical composition of the product of the neutralization process is approximately 50% stearoyl-mono-lactylate, 20% stearoyl-di-lactylate (equivalent to structure of Sodium Stearoyl Lactylate or Calcium Stearoyl Lactylate), 5% stearoyl-tri-lactylate and trace amounts of stearoyl-tetra-lactylate. Other components may include sodium/calcium salts of fatty acids (depending on the ingredient, i.e., if the ingredient is Sodium Stearoyl Lactylate or Calcium Stearoyl Lactylate) or free fatty acids (15 - 20%), non-neutralized stearoyl lactylic acid, sodium/calcium lactate, and free lactic acid or polymers of lactic acid. Additionally, the actual fatty acid profile of Sodium Stearoyl Lactylate and Calcium Stearoyl Lactylate will depend upon the source of the fatty acids. However, the *Dictionary* describes Sodium Stearoyl Lactylate and Calcium Stearoyl Lactylate as the salts of the stearic acid ester of lactyl lactate (i.e., no indication of stearoyl-mono-lactylate, stearoyl-tri-lactylate, or stearoyl-tetra-lactylate).

Impurities

Calcium Stearoyl Lactylate

The *Food Chemicals Codex* specifications for Calcium Stearoyl Lactylate are as follows: lead (not more than 2 mg/kg), acid value (between 50 and 86), ester value (between 125 and 164), calcium content (between 4.2% and 5.2%), and total lactic acid (between 32% and 38%).[6] According to European Commission regulations, specifications relating to the purity of Calcium Stearoyl Lactylate are as follows: calcium (not less than 1% and not more than 5.2%), ester value (not less than 125 and not more than 190), acid value (not less than 50 and not more than 130), total lactic acid (not less than 15% and not more than 40%), arsenic (not more than 3 mg/kg), lead (not more than 2 mg/kg), mercury (not more than 1 mg/kg), and cadmium (not more than 1 mg/kg).[7]

Sodium Stearoyl Lactylate

The *Food Chemicals Codex* specifications for Sodium Stearoyl Lactylate are as follows: lead (not more than 2 mg/kg), acid value (between 60 and 80), ester value (between 120 and 190), sodium content (between 3.5% and 5%), and

total lactic acid (between 23% and 34%).[6] According to European Commission regulations, the following specifications relate to the purity of Sodium Stearoyl Lactylate: sodium (not less than 2.5% and not more than 5%), ester value (not less than 90 and not more than 190), acid value (not less than 60 and not more than 130), total lactic acid (not less than 15% and not more than 40%), arsenic (not more than 3 mg/kg), lead (not more than 2 mg/kg), mercury (not more than 1 mg/kg), and cadmium (not more than 1 mg/kg).[4]

USE

Cosmetic

The safety of the alkanoyl lactyl lactate salts is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database.[8] Use concentration 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, Sodium Stearoyl Lactylate is reported to be used in 358 cosmetic products (334 leave-on and 24 rinse-off products).[8] Of the alkanoyl lactyl lactate salts that are being reviewed in this safety assessment, this is the greatest reported use frequency. The results of a concentration of use survey conducted by the Council in 2017 indicate that Sodium Lauroyl Lactylate is being used at maximum use concentrations up to 10% in skin cleansing products (rinse-off products).[9] Calcium Stearoyl Lactylate, Sodium Lauroyl Lactate, and Sodium Stearoyl Lactylate are being used at maximum use concentrations up to 7% in leave-on products (tonics, dressings, and other hair grooming aids); this is the highest maximum use concentration in leave-on products that is being reported for the alkanoyl lactyl lactate salts. The highest maximum use concentration in leave-on cosmetic products that are applied directly to the skin is 6.1% for Sodium Lauroyl Lactylate in body and hand products that are not sprayed. Further use data are presented in Table 3.

According to VCRP and Council survey data, 3 of the 10 alkanoyl lactyl lactate salts reviewed in this safety assessment are not reported to be in use (Table 4).

Cosmetic products containing alkanoyl lactyl lactate salts may be applied to the skin or, incidentally, may come in contact with the eyes (at maximum use concentrations up to 0.2%, for Sodium Stearoyl Lactylate in eye lotions). Similarly, products containing these ingredients may incidentally come in contact with mucous membranes (at maximum use concentrations up to 3.5%, for Sodium Isostearoyl Lactylate in bath soaps and detergents). The highest maximum use concentration of alkanoyl lactyl lactate salts in products that may be incidentally ingested is 0.00011% (for Sodium Stearoyl Lactylate in lipsticks). Products containing alkanoyl lactyl lactate salts 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.

The alkanoyl lactyl lactate salts reviewed in this safety assessment are not included on the European Union's list of substances that are restricted or list of substances that are prohibited in cosmetic products.[10]

Non-Cosmetic

Calcium Stearoyl Lactylate and Sodium Stearoyl Lactylate

Both Calcium Stearoyl Lactylate and Sodium Stearoyl Lactylate have been known to have a dough strengthening effect in the process of bread making (high-protein breads).[11] Both salts can form a complex with gluten to stabilize the gluten-network in dough. It has been noted that the dough strengthening effect of these salts may be due to formation of this complex.

The US FDA has determined that Calcium Stearoyl Lactylate (defined as a mixture of calcium salts of stearoyl lactylic acid and minor proportions of other calcium salts of related acids) may be used safely as a direct food additive, provided that the specifications defined in the *Food Chemicals Codex* are met [21 CFR 172.844]. Furthermore, the FDA has established limits for this ingredient in food ranging from 0.05% to 0.5%, depending on the food product type. The FDA has also established a limit of 0.5 parts for each 100 parts by weight of flour for Calcium Stearoyl Lactylate in yeast-leavened bakery products and prepared mixes for yeast-leavened bakery products.

The FDA has also determined that Sodium Stearoyl Lactylate (defined as a mixture of sodium salts of stearoyl lactylic acids and minor proportions of sodium salts of related acids) may be used safely as a direct food additive, provided that it meets the specifications of the *Food Chemicals Codex* [21 CFR 172.846]. (The *Food Chemicals Codex* specifications for Sodium Stearoyl Lactylate are stated in the section on Impurities.) Furthermore, the FDA has established limits for this

ingredient in food ranging from 0.2% to 0.5%, depending on the food product type. The FDA has also established a limit of 0.5 parts for each 100 parts by weight of flour for Sodium Stearoyl Lactylate in baked products, pancakes, and waffles.

Following a request by the European Commission, the Panel of Food Additives and Nutrient Sources added to Food (ANS) was asked to issue a scientific opinion on the safety of Sodium Stearoyl Lactylate and Calcium Stearoyl Lactylate when used as food additives.[4] The Panel concluded that based on the no-observed-adverse-effect-level (NOAEL) of 2200 mg/kg body weight/day Sodium Stearoyl Lactylate that was derived from a one-year oral toxicity study in rats and an uncertainty factor of 100, an acceptable daily intake (ADI) of 22 mg/kg body weight/day for Sodium Stearoyl Lactylate and Calcium Stearoyl Lactylate, either singly or in combination, can be established. The 1-year oral study is summarized in the section on Chronic Toxicity.

TOXICOKINETIC STUDIES

Dermal Penetration

Data on the dermal penetration of the alkanoyl lactyl lactate salts reviewed in this safety assessment were not found in the published literature, nor were these data submitted.

Absorption, Distribution, Metabolism, and Excretion

In Vitro

Calcium Stearoyl Lactylate

The hydrolysis of [^{14}C]-Calcium Stearoyl Lactylate, radiolabeled at the lactylate moiety, was demonstrated in vitro using liver homogenates from rats, mice and guinea pigs.[12] [^{14}C]-Calcium Stearoyl Lactylate was rapidly hydrolyzed to lactic acid and stearic acid. Hydrolysis was also demonstrated using whole blood from rats and mice, but no significant hydrolysis of Calcium Stearoyl Lactylate was detected using human blood. Also, in a single sample of human duodenal mucosa, [^{14}C]-Calcium Stearoyl Lactylate was rapidly hydrolyzed to stearic acid and lactic acid.

Animal

Oral

Calcium Stearoyl Lactylate

The absorption, metabolism, tissue distribution and excretion of Calcium Stearoyl Lactylate was studied using groups of 4 male Tuck TO mice and groups of 4 male Dunkin-Hartley guinea pigs.[12] A single oral dose of an aqueous suspension of [^{14}C]-Calcium Stearoyl Lactylate (90 or 900 mg/kg body weight) was administered by gavage. Radioactivity was determined in exhaled air, urine, feces, liver, kidneys, heart, lungs, spleen, testes, and in the gastrointestinal tract. Following oral administration, rapid absorption of radioactivity from the gastrointestinal tract was observed in mice as well as in guinea pigs. More than 50% of the applied radioactivity was exhaled as $^{14}CO_2$ within 7 h. In both species, ~80% of the applied dose was exhaled as $^{14}CO_2$ within 48 h. Most of the remaining radioactivity was excreted in the urine within 24 h after dosing. Only minor amounts were detected in the feces of both species. No relevant differences were detected between the 90 and 900 mg/kg doses of [^{14}C]-Calcium Stearoyl Lactylate. Approximately 2 % (in mice) or 6 % (in guinea pigs) of the administered dose remained in the tissues, mainly in the liver and gastrointestinal tract. Only traces of radioactivity were found in other organs (kidneys, lungs, testes, spleen, and heart). Thin layer chromatography of the urine of mice and guinea pigs indicated that lactic acid is a metabolite of Calcium Stearoyl Lactylate. Furthermore, the authors suggested that the additional radioactivity in the urine of treated animals is lactylate (i.e., without the stearic acid residue).

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

Calcium Stearoyl Lactylate

In an acute oral toxicity study involving male rats (strain not stated), an oral LD_{50} of 25 g/kg body weight was reported for Calcium Stearoyl Lactylate.[2] Details relating to the test protocol were not included.

Sodium Isostearoyl Lactylate

The acute oral toxicity of Sodium Isostearoyl Lactylate was evaluated using white rats (number not stated).[5] Administration of a single oral dose was followed by a 14-day observation period. An LD_{50} of > 6.1 g/kg was reported.

Sodium Lauroyl Lactylate

In an acute oral toxicity study in which male rats (number not stated) were dosed orally with Sodium Lauroyl Lactylate, the LD_{50} was 6.81 g/kg.[2] The test protocol was not stated.

The acute oral toxicity of Sodium Lauroyl Lactylate was also evaluated using male and female rats (numbers and strains not stated).[13] The doses administered orally (dosing method not stated) ranged from 2.4 g/kg to 6 g/kg. Additional details were not included. The oral LD_{50} was estimated to be 4.88 g/kg.

Sodium Stearoyl Lactylate

In an acute oral toxicity study involving male rats (strain not stated), an oral LD_{50} of 25 g/kg body weight was reported for Sodium Stearoyl Lactylate.[2] Details relating to the test protocol were not included.

Short-Term, Subchronic, and Chronic Toxicity Studies

The short-term, subchronic, and chronic toxicity studies on alkanoyl lactyl lactate salts that are summarized below are presented in more detail in Table 5.

Sodium Caproyl/Lauroyl Lactylate (25 µl, in acetone-olive-oil (AOO) vehicle) was applied to the ears of 4 mice of the CRL:NMRI BR strain at a concentration of 25% or 50% on 3 consecutive days.[13] There was no evidence of systemic toxicity. Local lymph node assay (LLNA) results are presented in the section on Sensitization. Calcium Stearoyl Lactylate was evaluated in short-term oral toxicity studies at dietary concentrations ranging from 0.5% to 12.5%.[14] Groups of up to 32 rats were tested. Increased liver weight was observed at concentrations of 2% and 12.5%, but not at 0.5% (43-day feeding study), 5% and 7.5% in the diet (1-month feeding study), and at 5% in the diet (4-week feeding study). However, in other feeding studies at 5% in the diet (27 days, 32 days, and duration unspecified), liver weight/histology was normal. Kidney histology was normal in a feeding study on 0.5% Calcium Stearoyl Lactylate in which the duration was not specified. In short-term feeding studies on Sodium Stearoyl Lactylate, a transient increase in liver weight was observed in 20 rats fed 5% in the diet for 28 days, and organ weights were normal in a dog fed up to 15% in the diet for 1 month.

The subchronic oral toxicity of Calcium Stearoyl Lactylate was evaluated in a study in which groups of 10 male and 10 female rats were fed dietary concentrations of 0.5%, 5%, and 12.5% for 98 days.[14] There was no evidence of histological abnormalities in internal organs, but lipogranulomata in adipose tissue were detected at the 12.5% concentration. Relative weights of the liver, spleen, and brain were also increased after feeding with 12.5% Calcium Stearoyl Lactylate. The Joint FAO/WHO Expert Committee on Food Additives noted that the appearance of lipogranulomata and increased liver weight are related to excessive intake of abnormal proportions of long-chain fatty acids. Groups of 10 male and 10 female rats (strain not stated) were fed Sodium Stearoyl Lactylate in the diet at concentrations of 0.5%, 5%, and 12.5% for 102 days. The results of gross and histopathological evaluations were normal.

In a chronic study, groups of 5 rats were maintained on diets containing 8 to 22% Calcium Stearoyl Lactylate for periods of up to 6 months.[14] Mortality was high (number of deaths not reported) at concentrations of $\geq$ 20%. Relative liver weights were normal at a saturated to unsaturated (S:U) fatty acid ratio of 0.6, but increased with higher ratios in the absence of histopathological abnormalities. When the experiment was repeated using 40 male and 40 female rats fed 25% Calcium Stearoyl Lactylate in the diet, all of the animals developed severe lipogranulomata. In a 1-year chronic oral toxicity study, groups of 60 Wistar rats were fed a basal diet that yielded doses of Sodium Stearoyl Lactylate up to 2214 mg/kg/day (males) and 2641 mg/kg/day (females).[15] No treatment-related toxic effects were observed, and NOAELs of 2214 mg/kg/day and 2641 mg/kg/day were reported for males and females, respectively. Results relating to tumorigenicity in this study are included in the section on Carcinogenicity.

There were no test substance-related gross or microscopic changes in 4 Beagle dogs fed a diet containing 7.5% Calcium Stearoyl Lactylate for 2 years.[14]

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY

Data on the developmental and reproductive toxicity of the alkanoyl lactyl lactate salts reviewed in this safety assessment were not found in the published literature, and unpublished data were not submitted.

GENOTOXICITY STUDIES

In Vitro

Calcium Stearoyl Lactylate

The genotoxicity of Calcium Stearoyl Lactylate (in benzene), with and without metabolic activation, was evaluated in the Ames test using the following *Salmonella typhimurium* strains: TA92, TA94, TA98, TA100, TA1535, and TA1537.[16] Doses of the test substance at up to 300 µg/plate were tested. Cytotoxicity data on the test substance were not included. Calcium Stearoyl Lactylate was non-genotoxic with and without metabolic activation.

In a chromosome aberrations test involving a Chinese hamster fibroblast cell line, the genotoxicity of Calcium Stearoyl Lactylate (in ethanol) was evaluated at concentrations up to 63 µg/ml (highest non-cytotoxic dose) without metabolic activation.[16] One hundred metaphases per concentration were analyzed for polyploid cells and structural chromosomal aberrations. Chromosome and chromatid gaps were included in the evaluation. Calcium Stearoyl Lactylate did not cause polyploidy or clastogenic effects.

Sodium Caproyl/Lauroyl Lactylate

The genotoxicity of Sodium Caproyl/Lauroyl Lactylate (in dimethyl sulfoxide (DMSO)) was evaluated in the Ames test using the following *S. typhimurium* strains, with and without metabolic activation: TA97a, TA98, TA100, TA102, and TA1535.[13] The test substance was tested at doses up to 502 µg/plate, considering that doses of 1500 and 5000 µg/plate were cytotoxic. Water and DMSO served as the negative and solvent controls, respectively. The positive controls were: sodium azide, benzo[a]pyrene, 4-nitro-*O*-phenylenediamine, and 2-aminoanthracene. Sodium Caproyl/Lauroyl Lactylate was non-genotoxic in all of the bacterial strains that were tested. The positive controls were genotoxic.

In Vivo

In vivo genotoxicity data on the alkanoyl lactyl lactate salts reviewed in this safety assessment were not found in the published literature, and unpublished data were not submitted.

CARCINOGENICITY STUDIES

Sodium Stearoyl Lactylate

As described earlier, a 1-year chronic oral toxicity study was performed in accordance with Organization for Economic Co-operation and Development (OECD) Test Guideline (TG) 452 using 3 groups of 60 rats (30 males and 30 females per group) that were fed a basal diet that yielded mean daily Sodium Stearoyl Lactylate intakes of 558, 1115, and 2214 mg/kg/day (males) and 670, 1339, and 2641 mg/kg/day (females).[15] The corresponding basal diet concentrations were 1.25%, 2.5%, and 5%, respectively. The negative control group was fed basal diet only. At histopathological examination, the incidence of endometrial stromal polyps in the uterus was reported as follows: 1 control female rat, 2 female rats fed 1.25% Sodium Stearoyl Lactylate in the diet, 6 female rats fed 2.5% in the diet, and 6 female rats fed 5% in the diet. However, these data lack statistical significance, and there is an absence of biological evidence to suggest a mechanism for the slightly higher incidence in the groups fed 2.5% and 5%. Furthermore, a comparison of these data with historical incidences of this tumor type (up to 10 % in control rats of 1 year studies in the laboratory conducting this study) demonstrated that endometrial stromal polyps are common in rats of this strain and age. It was concluded that the endometrial polyps observed in females fed Sodium Stearoyl Lactylate in the diet were not treatment-related.

OTHER RELEVANT STUDIES

Protein Binding

Sodium Stearoyl Lactylate

Sodium Stearoyl Lactylate was mixed with gluten (protein in wheat, barley, and rye) in the presence of water.[17] Approximately 49% of the Sodium Stearoyl Lactylate remained bound until it was released by protease digestion of the protein. Details relating to the protocol for this experiment were not included. However, using a Tissue Metabolism Simulator Skin Sensitization model (TIMES-SS), it was determined that Sodium Lauroyl Lactylate is a non-binder to skin proteins, despite being a weak sensitizer in the LLNA (see Sensitization section).[18] TIMES-SS is defined as an expert system describing structure-toxicity and structure-metabolism relationships through a number of transformations simulating skin metabolism and interaction of the generated reactive metabolites with skin proteins.

DERMAL IRRITATION AND SENSITZATION STUDIES

The skin irritation and sensitization studies summarized below are presented in detail in Table 6

Irritation

Sodium Caproyl/Lauroyl Lactylate was considered non-corrosive when the irritation/corrosive potential of this ingredient was evaluated using a tissue model that consisted of human-derived epidermal keratinocytes (EpiDerm® tissue model).[13] The skin irritation potential of alkanoyl lactyl lactate salts has been evaluated in the following experiments involving albino rabbits:[2] undiluted Calcium Stearoyl Stearate (nonirritating), 10% Sodium Lauroyl Lactylate (nonirritating), and undiluted Sodium Stearoyl Lactylate (nonirritating; primary irritation index (PII) = 0.5 in 2 studies).[2,19] Sodium Caproyl/Lauroyl Lactylate (in AOO vehicle) caused erythema and an increase in ear thickness in 4 mice (CRL:NMRI BR strain) when tested at concentrations of 25% and 50%.[13] In a skin irritation test on Sodium Isostearyl Lactylate involving 6 albino rabbits, the PII was 7.17 (severe irritation) for the undiluted ingredient and 1.13 (slight irritation) for 15% Sodium Isostearyl Lactylate.[5]

The skin irritation potential of Sodium Stearoyl Lactylate was evaluated using 51 subjects.[20] Twenty-five and 26 subjects were patch tested with 2% and 5% Sodium Stearoyl Lactylate in petrolatum, respectively. Details relating to the test protocol were not included. Sodium Stearoyl Lactylate was classified as having skin irritation potential. A diluted hair styling product (Calcium Stearoyl Lactylate effective concentration = 2.5%) was classified as a skin irritant in a study involving 54 subjects.[21] In 4 separate skin irritation studies, each involving 50 subjects, a hair molding cream containing 7% Calcium Stearoyl Lactylate was classified as non-irritating to the skin [22,23,24,25]

Sensitization

The skin toxicity of Sodium Stearoyl Lactylate was investigated using reconstructed human epidermis (RHE) and detection of the inflammation markers interleukin (IL)-1α and IL-8.[26] Sodium Stearoyl Lactylate was predicted to be an allergen based on the results of this assay. The LLNA was used to evaluate the sensitization potential of Sodium Caproyl/Lauroyl Lactylate and Sodium Lauroyl Lactylate using the following test concentrations (in AOO vehicle): 2.5%, 5%, 10%, 25%, or 50%.[13] Sodium Caproyl/Lauroyl Lactylate was classified as a weak-moderate sensitizer (EC3 = 12.4%; EC3 = 9.3%),[13] and Sodium Lauroyl Lactylate was classified as a weak sensitizer (EC3 = 15%).[27,28] An EC3 of 15% was also reported for a Sodium Lauroyl Lactylate trade name material in the LLNA.[29] Sodium Lauroyl Lactylate (challenge concentration = 0.5%; injection and dermal induction doses not stated) was classified as a weak sensitizer in the guinea pig maximization test (10 guinea pigs).[27] A silicone antifoam emulsion containing Sodium Stearoyl Lactylate (75% dilution; effective test concentration = 1.5 %) Sodium Stearoyl Lactylate) was a non-sensitizer in guinea pigs.[30]

Computational Analyses/Predictions

The modeling of skin sensitization data on a number of diverse compounds, including data on Sodium Stearoyl Lactylate, and calculated descriptors was performed to develop multiple predictive classification models.[31] The following 2 automated procedures were used to select significant and independent descriptors in order to build the models: 1) D-optimal design to select optimal members of the training and test sets and 2) k-Nearest Neighbor classification (kNN) method along with Genetic Algorithms (GA-kNN Classification). The EC3 values (from LLNAs) of the compounds were ranked quantitatively according to their potencies. Class 1 signified extreme/strong/moderate sensitizers (EC3 < 10%) and Class 2 signified weak/non-sensitizers (EC3 ≥ 10%). Sodium Stearoyl Lactylate was identified as a Class 2 sensitizer, and the LLNA data on this chemical are included in the preceding section. Of the 5 models developed, 4 placed Sodium Stearoyl Lactylate in Class 2 and 1 placed the chemical in Class 1. Thus, the consensus prediction based on the models 1-5 was Class 2.

OCULAR IRRITATION STUDIES

In Vitro

Sodium Caproyl/Lauroyl Lactylate

The ocular irritation potential of Sodium Caproyl/Lauroyl Lactylate was evaluated using the bovine corneal opacity and permeability test method for identifying ocular corrosives and severe irritants (OECD TG 437).[13] Corneas were exposed to the test substance (750 µl; 10% solution diluted in 0.9% sodium chloride solution) for 10 min, and exposure was followed by rinsing with and without phenol red. Exposure was followed by a 2-h observation period. A mean in vitro irritation score (for cornea) of 46.308 for the 10% solution was reported, classifying the solution as non-corrosive.

Animal

Calcium Stearoyl Lactylate, Sodium Lauroyl Lactylate, Sodium Stearoyl Lactylate, and Sodium Isostearoyl Lactylate

In an ocular irritation study involving 6 albino rabbits, Sodium Isostearoyl Lactylate (undiluted or 15% concentration, 0.1 ml) was instilled into one eye.[5] Ocular reactions were scored at 24 h, 48 h, and 72 h post-instillation. The undiluted ingredient was irritating to the eyes, whereas 15% Sodium Isostearoyl Lactylate was not. When other alkanoyl lactyl lactate salts were tested according to the same procedure using groups of 6 albino rabbits, the results were as follows: undiluted Calcium Stearoyl Lactylate (nonirritating), 10% Sodium Lauroyl Lactylate (nonirritating), and undiluted Sodium Stearoyl Lactylate (nonirritating, 2 tests).[2] In another study, undiluted Sodium Lauroyl Lactylate (0.1 g) was applied to the right eye of each of 6 albino rabbits according to the same procedure.[19] Mild conjunctivitis was observed in 3 of 6 rabbits, and Sodium Lauroyl Lactylate was classified as a non-irritant in rabbit eyes.

CLINICAL STUDIES

Case Reports

Sodium Stearoyl Lactylate

A female patient with a 20-year history of palmoplantar pustulosis and chronic hand and foot dermatitis had a positive patch test reaction (score not stated) to 5% Sodium Stearoyl Lactylate in petrolatum.[20] The patient was patch tested with ingredients of the cosmetic products that she had been using, and Sodium Stearoyl Lactylate was the only ingredient that caused a positive reaction. When the patient was re-tested with a 2% Sodium Stearoyl Lactylate (in petrolatum) preparation, a + reaction was observed. A use test that involved 2 daily applications of 5% Sodium Stearoyl Lactylate in petrolatum to the lower arm was also performed. Small papules and itching resulted after a few days, and the reaction was clearly positive on day 18. The control groups consisted of 51 subjects patch tested with 2% or 5% Sodium Stearoyl Lactylate in petrolatum, and Sodium Stearoyl Lactylate was classified as having skin irritation potential in this skin irritation test. (This study was described in the Irritation and Sensitization section.) The authors noted that the reproducible patch test and use test reactions are considered to be of an allergic nature, because of the clinical picture, patient history, and patch test results for the 51 controls. Furthermore, the authors noted that this patient seemingly belongs to a group of patients with sensitive, labile skin that easily contracts new allergies.

SUMMARY

The safety of 10 alkanoyl lactyl lactate salts as used in cosmetics is reviewed in this CIR safety assessment. According to the *Dictionary*, all of these ingredients are surfactants, while some have additional possible functions reported.

According to 2019 VCRP data, Sodium Stearoyl Lactylate is reported to be used in 358 cosmetic products (334 leave-on and 24 rinse-off products). Of the alkanoyl lactyl lactate salts that are reviewed in this safety assessment, this is the greatest reported use frequency. The results of a concentration of use survey conducted by the Council in 2017 indicate that Sodium Lauroyl Lactylate is being used at maximum use concentrations up to 10% in skin cleansing products (rinse-off products).[9] Calcium Stearoyl Lactylate, Sodium Lauroyl Lactate, and Sodium Stearoyl Lactylate are being used at maximum use concentrations up to 7% in leave-on products (tonics, dressings, and other hair grooming aids); this is the highest maximum use concentration in leave-on products that is being reported for the alkanoyl lactyl lactate salts. The highest maximum use concentration in leave-on cosmetic products that are applied directly to the skin is 6.1% for Sodium Lauroyl Lactylate in body and hand products that are not sprayed.

Sodium Stearoyl Lactylate, the most frequently used alkanoyl lactyl lactate salt in cosmetic products, can be manufactured by base-catalyzed esterification of lactic acid and stearic acid. *Food Chemicals Codex* and European Commission specifications on the composition of this ingredient as a food additive are available, and the same is true for Calcium Stearoyl Lactylate.

In a single sample of human duodenal mucosa in vitro, [^{14}C]-Calcium Stearoyl Lactylate was rapidly hydrolyzed to stearic acid and lactic acid. In an oral dosing study on [^{14}C]-Calcium Stearoyl Lactylate involving mice and guinea pigs, ~80% of the administered dose was exhaled as $^{14}CO_2$ within 48 h and most of the remaining radioactivity was excreted in the urine within 24 h post-dosing. Approximately 2% (in mice) and 6% (in guinea pigs) of the administered dose remained in the tissues, mainly in the liver and gastrointestinal tract.

In acute oral toxicity studies involving male rats, an oral LD_{50} of 25 g/kg body weight was reported for Sodium Stearoyl Lactylate and for Calcium Stearoyl Lactylate. The following other acute oral LD_{50} values have been reported: > 6.1 g/kg (Sodium Isostearoyl Lactylate, in rats), 6.81 g/kg (Sodium Lauroyl Lactylate, in male rats), and 4.88 g/kg (Sodium Lauroyl Lactylate, in male and female rats).

When Sodium Caproyl/Lauroyl Lactylate was applied to the ears of mice at concentrations of 25% and 50% (2 mice/group) on 3 consecutive days, none of the animals died, and there was no evidence of systemic toxicity.

Some of the findings reported in short-term feeding studies on Calcium Stearoyl Lactylate (rats) at various concentrations were: no deaths (at 12.5% in diet - 43 days), increased relative liver weight (at 5% and 7.5% in the diet - 1 month), no significant liver pathology (at 5% in diet - 27 days), increased liver weight (at 5% in diet - 4 weeks), relative liver weights normal (at 5% in diet - 32 days), liver histology normal (at 5% in diet - duration unknown), relative liver weights normal (at 5% in diet - duration unknown), and kidney histology normal (0.5% in diet - duration unknown). A transient increase in liver weights was observed in rats fed 5% Sodium Stearoyl Lactylate in the diet for 28 days, and organ weights were normal in a dog fed up to 15% Sodium Stearoyl Lactylate in the diet for 1 month.

In a subchronic oral toxicity study, groups of 20 male and female rats were fed Calcium Stearoyl Lactylate at dietary concentrations up to 12.5% for 98 days. Increased relative weights of major organs were observed after feeding with 12.5% Calcium Stearoyl Lactylate. There was no evidence of histological abnormalities in major organs, but lipogranulomata was observed in the adipose tissue of animals fed a dietary concentration of 12.5%. It has been noted that the appearance of lipogranulomata and the increased relative liver weight reported were related to the excessive intake of abnormal portions of long-chain fatty acids. The results of gross and histopathological evaluations of groups of 20 rats fed up to 12.5% Sodium Stearoyl Lactylate in the diet for 102 days were normal.

In a chronic oral toxicity study in which groups of 5 rats were fed diets containing 8% to 22% Calcium Stearoyl Lactylate for periods of up to 6 months, mortality was high (number of deaths not reported) at concentrations of $\geq$ 20%. Histopathological abnormalities were not observed in this study. Neither gross nor microscopic changes were observed in a 2-year study in which 4 Beagle dogs were fed 7.5% Calcium Stearoyl Lactylate in the diet. Liver weights were in the normal range. A 1-year chronic oral toxicity study involved groups of 60 male and female rats fed a basal diet containing Sodium Stearoyl Lactylate at concentrations up to 5%. The NOAEL for Sodium Stearoyl Lactylate was 5% in the diet (equivalent to 2214 mg/kg/day for males and 2641 mg/kg/day for females).

Sodium Caproyl/Lauroyl Lactylate and Calcium Stearoyl Lactylate were not genotoxic to any of the *S. typhimurium* strains evaluated in the Ames test, with or without metabolic activation. Calcium Stearoyl Lactylate also was not genotoxic, with or without metabolic activation, in the chromosome aberrations test involving a Chinese hamster fibroblast cell line.

In a 1-year oral study, the occurrence of endometrial stromal polyps in the uterus (though not statistically significant) was reported after groups of 60 Wistar WU rats (Crl:WI(Wu), outbred; 30 males and 30 females per group) were fed Sodium Stearoyl Lactylate in the diet at concentrations of 1.25%, 2.5%, and 5%. The incidence in treated rats was higher than that in concurrent controls. Data on the historical incidences of this this tumor type at the laboratory where the study was performed demonstrated that endometrial stromal polyps are common in the rat strain that was tested. Therefore, this finding was not treatment-related.

The following results are from skin irritation studies involving albino rabbits (number of animals not stated): undiluted Calcium Stearoyl Stearate (nonirritating), 10% Sodium Lauroyl Lactylate (nonirritating), and undiluted Sodium Stearoyl Lactylate (primary irritation index (PII) = 0.5, 2 tests). Sodium Caproyl/Lauroyl Lactylate (in AOO vehicle) caused erythema and an increase in ear thickness in 4 mice (CRL:NMRI BR strain; 2/group) when tested at concentrations of 25% and 50%. In a skin irritation test on Sodium Isostearyl Lactylate involving 6 albino rabbits, the primary irritation index was 7.17 for the undiluted ingredient and 1.13 for 15% Sodium Isostearyl Lactylate. In a human skin irritation study, 25 and 26 subjects were patch tested with 2% and 5% Sodium Stearoyl Lactylate in petrolatum, respectively. The 2% concentration produced 10 reactions that were classified as doubtful (i.e., probably irritating), and the 5% concentration produced 14 reactions with the same classification. It was concluded that Sodium Stearoyl Lactylate has skin irritation potential. A diluted hair styling product (Calcium Stearoyl Lactylate effective concentration = 2.5%) was classified as a skin irritant in a study involving 54 subjects. In 4 separate skin irritation studies, each involving 50 subjects, a hair molding cream containing 7% Calcium Stearoyl Lactylate was classified as non-irritating to the skin.

In LLNAs of Sodium Caproyl/Lauroyl Lactylate and Sodium Lauroyl Lactylate at test concentrations up to 50%, Sodium Caproyl/Lauroyl Lactylate was classified as a weak-moderate skin sensitizer and Sodium Lauroyl Lactylate was classified as a weak skin sensitizer. A Sodium Lauroyl Lactylate trade name material was also classified as a weak sensitizer in the LLNA. Sodium Lauroyl Lactylate was also classified as a weak skin sensitizer in a guinea pig maximization test in which 10 animals were challenged with a test concentration of 0.5%. A silicone antifoam emulsion containing Sodium Stearoyl Lactylate (75% dilution; effective test concentration = 1.13% Sodium Stearoyl Lactylate) was a non-sensitizer in 20 guinea pigs.

An in vitro assay involving the RHE and detection of inflammation markers (IL-1α [released by injured cells] and IL-8 [secondary inflammatory cytokine]) was used to evaluate the skin toxicity of Sodium Stearoyl Lactylate. Sodium Stearoyl Lactylate was predicted to be an allergen based on the results of this assay. In a study on the modeling of skin sensitization data on a number of diverse compounds, EC3 values (from LLNAs) were ranked for these compounds quantitatively based on sensitization potency. Sodium Stearoyl Lactylate was classified as a Class 2 (weak/non-sensitizers) sensitizer in the ranking.

Caproyl/Lauroyl Lactylate (10% in saline solution) was classified as a non-corrosive substance in the in vitro bovine corneal opacity and permeability test. The results of ocular irritation tests on alkanoyl lactyl lactate salts involving groups of

6 albino rabbits were as follows: undiluted Calcium Stearoyl Lactylate (nonirritating), undiluted Sodium Isostearoyl Lactylate (irritating), 15% Sodium Isostearoyl Lactylate (nonirritating),10% Sodium Lauroyl Lactylate (nonirritating), and undiluted Sodium Stearoyl Lactylate (nonirritating, 2 tests). In another study, undiluted Sodium Lauroyl Lactylate (0.1 g) was applied to the right eye of each of 6 albino rabbits.[19] Mild conjunctivitis was observed in 3 of 6 rabbits, and Sodium Lauroyl Lactylate was classified as a non-irritant.

A female patient with a 20-year history of hand and foot dermatitis had positive patch test reactions to Sodium Stearoyl Lactylate (2% and 5% in petrolatum) that were considered allergic in nature. A use test that involved 2 daily applications of 5% Sodium Stearoyl Lactylate in petrolatum to the lower arm of this patient was also performed. Small papules and itching resulted after a few days, and the reaction was clearly positive on day 18.

DISCUSSION

In LLNAs of Sodium Caproyl/Lauroyl Lactylate and Sodium Lauroyl Lactylate at test concentrations up to 50%, Sodium Caproyl/Lauroyl Lactylate was classified as a weak-moderate (EC3 = 12.4%; EC3 = 9.3%) skin sensitizer and Sodium Lauroyl Lactylate was classified as a weak skin sensitizer (EC3 = 15%). A Sodium Lauroyl Lactylate trade name material was also classified as a weak sensitizer in the LLNA (EC3 = 15%), and Sodium Lauroyl Lactylate was classified as a weak skin sensitizer in a guinea pig maximization test in which animals were challenged with a test concentration of 0.5%. In a case report, a patient with a history of hand and foot dermatitis had positive patch test reactions to Sodium Stearoyl Lactylate (2% and 5% in petrolatum) that were considered allergic in nature. Furthermore, following daily applications of 5% Sodium Stearoyl Lactylate in petrolatum to this patient, a positive reaction was observed. After reviewing these sensitization data on alkanoyl lactyl lactate salts, the Panel noted that the potential for induction of skin sensitization varies depending on a number of factors, including the area of product application; thus, formulators should assess the potential for final formulations to induce sensitization using a QRA or other accepted methodologies.

The Panel was also concerned that the potential exists for dermal irritation with the use of products formulated using alkanoyl lactyl lactate salts. The Panel also specified that products containing these ingredients must be formulated to be non-irritating.

Food Chemicals Codex specifications and European Commission regulations relating to the following components/ impurities of Calcium Stearoyl Lactylate/Sodium Stearoyl Lactylate are available: arsenic, calcium, cadmium, lactic acid, lead, mercury, and sodium. The Panel stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

CONCLUSION

The Panel concluded that the following ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment, when formulated to be non-irritating and non-sensitizing, which may be based on a QRA:

Calcium Stearoyl Lactylate	Sodium Cocoyl Lactylate	Sodium Oleoyl Lactylate*
Sodium Behenoyl Lactylate	Sodium Cupheoyl Lactylate*	Sodium Stearoyl Lactylate
Sodium Caproyl Lactylate*	Sodium Isostearoyl Lactylate	
Sodium Caproyl/Lauroyl Lactylate	Sodium Lauroyl Lactylate	

**Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

TABLES

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[1,CIR Staff]

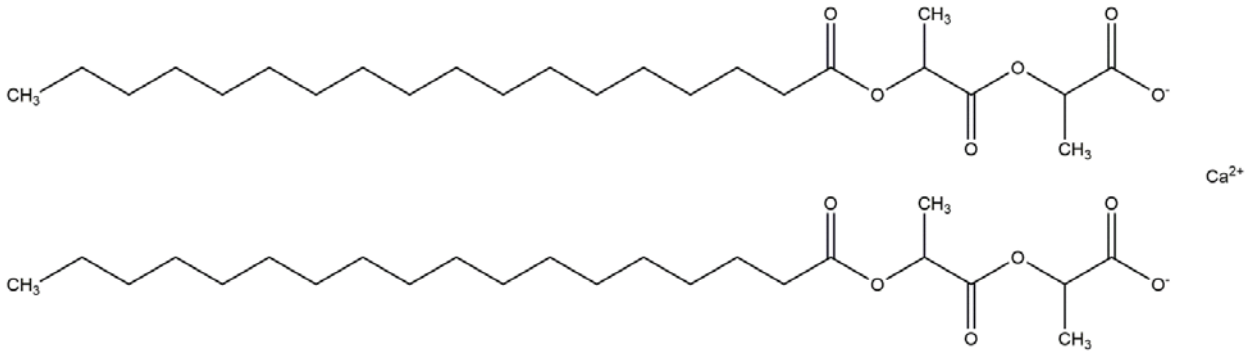
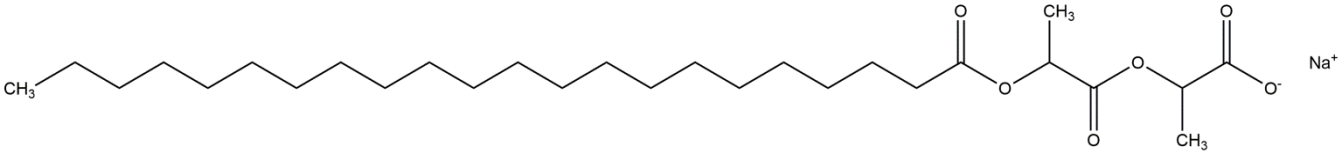
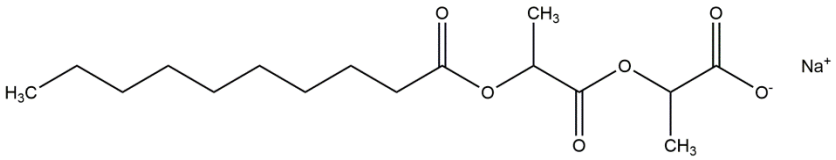
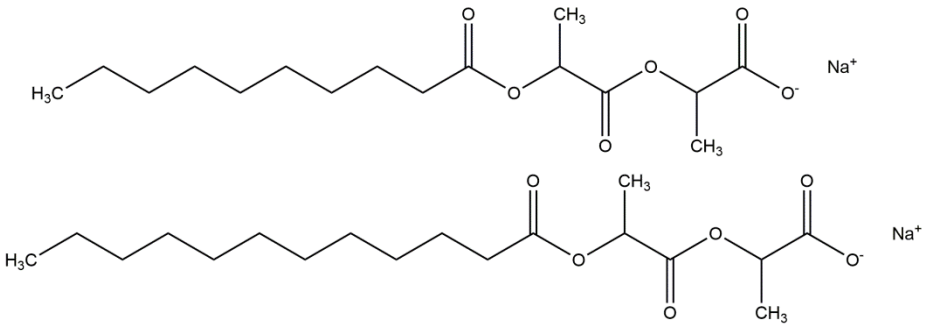
Ingredient CAS No.	Definition and Structures	Functions
Calcium Stearoyl Lactylate 5793-94-2	Calcium Stearoyl Lactylate is the calcium salt of the stearic acid ester of lactyl lactate. It conforms to the following formula: 	Surfactants-Emulsifying agents
Sodium Behenoyl Lactylate	Sodium Behenoyl Lactylate is the sodium salt of the behenic acid ester of lactyl lactate. It conforms to the following formula: 	Surfactants - Emulsifying Agents
Sodium Caproyl Lactylate 13557-74-9	Sodium Caproyl Lactylate is the sodium salt of the capryl ester of lactyl lactate. It conforms generally to the following formula:  [According to INCI naming conventions for these ingredients: a C10 ester is designated as Caproyl, a C8 ester could be designated as Capryoyl, and a C6 ester could be designated as Caprooyl.]	Surfactants - Emulsifying Agents
Sodium Caproyl/Lauroyl Lactylate 1312021-45-6	Sodium Caproyl/Lauroyl Lactylate is the organic compound that conforms generally to the following formula, where RCO- represents a mixture of capric and lauric acid groups:  [According to INCI naming conventions for these ingredients: a C10 ester is designated as Caproyl, a C8 ester could be designated as Capryoyl, and a C6 ester could be designated as Caprooyl.]	Antidandruff Agents; Antifungal Agents; Antimicrobial Agents; Surfactants-Cleansing Agents; Surfactants-Emulsifying Agents

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment.[1,CIR Staff]

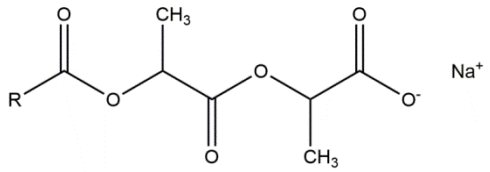
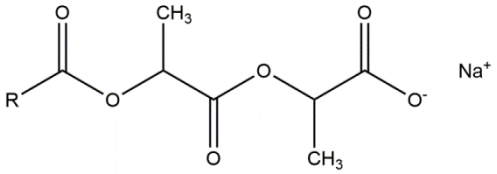
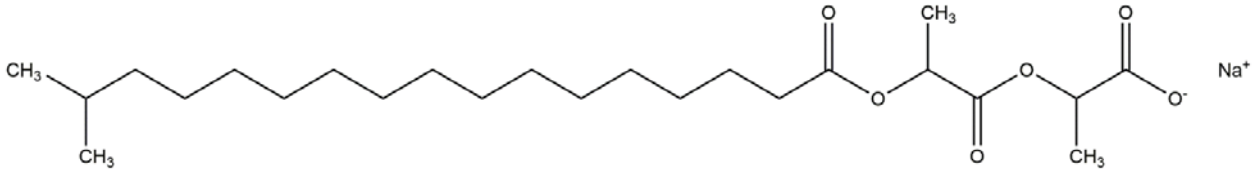
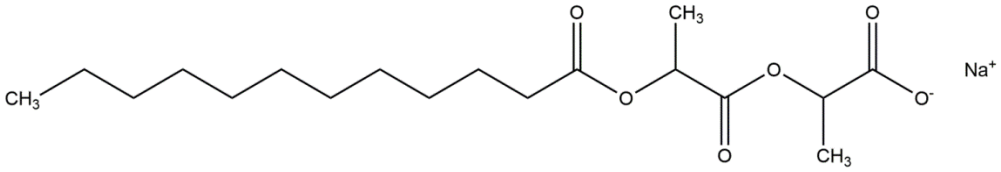
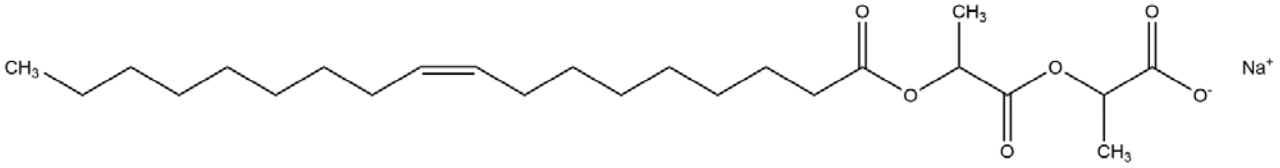
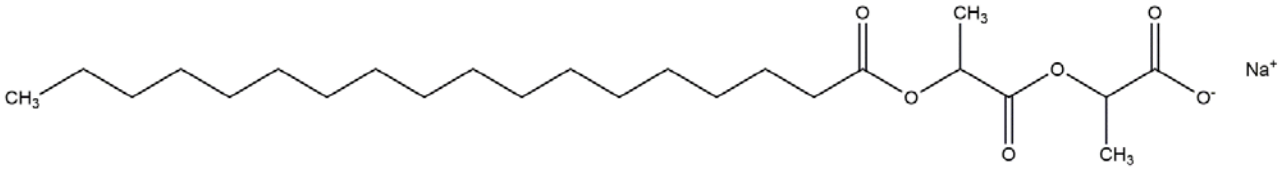
Ingredient CAS No.	Definition and Structures	Functions
Sodium Cocoyl Lactylate	Sodium Cocoyl Lactylate is the sodium salt of the coconut acid ester of lactyl lactate. It conforms to the following formula:  where RC(O)- represents the fatty acids derived from coconut oil.	Surfactants - Emulsifying Agents
Sodium Cupheoyl Lactylate	Sodium Cupheoyl Lactylate is the organic compound that conforms to the following formula:  where RC(O)- represents the fatty acids derived from the seed oil of the hybrid, *Cuphea viscosissima x Cuphea lanceolate.* [The approximate fatty acid composition of this seed oil is: 70% capric acid , 9% oleic acid, 6% palmitic acid , 5% linoleic acid, 4% myristic acid, and 3% lauric acid.[32]]	Surfactants - Cleansing Agents; Surfactants - Emulsifying Agents; Surfactants - Foam Boosters
Sodium Isostearoyl Lactylate 66988-04-3	Sodium Isostearoyl Lactylate is the sodium salt of the isostearic acid ester of lactyl lactate. It conforms to the following formula:  one example of an "iso"	Surfactants - Emulsifying Agents
Sodium Lauroyl Lactylate 13557-75-0 1312021-45-6	Sodium Lauroyl Lactylate is the sodium salt of the lauric acid ester of lactyl lactate. It conforms to the following formula: 	Surfactants - Emulsifying Agents
Sodium Oleoyl Lactylate	Sodium Oleoyl Lactylate is the sodium salt of the oleic acid ester of lactyl lactate. It conforms to the following formula: 	Surfactants - Emulsifying Agents
Sodium Stearoyl Lactylate 18200-72-1 25383-99-7	Sodium Stearoyl Lactylate is the sodium salt of the stearic acid ester of lactyl lactate. It conforms to the following formula: 	Surfactants - Emulsifying Agents

Table 2. Chemical and Physical Properties of Alkanoyl Lactyl Lactate Salts

Property	Value/Results	Reference
Calcium Stearoyl Lactylate		
Form	White to pale yellow, ivory-colored waxy material.	4
Formula weight (Da)	895.26	4
Solubility	Typically dispersible in warm water and soluble in hot edible oils and fats. Slightly soluble in hot water	4
log $P_{o/w}$	9.41(estimated)	4
Vapor pressure (mm Hg)	9.06×10^{-13}	4
Melting point (ºC)	45.7 to 48.7	4
Boiling point (ºC)	532 to 534	4
Flash point (ºC)	188.11; 166.2	4
Sodium Behenoyl Lactylate		
Formula weight (Da)	506.7	33
log K_{ow}	6.01 (estimated)	34
Sodium Caproyl Lactylate		
Formula weight (Da)	338.4	35
Sodium Caproyl/Lauroyl Lactylate		
Form	Yellowish to brownish/amber highly viscous liquid	13
Formula weight (Da)	338.4 - 366.4	35
Density (g/cm^3 at 20 ºC)	1.13 (estimated)	13
Water solubility (g/l at 20ºC)	0.12	13
Vapor pressure (mm Hg at ~ 25ºC)	2.14×10^{-5}	13
(mm Hg at ~ 20ºC	1.38×10^{-5}	13
Melting range (ºC)	0.7 to 10.2	13
Boiling point (ºC)	decomposition at ~ 240	13
Flash point (ºC)	183.5	13
Sodium Cocoyl Lactylate		
Form	White or off-white waxy solid or paste	36
Solubility	Soluble in water	36
Sodium Stearoyl Lactylate		
Form	White to pale yellow, ivory-colored waxy material.	4
Formula weight (Da)	405.58	4
Solubility	Typically dispersible in warm water and soluble in hot edible oils and fats. Soluble in ethanol, but insoluble in water. Very slightly soluble in cold water.	4
Specific gravity	1.063	4
log $P_{o/w}$	9.41(estimated); 2.58 (Sodium Stearoyl Lactylate trade name material, composition not stated)	4,29
Melting point (ºC)	48.889	4
Boiling point (ºC)	532 to 533	4
Flash point (ºC)	166.20	4
Sodium Isostearyl Lactylate		
Form	Straw or honey-colored, clear viscous liquid	5
Formula weight (Da)	450.592	33
Solubility	Dispersible in distilled water. Soluble in propylene glycol, ethyl alcohol, mineral oil, and isopropyl myristate	5
log K_{ow}	3.98 (estimated)	34
Sodium Lauroyl Lactylate		
Formula weight (Da)	366.43	33
log K_{ow}	1.10 (estimated)	34
Sodium Oleoyl Lactylate		
Formula weight (Da)	448.6	35
log K_{ow}	3.83 (estimated)	34
Flash point (°C)	0	37

Table 3. Frequency (2019) and Concentration of Use (2017) According to Duration and Type of Exposure.[8,9]

	Calcium Stearoyl Lactylate		Sodium Behenoyl Lactylate		Sodium Caproyl/Lauroyl Lactylate	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals*/Conc. Range**	**NR**	**7**	**7**	**1.9-2**	**2**	**NR**
Duration of Use						
Leave-On	*NR*	*7*	*7*	*1.9*	*2*	*NR*
Rinse off	*NR*	*NR*	*NR*	*2*	*NR*	*NR*
Diluted for (bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation - Sprays	NR	7[a]	5[a];1[c]	NR	2[a]	NR
Incidental Inhalation - Powders	NR	NR	1[c]	NR	NR	NR
Dermal Contact	NR	NR	7	1.9-2	2	NR
Deodorant (underarm)	NR	NR	NR	NR	1[a]	NR
Hair - Non-Coloring	NR	7	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	2	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Sodium Cocoyl Lactylate		Sodium Isostearoyl Lactylate		Sodium Lauroyl Lactylate	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	**4**	**NR**	**27**	**0.04-3.5**	**226**	**0.001-10**
Duration of Use						
Leave-On	*1*	*NR*	*9*	*0.04-1*	*108*	*0.001-7*
Rinse off	*3*	*NR*	*18*	*0.08-3.5*	*113*	*0.53-10*
Diluted for (bath) Use	*NR*	*NR*	*NR*	*0.5*	*5*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	8	NR
Incidental Ingestion	NR	NR	1	NR	NR	NR
Incidental Inhalation – Sprays	1[c]	NR	1[a];2[c]	0.04[a]	47[a];35[c]	7[a]
Incidental Inhalation - Powders	1[c]	NR	2[c]	0.5-1[b]	35[c]	0.001-6.1[b]
Dermal Contact	1	NR	20	0.5-3.5	211	0.001-10
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	3	NR	6	0.5-2	14	0.078-7
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	3	0.5-3.5	80	1.9
Baby Products	NR	NR	NR	NR	1	NR

	Sodium Stearoyl Lactylate	
	# of Uses	Conc. (%)
Totals/Conc. Range	**358**	**0.00011-7**
Duration of Use		
Leave-On	*334*	*0.00011-7*
Rinse off	*24*	*0.00011-0.02*
Diluted for (bath) Use	*NR*	*NR*
Exposure Type		
Eye Area	20	0.18-0.2
Incidental Ingestion	5	0.00011
Incidental Inhalation – Sprays	208[a];73[c]	0.1-7[a]
Incidental Inhalation - Powders	1;5[b];73[c]	0.001-0.63[b]
Dermal Contact	354	0.00011-1.1
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	3	7
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	7	0.00011
Baby Products	5	0.45

NR = Not Reported; Totals = Rinse-off + Leave-on + Diluted for Use Product Uses

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

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

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

Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum of total uses.

Table 4. Alkanoyl Lactyl Lactate Salts Not Reported to Be in Use in Cosmetic Products.[8,9]

Ingredients
Sodium Caproyl Lactylate
Sodium Cupheoyl Lactylate
Sodium Oleoyl Lactylate

Table 5. Short-Term, Subchronic, and Chronic Toxicity Studies

Ingredient	Animals	Protocol	Results
Short-Term Dermal Toxicity Study			
Sodium Caproyl/Lauroyl Lactylate (25% or 50% in AOO vehicle))	4 mice (CRL:NMRI BR strain); 2 tested per concentration	Range-finding test that was performed prior to local lymph node assay (LLNA). Because test substance was highly viscous, application in undiluted form was not possible. Based on solubility, maximum available concentration was 50%. Test substance (25 µl) applied to ears on 3 consecutive days	None of the animals died. No evidence of systemic toxicity or significant effects on body weight.[13]
Short-Term Oral Studies			
Calcium Stearoyl Lactylate (0.5%, 2%, and 12.5% in the diet)	Groups of 5 male rats (strain not stated)	Feeding for 43 days	No deaths. Increased weight of liver, heart, brain, stomach, and testes (at 12.5% concentration). Increased relative liver weight (at 2% concentration). Reduced growth (at 2% and 12.5% concentrations).[14]
Calcium Stearoyl Lactylate (0.1%, 1%, 2%, 3%, 4%, 5%, and 7.5% in diet)	Groups of 25 rats (strain not stated)	Feeding for 1 month	Growth retardation and increased relative liver weight at concentrations of 5% and 7.5%.[14]
Calcium Stearoyl Lactylate (5% in diet)	Groups of 10 rats (strain not stated)	Paired feeding for 27 days	Decreased food efficiency. Increased liver weight, but no effects on liver histopathology, except slight increase in glycogen.[14]
Calcium Stearoyl Lactylate (5% in diet)	Groups of 12 rats (strain not stated)	Feeding for 4 weeks	Liver weights of test group greater than those of controls fed diet without Calcium Stearoyl Lactylate. No other pathological changes observed.[14]
Calcium Stearoyl Lactylate (5% in diet)	30 male rats (strain not stated)	Feeding for 32 days. Groups of 5 killed at days 32, 60, 90, and 140.	Relative liver weights were normal.[14]
Calcium Stearoyl Lactylate (5% in diet)	Groups of 5 male rats (strain not stated)	Feeding duration not stated	Slightly reduced body weight. Mortality was not affected by treatment. Liver histology revealed no abnormalities.[14]
Calcium Stearoyl Lactylate (5% in diet)	Groups of 32 male rats (strain not stated)	Feeding duration not stated	Relative liver weights less than that of control rats fed diet without Calcium Stearoyl Stearate.[14]
Calcium Stearoyl Lactylate (0.5% in diet)	Groups of 10 male and 10 female rats (strain not stated)	Paired feeding (duration not stated)	Histology of livers and kidneys normal. X-rays of femurs comparable.[14]
Sodium Stearoyl Lactylate (5% in diet)	20 male rats (strain not stated)	Feeding for 28 days. Groups of 5 killed at days 32, 60, 90, and 140.	Relative liver weights slightly elevated. Liver weights normal after 90 days.[14]

Table 5. Short-Term, Subchronic, and Chronic Toxicity Studies

Ingredient	Animals	Protocol	Results
Sodium Stearoyl Lactylate (7.5%, 12.5%, and 15% in diet)	1 dog	Sodium Stearoyl Lactylate at 7.5% in the diet for 1 month, followed by 12.5% in the diet for 2 weeks, and followed by 15% in the diet for an additional month	No evidence of hematological changes. Organ weights and microscopic appearance of the tissues were normal.[14]
Subchronic Oral Studies			
Calcium Stearoyl Lactylate (0.5%, 5%, and 12.5% in the diet)	Groups of 10 male and 10 female rats (strain not stated)	Feeding in the diet for 98 days	Slight growth retardation at 5% in diet and significant growth retardation at 12.5% in diet. Increased relative liver, stomach, heart, spleen, and brain weights at 12.5% in diet. No evidence of histological abnormalities in kidneys, brain, lungs, spleen, or liver at 12.5% in diet, but lipogranulomata detected in adipose tissue. No increase in stainable liver fat. Urinalyses, blood morphology, and radiological studies of femurs were normal. Joint FAO/WHO Expert Committee on food Additives noted that the appearance of lipogranulomata and increased liver weight are related to excessive intake of abnormal proportions of long-chain fatty acids.[14]
Sodium Stearoyl Lactylate (0.5%, 5%, and 12.5% in the diet)	Groups of 10 male and 10 female rats (strain not stated)	Feeding in the diet for 102 days	When compared to controls fed diet without Sodium Lauroyl Lactylate, there were no abnormalities regarding urinalyses, hematology, or fecal excretion. Liver, brain, stomach, and spleen weights increased at 12.5% in diet. Results of gross and histopathological evaluations were normal.[14]
Chronic Oral Studies			
Calcium Stearoyl Lactylate (8% to 22% in the diet)	Groups of 5 rats (strain not stated)	Feeding in diet for 6 months.	Growth depression at ≥ 16% in diet. High mortality (deaths not reported) at ≥ 20% in diet. Relative liver weights normal at saturated to unsaturated (S:U) fatty acid ratio of 0.6 (17% fat plus 3% Calcium Stearoyl Lactylate), but increased with higher ratios. Lipogranulomata appeared at ratios of > 1.4. Disappearance of lipogranulomata in 4 to 6 months, after restoration to basal diet containing 20% fat. Histopathological abnormalities not observed.[14]
Calcium Stearoyl Lactylate (25% in the diet)	40 male and 40 female rats (strain not stated)	Feeding in diet for up to 6 months.	All animals developed severe lipogranulomata, with high mortality (deaths not reported). Growth rate was depressed. When animals were placed on basal diet containing 20% fat (half corn oil and half lard), recovery of growth rate was noted.[14]
Calcium Stearoyl Lactylate (7.5% in the diet)	2 groups of 4 Beagle dogs (1 male, 3 females per group; one group was control)	Feeding in diet for 2 years	No noteworthy differences when 2 groups were compared. Urinalysis and hematological findings and liver weights were normal. No gross or microscopic changes observed.[14]
Sodium Stearoyl Lactylate (1.25%, 2.5%, and 5% in diet)	3 groups of 60 Wistar WU rats (Crl:WI(Wu), outbred; 30 males and 30 females per group)	Feeding in diet for 1 year	Hematological, clinical chemistry, and urinalysis findings were normal. NOAEL = 2214 mg/kg/day (males) and 2641 mg/kg/day (females).[15]

Table 6. Skin Irritation and Sensitization Studies on Alkanoyl Lactyl Lactate Salts.

Test Substance	Animals/Subjects/Cells	Test Protocol	Results
Irritation (In Vitro)			
Sodium Caproyl/Lauroyl Lactylate	EpiDerm® tissue model: normal human-derived epidermal keratinocytes cultured to form multi-layered highly differentiated model of human epidermis	Test substance (~ 25 mg) applied, with 25 µl of deionized water, topically to the model for 3 min to 1 h. Cell viability measured by dehydrogenase conversion of {(3-4,5-dimethylthiazole 2-yl) 2,5-diphenyltetrazoli-umbromide (MTT) into blue formazan salt. Optical density of extracted formazan determined via spectrophotometry. Mean formazan production (irritation parameter) calculated from decrease in absorbance values when compared to negative control (deionized water)	Test substance considered non-corrosive because following criteria for non-corrosive substance were fulfilled: formazan production after 3 min of incubation was > 50% of negative control, and formazan production after 1 h of incubation was > 15% of negative control. Positive control (potassium hydroxide) caused clear corrosive effects after both treatment intervals.[13]
Irritation (Animal)			
Calcium Stearoyl Lactylate (undiluted)	Albino rabbits (number not stated)	Test protocol not stated	Non-irritant.[2]
Sodium Caproyl/Lauroyl Lactylate (25% or 50% in AOO vehicle). [Because test substance was highly viscous, maximum available concentration was 50%.]	2 mice/group (CRL:NMRI BR strain)	Range-finding test performed prior to LLNA. Test substance (25 µl) applied on 3 consecutive days. Measurement of ear thickness on day 1 prior to application and on days 3 (~ 48 h after first dose) and 6.	Erythema observed at both concentrations on days 1 to 6 (maximum score of 2), but reaction not considered significant. Increased ear thickness also observed at both concentrations. Maximum value for ear thickness (18.2%) observed at 50% concentration. Test substance did not cause significant skin irritation at either test concentration.[13]
Sodium Isostearoyl Lactylate (undiluted and 15% concentration)	6 albino rabbits	Test substance (0.5 ml) applied for 24 h under 1″ x 1″ occlusive patch secured with adhesive tape. Application to abraded and intact skin. Reactions scored at 24 h and at 48 h later. PII calculated (scale not stated)	PII = 7.17 (undiluted ingredient) and 1.13 (15% concentration). Individual irritation scores not reported.[5]
Sodium Lauroyl Lactylate (10%)	Albino rabbits (number not stated)	Test protocol not stated	Non-irritant.[2]
Sodium Stearoyl Lactylate (undiluted)	Albino rabbits (number not stated)	Test protocol not stated. PII calculated (scale not stated)	PII = 0.5.[2]
Sodium Stearoyl Lactylate (undiluted)	6 albino rabbits	Undiluted Sodium Stearoyl Lactylate (0.5 g moistened with physiological saline) applied for 24 h under 1 in^2 surgical gauze patch to the saddle area (abraded and intact skin). Each patch secured with adhesive tape, rubber dental damming, and an outer layer of gauze. Reactions scored at 24 h and 72 h.	At 24 h, slight erythema at 5 intact and 5 abraded sites. At 72 h, very slight erythema only at 1 intact site and 1 abraded site. PII of 0.50 reported, and Sodium Stearoyl Lactylate was neither classified as a primary skin irritant nor a corrosive material.[19]
Irritation (Human)			
Hair styling product containing 5% Calcium Stearoyl Lactylate (50% in distilled water; effective concentration = 2.5%)	54 subjects (17 males, 37 females)	Semi-occlusive patch containing 0.2 ml of the test substance applied for 48 h along paraspinal region of back. Dose per cm^2 not stated. Sodium lauryl sulfate and distilled water served as positive and negative controls, respectively.	Test substance produced slight to mild erythema (scores of + to 1) in 18 of the subjects tested. Results also indicated that negative control caused slight to moderate skin irritation in 7 subjects. The positive control caused skin irritation in 49 subjects. The diluted hair styling product was classified as having skin irritation potential that is consistent with the product type (styling products).[21]
Hair molding cream containing 7% Calcium Stearoyl Lactylate	50 subjects (18 males, 32 females)	Product (20 µl) applied for 24 h to the ventral forearm using Finn chambers (8 mm). Reactions scored at 24 h, 48 h, and 72 h post-application. Sodium dodecyl sulfate (2%) and demineralized water served as positive and negative controls, respectively.	The mean 24-h irritation score for the product was not statistically significantly different (p = 1) from the negative control, and the product was classified as a non-irritant.[22]

Table 6. Skin Irritation and Sensitization Studies on Alkanoyl Lactyl Lactate Salts.

Test Substance	Animals/Subjects/Cells	Test Protocol	Results
Hair molding cream containing 7% Calcium Stearoyl Lactylate	50 subjects (14 males, 36 females)	Same protocol (immediately above)	The mean 24-h irritation score for the product was not statistically significantly different (p = 1) from the negative control, and the product was classified as a non-irritant.[23]
Hair molding cream containing 7% Calcium Stearoyl Lactylate	50 subjects (18 males, 32 females)	Same protocol	The mean 24-h irritation score for the product was not statistically significantly different (p = 1) from the negative control, and the product was classified as a non-irritant.[24]
Hair molding cream containing 7% Calcium Stearoyl Lactylate	50 subjects (19 males, 31 females)	Same protocol	The mean 24-h irritation score for the product was not statistically significantly different (p = 0.13) from the negative control, and the product was classified as a non-irritant.[25]
Sodium Lauroyl Lactylate (2% and 5% in petrolatum)	25 tested with 2%; 26 tested with 5%	Protocol details not state	Fifteen negative reactions and 10 doubtful reactions (probably irritant) to 2% Sodium Lauroyl Lactylate. Eleven negative reactions and 14 doubtful reactions to 5% Sodium Lauroyl Lactylate (also, + reaction in 1 subject). Study results indicated that Sodium Lauroyl Lactylate has skin irritation potential.[20]
Sensitization (in vitro)			
Sodium Stearoyl Lactylate	RHE	In vitro assay used to assess skin toxicity was detection of the inflammation markers interleukin (IL)-1α and IL-8. It was noted that inflammation markers have been released in the growth medium of RHE as a consequence of the immune response to the presence of surfactants. Value for IL release of >1 corresponds to production of IL-1α or IL-8 induced by presence of surfactant. Il-α is expressed as an intracellular protein; it accumulates in keratinocytes and is released by injured cells or after membrane alteration. IL-8 is a secondary inflammatory cytokine, secreted in response to IL-1α release during inflammation. Relative inflammation potency was evaluated by measuring release of interleukins by flow cytometry. Threshold for IL-1α and IL-8 release was defined as 3 times that of the control (untreated RHE)	IL-8/IL-1α ratio was 5.85 (i.e., > 1). Value for release of IL-8 (3.407) was above the threshold of 3, whereas the value for the release of IL-1α (0.582) was not. Chemicals applied to the skin can be considered allergens when the extracellular IL-8 > 1L-1α, and as irritants when extracellular IL-8 < IL-1α. Sodium Stearoyl Lactylate was predicted to be an allergen.[26]
Sensitization (Animal)			
Sodium Caproyl/Lauroyl Lactylate (2.5%, 5%, 10%, 25%, and 50% in AOO vehicle)	Groups of 4 CRL:NMRI BR mice	LLNA (OECD TG 429). Mice were treated topically on dorsum of both ears with 25 µl of test substance or equal volume of vehicle alone. At day 6 after initiation of exposure, all mice injected (tail vein) with phosphate buffered saline containing tritiated thymidine. Mice killed 5 h later, and draining lymph nodes excised and pooled for each experiment. Test substance concentration required to produce stimulation of proliferation of at least 3-fold greater when compared to controls (i.e., EC3 value) calculated to provide measure of relative skin sensitizing potential.	EC3 (calculated by linear interpolation) = 12.4%, classifying test substance as a weak sensitizer. EC3 (calculated based on equation of regression curve) = 9.3%, classifying test substance as moderate sensitizer. Study results indicated that, at the concentrations tested in AOO, Sodium Caproyl/Lauroyl Lactylate has sensitization potential (sensitizer). Collectively, the EC3 values calculated using the 2 methods (dose response and regression curve) classify Sodium Caproyl/Lauroyl Lactylate as a weak-moderate sensitizer in the LLNA.[13]
Sodium Lauroyl Lactylate (2.5%, 5%, 10%, 25%, and 50% in AOO vehicle)	Groups of 4 CBA/Ca female mice	LLNA (OECD TG 429). Protocol similar to that stated immediately above, except for the mouse strain used and intravenous injection on day 5.	EC3 = 15%, classifying Sodium Lauroyl Lactylate as a weak sensitizer.[27,28]
Sodium Lauroyl Lactylate trade name material	Groups of CBA female mice	LLNA (OECD TG 429)	EC3 = 15%, classifying Sodium Lauroyl Lactylate as a weak sensitizer.[29]

Table 6. Skin Irritation and Sensitization Studies on Alkanoyl Lactyl Lactate Salts.

Test Substance	Animals/Subjects/Cells	Test Protocol	Results
Sodium Lauroyl Lactylate (0.5%)	15 Dunkin-Hartley guinea pigs (10 treated, 5 controls)	Guinea pig maximization test (OECD TG 406). Injection and dermal doses not stated. Challenge concentration of 0.5%.	Weak sensitizer.[27]
A silicone antifoam emulsion containing 2% Sodium Stearoyl Lactylate (75% dilution; effective test concentration = 1.5% Sodium Stearoyl Lactylate)	20 adult female guinea pigs (Dunkin-Hartley strain). Ten guinea pigs (treated with sterile water, solvent) served as controls.	Guinea pig model using methods of Buehler. During induction, test substance (0.5 ml) applied to left flank for 6 h, under a 20 x 20 mm gauze patch secured with adhesive strapping. At 24 h after patch removal, reactions scored. Procedure repeated at weekly intervals (days 8 to 9 and 16 to 15 of study). Challenge phase initiated on day 29. A 20 x 20 mm absorbent patch containing test substance (0.5 ml) applied (secured with adhesive strapping) for 6 h to right flank. A patch containing sterile water (control) also applied to right flank. At 24 h and 48 h after patch removal, reactions scored.	No reactions at test or control sites during induction or following challenge patch application. Test substance was a non-sensitizer in guinea pigs.[30]

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2019 FDA VCRP Data

Calcium Stearoyl Lactylate - No Data

Sodium Behenoyl Lactylate

12D - Body and Hand (exc shave)	1
12F - Moisturizing	4
12I - Skin Fresheners	1
12J - Other Skin Care Preps	1
Total	**7**

Sodium Caproyl Lactylate - No Data

Sodium Caproyl/Lauroyl Lactylate

10B - Deodorants (underarm)	1
12F - Moisturizing	1
Total	2

Sodium Cocoyl Lactylate

05F - Shampoos (non-coloring)	3
12C - Face and Neck (exc shave)	1
Total	**4**

Sodium Cupheoyl Lactylate - No Data

Sodium Isostearoyl Lactylate

05A - Hair Conditioner	1
05F - Shampoos (non-coloring)	4
05I - Other Hair Preparations	1
07E - Lipstick	1
07I - Other Makeup Preparations	1
10A - Bath Soaps and Detergents	2
11G - Other Shaving Preparation Products	4
12A - Cleansing	6
12C - Face and Neck (exc shave)	2
12F - Moisturizing	1
12H - Paste Masks (mud packs)	1
12J - Other Skin Care Preps	3
Total	**27**

Sodium Lauroyl Lactylate

01C - Other Baby Products	1
02A - Bath Oils, Tablets, and Salts	5
03D - Eye Lotion	5
03F - Mascara	1
03G - Other Eye Makeup Preparations	2
05A - Hair Conditioner	2
05F - Shampoos (non-coloring)	12

07C - Foundations	7
07G - Rouges	1
07H - Makeup Fixatives	1
07I - Other Makeup Preparations	3
10A - Bath Soaps and Detergents	74
10E - Other Personal Cleanliness Products	1
11A - Aftershave Lotion	1
11G - Other Shaving Preparation Products	2
12A - Cleansing	19
12C - Face and Neck (exc shave)	30
12D - Body and Hand (exc shave)	5
12F - Moisturizing	40
12G - Night	7
12H - Paste Masks (mud packs)	3
12J - Other Skin Care Preps	4
Total	**226**

Sodium Oleoyl Lactylate - No Data

Sodium Stearoyl Lactylate

01B - Baby Lotions, Oils, Powders, and Creams	5
03D - Eye Lotion	13
03F - Mascara	1
03G - Other Eye Makeup Preparations	6
05F - Shampoos (non-coloring)	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	2
07B - Face Powders	1
07C - Foundations	4
07D - Leg and Body Paints	10
07E - Lipstick	5
07I - Other Makeup Preparations	2
10E - Other Personal Cleanliness Products	2
12A - Cleansing	15
12C - Face and Neck (exc shave)	46
12D - Body and Hand (exc shave)	27
12F - Moisturizing	183
12G - Night	18
12H - Paste Masks (mud packs)	6
12J - Other Skin Care Preps	6
13A - Suntan Gels, Creams, and Liquids	1
13B - Indoor Tanning Preparations	3
13C - Other Suntan Preparations	1
Total	**358**

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: November 26, 2018

SUBJECT: Draft Report: Safety Assessment of Alkyl Lactyl Lactate Salts as Used in Cosmetics (draft prepared for the December 3-4, 2018 CIR Expert Panel Meeting)

The Council respectfully submits the following comments on the draft report, Safety Assessment of Alkyl Lactyl Lactate Salts as Used in Cosmetics.

Impurities - The European Food Safety Authority (EFSA) operates independently of the EU government. Therefore, European Commission regulations should not be cited to an EFSA reference (reference 4).

Cosmetic Use, Table 4 - A table is not necessary to list the three ingredient for which no uses were reported.

Carcinogenicity; Summary - As the incidence of endometrial stromal polyps was within the range of control rats from the lab where the study was conducted, it is not appropriate to state "rather high incidence." It should be stated that the incidence in treated rats was higher than concurrent controls.

Irritation; Summary; Table 6 - The "moulding" products were hair molding products not "skin" molding products as stated in the CIR report. It is not clear how a product could be used to "mold" the skin.

Table 1 - The fatty acid range found in cuphea oil should be added to Table 1. The following reference (abstract provided below) appears to include information about the specific hybrid included in the definition of the INCI name:

Evangelista R, Cermak S. 2007. Full-press oil extraction of Cuphea (PSR23) seeds. *Journal of the American Oil Chemists' Society*. 84. 10.1007/s11746-007-1142-5.

Abstract
Cuphea PSR23, a semi-domesticated, high-capric-acid hybrid from *Cuphea viscosissima* x *Cuphea lanceolata*, is being developed as a potential commercial alternative source of medium-chain fatty acids. The present study evaluated the effects of initial seed moisture and final moisture contents of cooked flaked seed on Cuphea's pressing characteristics

and the quality of the extracted oil. Seeds with 9 and 12% initial moisture contents (MC) were flaked and cooked at different residence times to produce cooked seeds with MC of 3.0-5.5%. Cooked seeds were pressed using a laboratory screw press. Eighty and 84% oil were extracted from cooked seeds with 5.5 and 3.0% MC, respectively. The seeds with 9% initial MC exhibited lower pressing load increase (9.1 per 1% decrease in MC) than the seeds with 12% initial MC (16.4 per 1% decrease in MC). The pressing rate decreased by 3% as the cooked flaked seed MC decreased. The amount of foots in the oil increased from 3 to 6.6% and chlorophyll content increased from 200 to 260 ppm as cooked flaked seed MC decreased from 5.5 to 3.0%. FFA contents were 2.5% for all treatments MC studied. The phosphatide content increased as the cooked flaked seed MC decreased but the amounts were still within the levels of water-degummed oil.

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: January 11, 2019

SUBJECT: Tentative Report: Safety Assessment of Alkanoyl Lactyl Lactate Salts as Used in Cosmetics (release date January 4, 2019)

The Council respectfully submits the following comments on the tentative report, Safety Assessment of Alkanoyl Lactyl Lactate Salts as Used in Cosmetics.

Chemistry - The color scheme used in Figures 1 and 2 should be the same. Currently, the oxygen connecting the alkanoyl group to the lactyl lactate is the same color (red) as the lactyl lactate group in Figure 1, but a different color (black) than the alkanoyl group (blue) and the lactyl lactate group (red) in Figure 2.

Cosmetic Use - Since the VCRP and the Council survey are not comprehensive, it would be more appropriate to state that no uses of three ingredients were reported (rather than that the three ingredients "are not being used in cosmetic products in the US").

Summary - Although the USP now publishes the *Food Chemical Codex*, the Summary should indicate that the specifications are from the *Codex* rather than the "United States Pharmacopoeial Convention". If there are USP specifications, they should be added earlier in the report.

Discussion - Please state the range of EC_3 values reported for the LLNAs.

Table 6 - Since the *in vitro* study of Sodium Stearoyl Lactylate (reference 19) predicted that it would be an allergen, perhaps this study should be moved to the sensitization section of this table. Did the authors (reference 19) conclude anything about the irritation potential of Sodium Stearoyl Lactylate?

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