Safety Assessment of Palm Tree (açaí and juçara)-derived Ingredients as Used in Cosmetics

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

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

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

From: Wilbur Johnson, Jr.
Senior Scientific Analyst, CIR

Date: May 15, 2020

Subject: Draft Final Report on Palm Tree (açaí and juçara) -Derived Ingredients

Enclosed is a Draft Final Report (*palmtr062020rep*) on 8 palm tree (açaí and juçara)-derived ingredients. This family comprises cosmetic ingredients that are derived from two palm tree species, *Euterpe edulis* and *Euterpe oleracea*. A Revised Tentative Report with the following conclusions was issued at the December 9-10, 2019 Expert Panel for Cosmetic Ingredient Safety (Panel) meeting: Euterpe Edulis Fruit Extract, Euterpe Edulis Juice Extract, Euterpe Oleracea Fruit Extract, Euterpe Oleracea Juice, Euterpe Oleracea Pulp Powder, Euterpe Oleracea Seed Powder, and Hydrolyzed Euterpe Oleracea Fruit are safe in cosmetics in the present practices of use and concentration described in the safety assessment. The Panel further concluded that the available data are insufficient to make a determination of safety for Euterpe Oleracea Palm Heart Extract under the intended conditions of use in cosmetic formulations. The data needs on this ingredient (previously requested) include:

- Composition data; if the composition of this ingredient is found to be significantly different from the other ingredients in this group, skin irritation and sensitization data would be needed

To date, there has been no response to this data request.

Comments on the safety assessment that were received from the Council prior to the December 2019 Panel meeting (*palmtr062020pcpc1*) and after announcement of the Revised Tentative Report (*palmtr062020pcpc2*) are also enclosed and have been addressed.

Also included in this package for your review are the report history (*palmtr062020hist*), flow chart (*palmtr062020flow*), literature search strategy (*palmtr062020strat*), ingredient data profile (*palmtr062020prof*), 2020 FDA VCRP data (*palmtr062020FDA*), and the minutes from previous Panel meetings (*palmtr062020min*).

When compared to the 2019 FDA VCRP data, the 2020 FDA VCRP data do not indicate any significant changes in the use frequencies of palm tree-derived ingredients. In 2019, Euterpe Oleracea Fruit Extract was being used in 430 product formulations, but the use frequency only increased to 469 in 2020. No changes in use frequencies of the remaining ingredients in this safety assessment are being reported.

After reviewing these documents, the Panel should be prepared to issue a Final Report.

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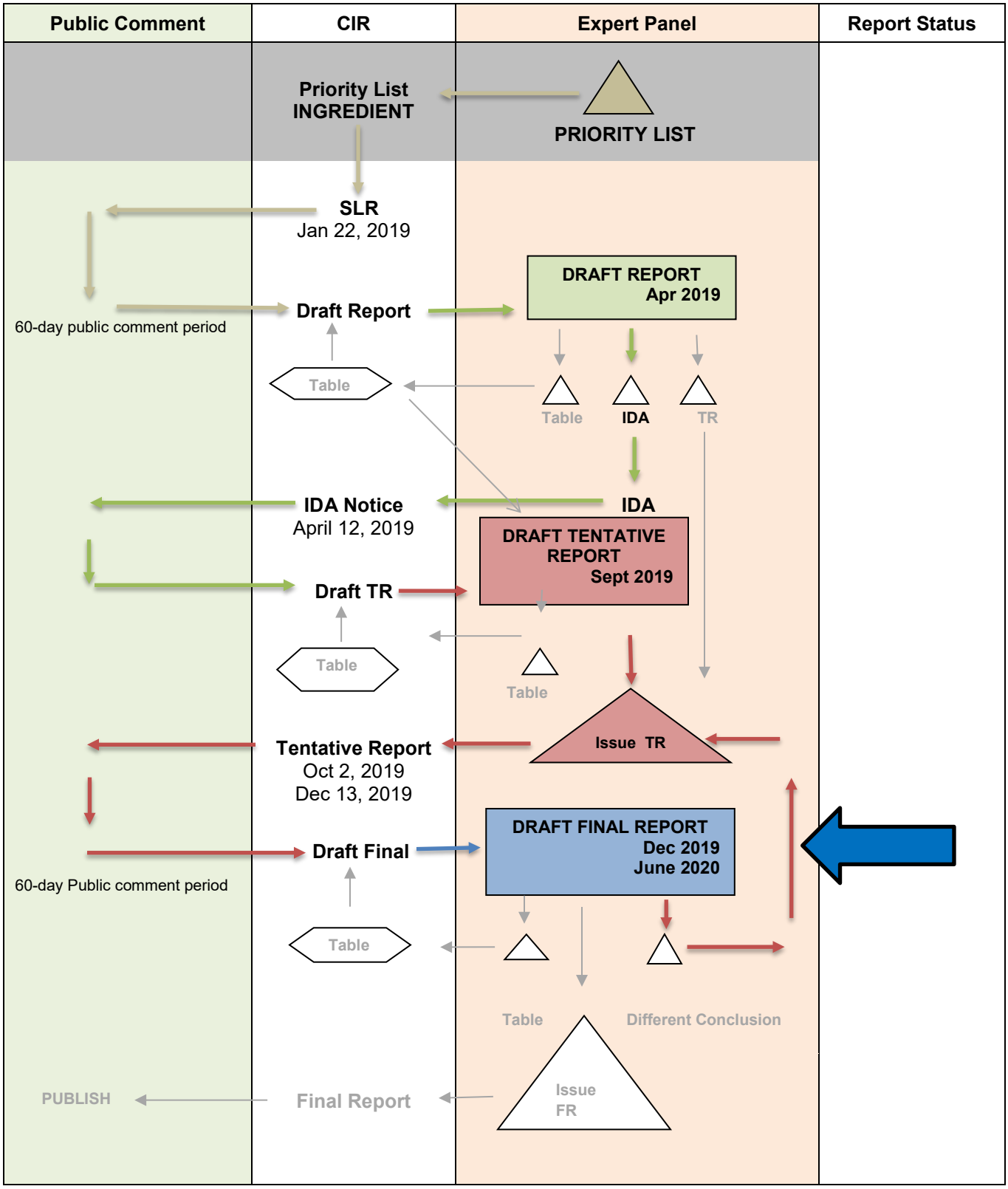
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Palm Tree (juçara and acai)-derived ingredients

MEETING June 2020



History of:

Palm Tree-Derived Ingredients

A Scientific Literature Review (SLR) on Palm Tree-Derived Ingredients was issued on January 22, 2019. Comments and unpublished data were received from the Council before/after announcement of the SLR.

Draft Report, Teams/Panel: April 8-9, 2019

The draft report has been revised to include the following unpublished data that were received from the Council:

(1) Use concentration data
(2) Compositional breakdown data on organic Euterpe Oleracea Juice (freeze dried)
(3) Method of manufacturing data on Euterpe Oleracea Juice (freeze dried)
(4) Compositional breakdown data on a Euterpe Oleracea Fruit Extract trade name material
(5) Properties data (specifications) on a Euterpe Oleracea Fruit Extract trade name material
(6) Method of manufacturing data on a Euterpe Oleracea Fruit Extract trade name material
(7) In vitro dermal and ocular irritation data (in vitro models) on a Euterpe Oleracea Fruit Extract trade name material
(8) In chemico skin sensitization data on a Euterpe Oleracea Fruit Extract trade name material
(9) In vitro skin sensitization data on a Euterpe Oleracea Fruit Extract trade name material
(10) In vitro genotoxicity data on a Euterpe Oleracea Fruit Extract trade name material
(11) Cellular viability assay on a Euterpe Oleracea Fruit Extract trade name material

Comments on the safety assessment (SLR) that were received from the Council have been addressed, and the draft report has also been updated to include current FDA VCRP data.

The Panel issued an insufficient data announcement. Specifically, the Panel determined that the available data are insufficient to arrive at a conclusion on the safety of the following ingredients: Euterpe Edulis Fruit Extract, Euterpe Edulis Juice Extract, Euterpe Oleracea Fruit Extract, Euterpe Oleracea Juice, Euterpe Oleracea Palm Heart Extract, Euterpe Oleracea Pulp Powder, Euterpe Oleracea Seed Powder, and Hydrolyzed Euterpe Oleracea Fruit. The complete list of data needs on these 8 ingredients includes:

For all of the ingredients above

- 28-day dermal toxicity

Euterpe Edulis Fruit Extract and Euterpe Edulis Juice Extract

- Method of manufacture
- Skin sensitization data at maximum use concentrations
- Genotoxicity
- Confirmation that these ingredients are foods

Euterpe Oleracea Seed Powder and Hydrolyzed Euterpe Oleracea Fruit

- Method of Manufacture

Euterpe Oleracea Palm Heart Extract

- Skin irritation and sensitization data at maximum use concentrations

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

To date, there has been no response to the IDA that was issued at the April Panel meeting.

The draft tentative report has been revised to include the HRIPT on a face and neck product containing 3% Euterpe Oleracea Pulp Powder that was included in the wave 2 data submission reviewed at the April meeting. Furthermore, a draft discussion and draft conclusion have been added for the Panel's review.

Draft report comments that were received from the Council prior to the April Panel meeting have been addressed. Also, a request that the title of this safety assessment be changed to Palm (acai and juçara)-Derived Ingredients was received after the April Panel meeting, and this request needs to be addressed by the Panel.

The Panel issued a tentative report with the following conclusion:

The Panel concluded that Euterpe Oleracea Fruit Extract, Euterpe Oleracea Juice, and Euterpe Oleracea Pulp Powder are safe in cosmetics in the present practices of use and concentration described in the safety assessment when formulated to be non-sensitizing. The Panel further concluded that the available data are insufficient to support a conclusion of safety for the following 5 ingredients under intended conditions of use in cosmetic formulations.

Euterpe Edulis Fruit Extract*
Euterpe Edulis Juice Extract*
Euterpe Oleracea Palm Heart Extract
Euterpe Oleracea Seed Powder*
Hydrolyzed Euterpe Oleracea Fruit

*Uses not reported.

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

The Panel issued a revised tentative report with the following conclusion:

The Panel concluded that the following 7 palm tree (Euterpe edulis (juçara) and Euterpe oleracea (açaí)-derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Euterpe Edulis Fruit Extract*
Euterpe Edulis Juice Extract*
Euterpe Oleracea Fruit Extract
Euterpe Oleracea Juice
Euterpe Oleracea Pulp Powder
Euterpe Oleracea Seed Powder*
Hydrolyzed Euterpe Oleracea Fruit

* 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.

The Panel further concluded that the available data are insufficient to make a determination of safety for Euterpe Oleracea Palm Heart Extract under the intended conditions of use in cosmetic formulations. The data needs on this ingredient (previously requested) include:

- Composition data; if the composition of this ingredient is found to be significantly different from the other ingredients in this group, skin irritation and sensitization data would be needed

Draft Final Report, Teams/Panel: June 8-9, 2020

Comments on the draft final report were received from the Council prior to the December 2019 Panel meeting. Comments on the revised tentative report that was announced were also received from the Council. All comments have been addressed.

To date, there has been no response to the data requests on Euterpe Oleracea Palm Heart Extract

Palm Tree-derived Ingredients Data Profile* –June 8-9, 2020 – Wilbur Johnson, Jr.																															
						Toxico-kinetics		Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	GRAS	Method of Mfg	Constituents	Impurities	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Euterpe Edulis Fruit Extract				X																										
Euterpe Edulis Juice Extract					X																									
Euterpe Oleracea Fruit Extract	X		X	X	X							X				X			X	X			X				X			
Euterpe Oleracea Juice	X		X	X			X		X			X				X	X													
Euterpe Oleracea Palm Heart Extract	X																													
Euterpe Oleracea Pulp Powder	X		X		X														X						X					
Euterpe Oleracea Seed Powder					X																									
Hydrolyzed Euterpe Oleracea Fruit	X																													

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

[Palm Tree-Derived Ingredients–8/29/2018; 2/24/2019; 7/30/2019; 10/25/2019; 2/5/2020]

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECE-TOC	Web
Euterpe Oleracea Fruit Extract	879496-95-4; 906351-38-0	1/1	50/12	0	2/0	No	No	No	No	No	No	No	No	No	No	No	No	
Euterpe Edulis Fruit Extract		1/1	60/3	0	0	No	No	No	No	No	No	No	No	No	No	No	No	
Euterpe Edulis Juice Extract		1/1	67/2	0	0	No	No	No	No	No	No	No	No	No	No	No	No	
Euterpe Oleracea Juice		1/1	38/10	27/3	1/0	No	No	No	No	No	No	No	No	No	No	No	No	
Euterpe Oleracea Palm Heart Extract	879496-95-4; 906351-38-0	1/1	5/2	0	0	No	No	No	No	No	No	No	No	No	No	No	No	
Euterpe Oleracea Pulp Powder	879496-95-4; 906351-38-0	1/1	5/1	0	1/1	No	No	No	No	No	No	No	No	No	No	No	No	
Euterpe Oleracea Seed Powder	879496-95-4; 906351-38-0	1/1	100/5	0	0	No	No	No	No	No	No	No	No	No	No	No	No	
Hydrolyzed Euterpe Oleracea Fruit			276/6	0	0	No	No	No	No	No	No	No	No	No	No	No	No	
Genus and Species Names (Not Cosmetic Ingredients)																		
Euterpe Oleracea			40/3	155/4	2/0	EAFUS on ext.	No	No	No	No	No	No	No	No	No	No	No	
Euterpe Edulis			4/2	58/1	1/1	No	No	No	No	No	No	No	No	No	No	No	No	

LINKS

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

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

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

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

Fragrance Websites, if applicable
IFRA (International Fragrance Association) – http://www.ifraorg.org/
RIFM (the Research Institute for Fragrance Materials) should be contacted

Qualifiers

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

APRIL 2019 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team –April 9, 2019

DR. BELSITO: Palm. Okay. So this is the first time we're looking at this report, eight palm tree derived ingredients, and the question is what we think. I thought that all of them except for palm heart were okay. Oh, no. The question was did we need dermal absorption 28-day dermal for all of them? But I wasn't so sure that we could not read across between edulis and oleracea to clear all the endpoints except for palm heart. I didn't know what you guys thought.

Palm heart is clearly insufficient for composition, absorption, sensitization, and irritation. I don't have a clue what's involved. But then we have -- if you combine edulis with oleracea, I think we have all the tox data we need. But if you are not willing to combine those species, then we are missing points for both.

DR. SNYDER: So I had a question, Wilbur, on page 15 under the subchron section. Are those real doses there 10, 20, and 40 grams per kilogram? Is that correct?

MR. JOHNSON: I'll check the publication.

DR. SNYDER: Can we make sure it wasn't milligrams?

MR. JOHNSON: Okay.

DR. SNYDER: I think that seems kind of high.

DR. BELSITO: So my point about dermal and absorption is we have no repro toxicity. But we know that the acai berry juice is GRAS. And then it just says hearts of palms are derived from the same species, so it doesn't mean anything.

DR. SNYDER: No, we'd need absorption; and if it's absorbed, then we're going to have to have additional toxic endpoints. I think there's a likelihood of the systemic toxicity is low, based upon what little bit of data we have.

DR. BELSITO: So we're going insufficient for all of them for composition.

DR. SNYDER: Composition, absorption.

DR. BELSITO: We have some composition though. Or is that not enough?.

DR. LIEBLER: We have several tables of constituents.

DR. BELSITO: Right.

DR. LIEBLER: In the oleracea and the --

DR. BELSITO: Edulis.

DR. LIEBLER: Edulis, right. And I hadn't considered your suggestion of using that information to declare these equivalent enough to cross reference the tox data.

DR. BELSITO: Because then the only tox data we're missing is DART data.

DR. SNYDER: As to whether it's absorbed or not.

DR. BELSITO: Right.

DR. SNYDER: So if we get the absorption data, then if it's absorbed, we need the repro done on all studies. But if it's not absorbed, then we're okay. Because the systemic doesn't look like there's much systemic issues.

MR. JOHNSON: I checked the publication and actually those doses are 10, 20, and 40 grams per kilogram.

DR. SNYDER: They are? Wow, not very toxic.

DR. KLAASSEN: Or not absorbed.

DR. SNYDER: Yeah, that's true.

MR. JOHNSON: Dr. Belsito, you made a comment about the Euterpe oleracea fruit extract, acai berry extract, being GRAS. It was brought to my attention by the Council that actually the trade name material for Euterpe oleracea fruit extract is mentioned in that GRAS classification. But as it turns out, the CAS number is the number for the fruit oil, and not actually Euterpe oleracea fruit extract.

So the trade name, you know, matches what's in the GRAS classification, but the CAS number does not. So if the Council is under the impression that those data --

DR. BELSITO: Then that needs to be removed.

MR. JOHNSON: It's on the fruit oil, so that would have to be taken out.

DR. BELSITO: Yeah, okay. So none of these are GRAS. Okay. So, basically, then what we're saying is all of them are insufficient for composition and 28-day dermal.

DR. SNYDER: Absorption.

DR. BELSITO: Absorption.

DR. SNYDER: Well, if absorption's available. If there's no absorption data, then we run 28-day dermal. And if absorbed, then we want repro tox.

DR. LIEBLER: But we can't really do absorption on botanicals.

DR. SNYDER: Right. We want to a 28-day dermal.

MR. JOHNSON: Dr. Belsito, when you have a chance, will read that list again of data needs?

DR. BELSITO: It isn't very long. It's insufficient for composition and dermal absorption.

DR. SNYDER: 28-day.

DR. BELSITO: 28-day dermal.

MR. JOHNSON: 28-day dermal absorption.

DR. BELSITO: And then, if absorbed, other toxicity endpoints. And then for heart of palm, sensitization and irritation.

DR. LIEBLER: Why are you saying insufficient for composition, Don?

DR. BELSITO: I thought that's what you said, Dan.

DR. LIEBLER: No, no. We are good on composition.

DR. BELSITO: So you're happy with the composition.

DR. LIEBLER: Yeah, we got a lot of data. The only thing I have insufficient is method of manufacture and composition for the seed ingredient. So we've got that oleracea seed powder. That's the seed ingredient I'm referring to.

Now, if somebody can convince me that the fruit extract or the pulp powder or any of those actually contain the seed as well, then I'm okay with our composition. But unless that's clear, then the seed powder is separate. We don't have anything on that. We didn't have any competition on the seed powder.

DR. BELSITO: Okay. So then what I have is insufficient for method of manufacture and composition of oleracea seed powder.

DR. LIEBLER: Yes.

DR. BELSITO: Okay. 28-day dermal for all. Is that right?

DR. LIEBLER: Mm-hmm.

DR. BELSITO: Sensitization and irritation for palm heart.

DR. LIEBLER: Right.

DR. BELSITO: And that's it. Is that correct?

DR. LIEBLER: Mm-hmm.

MR. JOHNSON: One concern that I have -- we have a lot of compositional data in the report. But how do those data relate to what is actually being used in cosmetics? Because these data weren't received from industry.

DR. BELSITO: I think we always have that problem. Don't we?

DR. LIEBLER: That's a question for industry.

DR. BELSITO: I mean, as we always say, we're basing our conclusion based upon what's in the report. And our conclusion is that what's being used by industry will be similar to what we're told in this report.

DR. SNYDER: That's our assumption.

DR. LIEBLER: Is there any reason to suspect that the materials, that the precursors, the fruits and so on, as sourced for cosmetic ingredients are different than those sourced for foods?

I wouldn't think so, but you could raise the question and say we don't know for sure. I would have to agree. But I don't think it's a reasonable assumption that there are different.

MR. JOHNSON: And another question. Based upon the available data, are Euterpe oleracea and Euterpe edulis similar enough for both species to remain in the same report?

DR. LIEBLER: Oh, I think so. But yeah, in fact, the method of manufacture for the edulis fruit ingredients is not nearly as extensive as it is for the oleracea. But I think we can reasonably infer from the oleracea descriptions the method of manufacture, so I'm comfortable with that.

MR. JOHNSON: Okay.

MS. LORETZ: Are there things in the composition that are raising specifically concerns or --

DR. LIEBLER: No, the lack of composition data in method of manufacture for the seed is the only thing I have concern about, the seed powder.

MS. LORETZ: But you still want tox data in addition to the composition?

DR. LIEBLER: Right. We don't have any.

DR. SNYDER: We have limited on the fruit juice and the berry juice.

DR. LIEBLER: Right, since they're not GRAS.

DR. BELSITO: That was the Wave 2 data on the palm powder. So insufficient method of manufacture and composition of oleracea seed powder, 28-day dermal for all sensitization and irritation palm heart. Okay?

DR. LIEBLER: Right.

DR. BELSITO: Okay.

Marks Team –April 9, 2019

DR. MARKS: Oh, yeah. We're getting there. So, this is a first with palm, which is, of course, the common name. Let's see if I can pronounce the botanical name here. Wilbur, are you up again?

MR. JOHNSON: Yes, sir.

DR. MARKS: Okay, good. I had that my note covered it. This is a draft report on palm tree-derived ingredients. There are 8 palm tree-derived ingredients. Ooh, yes, Euterpe edulis and Euterpe oleracea. Man, I'm sure a botanist would have fun with that. I think I'm going to use palm, although it's important to differentiate between these two species, because Ron Shank brings that up. So, Tom and Ron, do you like these 8 ingredients? It's hard not to --

DR. SLAGA: Yeah.

DR. MARKS: Since they're -- but two different species. And the one it's used the most is the Palm Oleracea Fruit Extract, the Euterpe. 330. Low concentrations other than a pulp powder at 3 percent, but the rest are .04, .001. We don't have the concentration on the Hydrolyzed Euterpe Oleracea Fruit. Okay. So, like the ingredients? Needs? What needs do we have?

While you're thinking, I'll go ahead and read Ron Shank's. Euterpe oleracea is the source of acai juice. A-C-A-I, how do you say that?

MS. KOWCZ: Everybody says it differently. It could be acai. That's fine.

DR. MARKS: Acai juice, which is a GRAS ingredient, so no additional systemic tox are needed. If the in vitro skin sensitization tests are appropriate substitutes for in vivo human tests, then the Euterpe Oleracea Fruit Extract and pulp should be safe as used. Little information is presented for Euterpe edulis ingredients. So, this should go insufficient since these products don't appear to be used in cosmetics formulations. No concentrations can be defined or suggested testing. Needs would include genotox, DART, skin sensitization, at least.

And now we have a conflict with brown algae, because for brown algae, we said if we had the genus tox for food and GRAS, we said, okay, we'll accept that for the species within it. If we use this reasoning, we say we have the species; we can't look across from -- we have the genus, but we can't look across from species to species.

DR. HILL: Yeah, but that was --

DR. MARKS: So, I want to point that out, now, that we have an intellectual conflict.

DR. HILL: No, because we had information that all the species in that genus, that were recognized species, were known to be edible, which we don't have here. So, there was a specific case where we had the information about that genus.

DR. SLAGA: Right.

DR. MARKS: Okay.

MS. EISENMANN: I think that Euterpe edulis is also edible, but it's just not a commercial -- it's just not something that's -- it's in Brazil. They don't import as much as the acai, or however you want to say it. I wasn't convinced that the two should be reviewed together and was a little concerned about the term "palm," because it could get confused with the species of palm

that's used to make palm oil, which is a whole different issue, and wondered if this should just be in acai-derived ingredients instead of palm.

Because the other ones, we don't have use. We don't necessarily have a lot of composition data that says these are the same material. I mean, there are composition on bulk, but there isn't any discussion of whether or not those components are the same. I didn't think so. That was my thought, that maybe you just want to -- with this, just getting rid of two the ingredients. And then, you would change it to acai-derived ingredients instead of palm. Because --

MR. JOHNSON: Well, I compared the two species and I found a number of phenolic compounds in common when those two are compared. For example, the catechin, chlorogenic acid, ellagic acid, ferulic acid, gallic acid, and several others in common.

MS. EISENMANN: Okay. Well, then, maybe if you help us write a short paragraph on what components are in common in the ingredients.

MR. JOHNSON: Yes. Um-hm. Now, I must admit, also, that some of those components were identified in the fruit, and the fruit is not being reviewed in this safety assessment. The fruit extract is, but not the fruit. So, I'm talking about just comparing the species, this species.

DR. MARKS: So, Tom, Ron, what do you think? Delete the two Edulis species -- or I mean, Edulis ones with fruit extract, ones with juice extract? Or keep it in?

DR. HILL: I don't have any sense of how similar these are. So, if we're talking about the oleracea, the acai, as far as I understand, what's consumed is the berries. Are the seeds within the berries? I assume they are. That's why plants make berries.

MS. EISENMANN: That's the species the hearts of palm is also from, which is -- although it's listed, we don't have a supplier anymore. And I'm told that the company that was using it is getting out of it because they don't have a supplier anymore.

DR. HILL: The reason I ask that, really, besides comparing the Edulis with the Oleracea, is we don't have any data for seed extract. If you use the berries -- the acai berries, is that seed in all that goes into drinks? And does the seed just pass through undigested? Or is it juiced in such a way that the seeds are crushed up and all of that goes with the drinks that you can buy, just about pervasively these days?

DR. SLAGA: We had no data needs for the oleracea. And I read across to the other and said that we -- they both did say that we could delete the two.

DR. MARKS: Yeah, I think that's the issue. It would appear that we could be safe for all the oleracea species.

DR. HILL: First of all, how are these things similar? Because, I mean, we can leave the Edulis in there and declare them insufficient if we know there's enough similarity. You'd have a split conclusion. You're not trying to read across.

DR. MARKS: Right.

DR. HILL: And then, how do you clear -- that's why I'm asking the question. How do you clear the seed extract if, what we know about the berries, we're not including the seeds? So, how do you clear the seed extract? How do you clear the palm heart powder? I don't know what palm heart even is. And hydrolyzed fruit, I don't know what -- I want to process method of manufacturer and some further information about exactly what is this stuff.

DR. MARKS: Well, for the palm heart, there's only three uses.

DR. HILL: They're low concentration.

DR. MARKS: And the highest leave-on was .001. So, to me, the concentration was so low. I thought the fruit extract would get a lot of the compounds in this species, the oleracea. Therefore, I extended that to the -- and it's even at a very low concentration. The pulp powder, we have in Wave 2 at 3 percent sensitivity, and that was fine. So, I felt we could extend it to the seed and then the other fruit products, the hydrolyzed, because of the fruit extract.

DR. SLAGA: Right.

DR. HILL: Yeah. So, I'm going to abstain on that until I can do some more homework about what the nature of these things are, than I got the opportunity to do between when I saw it and now.

DR. MARKS: Yeah. So, I mean, one tentative report our team will be moving for would be safe for all these, versus safe for the oleracea species, and sufficient for the two Edulis ingredients. That's what Ron suggested. I'm fine with that. I'm not sure I want to delete it. It's in the same genus, so it just shows that we're differentiating the two.

And then, for the Edulis, we would want to know -- we have to say what we need. One would be, we obviously would want the sensitization data and we would want systemic toxicity data. Is it a food? We don't know whether it's a food in Brazil. Do we, Carol?

DR. SLAGA: I thought it was.

MS. EISENMANN: To my understanding, it is.

DR. MARKS: It is? But do we have a reference for that?

MS. EISENMANN: But I don't know that much about it.

DR. MARKS: Do we have a cookbook that has it in it? A Brazilian -- who reads Portuguese that could get a -- so, again, if we put insufficient, we need to alert as to why. And then, I guess --

DR. HILL: No data. That's easy.

DR. MARKS: Yeah. And then, if we use that conclusion, we normally do an insufficient data announcement on the first review because we usually don't put a tentative report with a conclusion without giving industry a chance. So --

DR. SLAGA: How about a sensitization and genotox? Ron had DART, but I don't think we need to.

DR. HILL: I don't have DART on this one.

DR. SLAGA: Well, no, Ron --

DR. HILL: Oh, Ron Shank.

DR. SLAGA: Ron Shank.

DR. MARKS: Sensitization and genotox for --

DR. SLAGA: Yeah, both of them you want to know what low concentration is.

DR. HILL: What I wrote about that, is we would not expect the DRPA to be informative in this case. Because if anything is going to sensitize, it's going to require metabolism that's likely to be present in these substances. And that pretty much leaves the KeratinoSens in vitro test as the only info that the -- and we have an HRIPT on the pulp powder. But I don't have any good senses to how well the pulp powder represents the berry, for example. And I don't necessarily think that the same thing is going to be in the seeds as in the berries as in the palm heart as in the whatever else. That's typically not the case.

Those constituents between parts typically vary greatly. But I don't know. So, sometimes, in these botanicals, we start to report with a botanical write-up that says, here's what the berry is like, and here's what the seeds are like. They're small, oily, and we eat them. Or the seeds are excluded when they're juiced, and -- like that. I think we need -- I mean, I'll do that homework myself and see what I can find. But I feel like that's needed knowledge anyway.

MR. JOHNSON: Dr. Marks, one question. You mentioned that Dr. Shank stated that the Euterpe Oleracea Fruit Extract is GRAS. But apparently, there was a mistake made, because the acai berry extract is a trade name for a Euterpe Oleracea Fruit Extract. But, according to FEMA, this actually relates to the cast number. And the cast number is for the fruit oil.

So, actually, as I'm saying that the trade name and the FEMA name are the same, but the cast number is different. So, it's very unlikely that this classification relates to the fruit oil and not the Euterpe Oleracea Fruit Extract. That was a comment from the counsel.

DR. HILL: Since it's fruit oil, I would think that might be coming from seeds. Seeds are mostly oil. That's going to be very different than whatever's there in the fruit which was my point.

DR. MARKS: So it seems like -- first of all, let's go back one step. Do we want to keep all the ingredients in here and not eliminate those two Edulis ingredients? Yes?

DR. SLAGA: Yes. Keep them all.

DR. MARKS: So, then, we're into, we have an insufficient data announcement. Basically, what we want is, for the Edulis species -- let me go -- you aren't totally sanguine with the oleracea species, are you, Ron Hill? You would like to see more about the seed.

DR. HILL: Seed and the palm heart.

DR. MARKS: Even the palms heart with that low concentration, the .001?

DR. HILL: I think that's due diligence in answering the question, what is this stuff? Yeah, I agree with you. The odds --

DR. SLAGA: But palm heart is eaten.

DR. HILL: Palm heart is eaten?

DR. SLAGA: Yeah.

DR. HILL: For this species?

MS. EISENMANN: Yes.

DR. SLAGA: Well, I mean, it's -- you go to Brazil --

DR. HILL: I don't even know what a palm heart is.

MS. EISENMANN: Yeah, they cut the palm tree. And it's the inside of the palm tree hearts.

DR. HILL: Apparently, I'm culturally challenged.

MS. EISENMANN: And that's the -- right. Yes.

DR. HILL: So, the heart of the trunk is what's eaten?

MS. EISENMANN: Yes.

MS. KOWCZ: It's actually very tender.

MS. EISENMANN: Of this species.

DR. HILL: All right. So, we have no reason to believe that that's anything like what's in the berries? Because berries are fruit.

MS. EISENMANN: Correct. And like I've said, the one supplier that we had listed is no longer making this. And the company that reported using this is getting out of it, because this supplier isn't making it. So, if you go insufficient with it, it doesn't matter because we don't have any suppliers. And you're not getting any more data on it, I'm telling you.

DR. HILL: Got it. I believe you.

DR. MARKS: Insufficient. Which one aren't you getting more data, again, Carol?

MS. EISENMANN: I know the palm heart extract.

DR. MARKS: Yeah. Okay.

MS. EISENMANN: They're not making it anymore. My guess is it sells much better as a food than it makes with making a cosmetic ingredient. I don't know if they get more money out of it that way.

DR. MARKS: For me, it's a non-issue without all the concentration. It's hard to believe there's -- but any rate --

DR. HILL: Well, no. That matters, because at that low concentration, if it's eaten, we should be fine. If somebody was going to sensitize, I think they would sensitize that way.

DR. MARKS: So, for the two Edulis ingredients, we basically have no data. We'd like to see sensitization and genotox. I put in there, are these foods also? Let's confirm that, or confirm they are foods, because that will be reassuring if they're eaten. Then, for the oleracea, we need -- basically, what is it in the -- we have the seed powder. Is there anything besides the seed powder? Is that the only one of the oleracea you were concerned about, Ron Hill?

DR. HILL: I'm sorry? I got a little --

DR. MARKS: I'm back to, now, under the oleracea.

DR. HILL: Oh, I have low data for the seed extract, the palm heart powder --

DR. MARKS: Is there a seed -- where are my --

DR. HILL: Seed extract.

DR. MARKS: Why am I not seeing seed extract?

DR. HILL: Is there no seed extract, just seed powder?

DR. MARKS: I was going to say, I see seed powder.

DR. HILL: Okay, my bad. All right. So, no data for the seed powder. Plus, we don't have method of manufacturer, and you say that we're not likely to get that one either or we don't know on that.

MR. JOHNSON: Oh yeah, we have method of manufacturer data on the Euterpe Oleracea Fruit Extract, the Euterpe Oleracea Juice, and Euterpe Oleracea Pulp Powder.

DR. HILL: Not the seed powder?

MR. JOHNSON: Not the seed powder.

DR. HILL: Not the hydrolyzed fruits?

MR. JOHNSON: Right.

DR. HILL: Not the seed powder and not the hydrolyzed fruit?

MR. JOHNSON: Right. Um-hm.

DR. HILL: And not the palm heart powder? But we eat those. And that's why I asked, do we eat the seeds?

DR. MARKS: So, what you would want -- it looks like, of the oleracea ingredients, it's really the seed powder you're most concerned about.

DR. HILL: I would also like to know how they make and what they're doing with the hydrolyzed fruit.

DR. MARKS: So, under the seed powder, what would you like? Everything?

DR. HILL: Method of manufacturer, and that's probably enough. But some indication of how similar the seed powder is, in terms of composition, to the things for which we do have data.

DR. MARKS: And then the other one was the fruit?

DR. HILL: Hydrolyzed fruit.

DR. MARKS: And what do you want for that?

DR. HILL: Method of manufacturer.

DR. MARKS: So, method of manufacturer for both of those. Okay. So, this was the one where, as I was reviewing these ingredients, I said, can we put a double asterisk at the bottom of the conclusion, like we do for use and concentration of unused ingredients, that we expect the composition to be similar for different species?

DR. HILL: If you're talking about the Edulis when you say different species --

DR. MARKS: Yeah. So, in other words, you could say, this is safe of presuming that the composition is same or similar. It's just a thought, but you know, we do it for use and concentration. So, we're saying we need a lot of data for the -- and we should get that. But if they're not being used, could we say, if the composition is similar, they should be safe? But that was my thought. I'd be interested in your response, Ron or Tom.

DR. HILL: Well, I'm kind of interested that it -- I mean, unless Edulis is a newly discovered species, it sort of surprises me that some natural product chemists haven't gone out and -- just because they get interested in what's in these things -- done the chemical characterization. But we didn't find any is what you're telling us?

DR. MARKS: Yeah. Okay, so, tomorrow, I'm going to move that we issue an insufficient data announcement. It's insufficient for the two Edulis ingredients. We really don't have any tox data. At a minimum, we need sensitization and genotox data. And we'd like to confirm that these are actually foods for the Oleracea Seed Powder and the Oleracea Hydrolyzed Fruit. We'd like to see the method of manufacturer. Okay?

MR. JOHNSON: So, Dr. Marks, the other oleracea ingredients are considered safe for conception of those two?

DR. MARKS: Yes.

MR. JOHNSON: Okay, thank you

Full Panel –April 10, 2019

DR. MARKS: So this is a draft report on eight palm tree derived ingredients, which means it's the first time we've looked at these ingredients. These ingredients were derived from two palm tree species, Euterpe -- if that's how you pronounce it -- edulis and Euterpe oleracea.

We found that there were data gaps, and so we would move that there be an insufficient data announcement. For the two edulis ingredients we had no data, so at a minimum we would want to see sensitization and genotox data, and we'd want to confirm that these actually are foods. For the oleracea seed powder, method of manufacture, for the oleracea hydrolyzed fruit, method of manufacture also.

So bottom line, insufficient data announcement. I don't know if --

DR. BERGFELD: Is the motion?

DR. MARKS: Yes.

DR. BERGFELD: Don's team.

DR. BELSITO: We're also insufficient. We have, maybe, slightly different request for needs. We thought we need a method of manufacture and composition for the oleracea seed powder, 28-day dermal for all, and sensitization and irritation for palm heart. But the others were okay in terms of sensitization and irritation.

DR. BERGFELD: Wilbur, you want to speak?

MR. JOHNSON: Yeah, I just want to confirm the combined --

DR. MARKS: Yep. Combine the needs?

DR. BELSITO: Yup.

MR. JOHNSON: Yeah.

DR. MARKS: That's what we'll move out for.

DR. BERGFELD: You want to list yours, Jim? Wilbur's going to take them down.

DR. MARKS: So for the two edulis ingredients, we have no data, so Dr. Belsito mentioned that we need method of manufacture, obviously, but also sensitization and genotox at a minimum, and confirm if they're foods. If they're foods, then it would be less concerning about systemic toxicity.

For the oleracea species, we had seed powder, and the hydrolyzed fruit, method of manufacture. And then, Don, why don't you add on your request, because you had some others, sensitization, and I think one or two other points that your team --

DR. BELSITO: 28-day dermal for all, and sensitization and irritation for palm heart. But they're buried in my notes. We're working to get them off of the thumb drive.

DR. BERGFELD: Are you okay, then?

MR. JOHNSON: I'm okay.

DR. BERGFELD: So we're moving ahead with an insufficient data announcement. We have needs as were stated here. And Ron Hill, you have a comment?

DR. HILL: Yeah, just one quick comment is I wanted to note that, especially as there's movement away -- has been complete movement away from animal evaluation for sensitization, that the DRPA only assesses direct protein reactivity. Did I say it backwards? I'm sorry. DPRA only measures the reactivity of things that are already electrophiles with proteins.

And so most of the things that we'd expect to see in botanicals aren't of that nature. So that leaves, in this particular instance, only the KeratinoSens assay to rely on.

And I just wanted to point out that there's only so much we can depend on that DPRA, because it's only measuring electrophiles reacting with proteins, that's all it measures. So we have to be aware of that as we move forward, and especially think about inserting it into a conclusion. Because there's nothing equivalent to metabolic activation being used with that DPRA, to my knowledge,

DR. BELSITO: No, there's not. There is a peroxidase DPRA, which looks at metabolic activation. The DPRA measures step one in the adverse outcome pathway, that's the ability to bind and form a hapten. So, it's just simply looking at that. KeratinoSens is looking at the ability of the molecule to activate keratinocytes, which is the second step of the adverse outcome pathway.

So they're just ways of looking, people are still playing with it. Right now, it appears the best two out of three, with a third step being looking at lymphocyte activation, or rather macrophage activation, with assays for that.

DR. LIEBLER: The DPRA is really more useful with pure compounds, rather than evaluating complex mixtures.

DR. BERGFELD: Any other comments?

DR. SADRIEH: You can also use the LuSens assays instead of KeratinoSens, that's another one. LuSens is also used for looking at the second key step. Instead of KeratinoSens, you can use that too.

DR. BELSITO: Right.

DR. HILL: And my point was, is that if sensitization requires metabolism in human skin, you will pick that up with a properly done HRIPT. But these in vitro tests that are being done might or might not, and that was my point?

DR. BERGFELD: Well, that'll be very nicely reflected in the minutes; and perhaps discussed in the discussion, if that comes to that.

All right, I'm going to call the question, insufficient data announcement with the needs have been elucidated. All those in favor? Thank you. It is approved unanimously.

SEPTEMBER 2019 PANEL MEETING – SECOND REVIEW/DRAFT TENTATIVE

Belsito Team – September 16, 2019

DR. LIEBLER: Nothing new.

DR. BELSITO: And nothing old.

DR. KLAASSEN: Lack of new data.

MS. EISENMANN: This is one where I'm not sure why you need a 28-day dermal for it.

DR. BELSITO: Yeah. I did a little research. They're both foods, okay?

MS. EISENMANN: Right.

DR. BELSITO: So can we discuss the 28-day dermal? And oleracea is the main source of heart of palm. The oleracea is called acai, also spelled acai' and it's cultivated for both its fruit and the edible hearts of palm. The Euterpe juice and pulp are also consumed. So, they're all foods.

MS. EISENMANN: There shouldn't be a concern of systemics because there's also data in the report. There's a NOAEL of -- that's hard to believe it's correct, 40 grams per kilogram. I think Wilbur looked it up last time and said that that couldn't be correct.

DR. SNYDER: Well, I asked him if that was correct, yeah.

DR. KLAASSEN: That's what it says.

MS. EISENMANN: And that's a 90-day study.

DR. BELSITO: I thought the Euterpe oleracea fruit extract, juice and pulp powder were safe as used. And the others were insufficient for method of manufacture and skin sensitization.

MR. JOHNSON: Just one more tab, Dr. Belsito.

DR. SNYDER: Originally, we went 28-day dermal all. The food extract we wanted method of manufacture, sensitization, genotox, and wanted to know whether it was a food.

DR. BELSITO: They are foods.

DR. SNYDER: Okay. And then the seed powder and the fruit, we wanted method of manufacture. The heart extract we wanted irritation and sensitization.

DR. BELSITO: Right.

DR. SNYDER: So, you're saying we're clearing the --

DR. BELSITO: We've got the oleracea fruit extract and juice are safe. And the -- okay, so wait a minute. The oleracea fruit extract and oleracea juice and oleracea pulp powder are safe as used. For the Euterpe edulis fruit extract and edulis juice extract we need manufacturing and skin sensitization. For the oleracea seed powder and hydrolyzed oleracea fruit we need method of manufacture. And for the palm heart we need skin irritation and sensitization.

MR. JOHNSON: Dr. Belsito, you mentioned that Euterpe edulis fruit extract and Euterpe edulis juice extract are used in foods. Is there a reference for that food use?

DR. BELSITO: Yeah. I didn't copy the references. I just copied out of the paper. One of them is a highly prized dish often called, "Millionaire's Salad" due to its price. But if you just go on Google and search it, you'll come up with a million references to the food uses, which is what I did. I think that's what I used. I can check right now.

MR. JOHNSON: Is that something you could reference?

DR. BELSITO: No, but you can go to the article. There's an article --

DR. KLAASSEN: They have in references, The Cosmetic Ingredient Dictionary.

MR. JOHNSON: On PDF Page 24, in the non-cosmetic use section, it is stated that heart of palm is the edible part of the apical meristem of palms. So, that would include Euterpe oleracea and Euterpe edulis. That's just the genus and species name, but not the specific ingredient names. So, there is a reference for that. That's the apical meristem.

DR. LIEBLER: I think we definitely don't need the 28-day dermal on any of these.

MR. JOHNSON: What's the reason for that, Dr. Liebler?

DR. LIEBLER: Foods.

MR. JOHNSON: Okay.

DR. LIEBLER: And for -- Euterpe oleracea juice we've got toxicity data.

DR. BELSITO: You can use the britannica.com reference if you want if you can use Encyclopedia Britannica. And then there are a million papers looking at neuroprotective effects of acai as an antioxidant fruit. It clearly is used as a food substance, both of them. It's not like GRAS. You're not going to find anything in regulation.

DR. LIEBLER: I guess basically, to Wilbur, is that he can follow some of the links to see if he gets to citable material on food use.

MR. JOHNSON: Yeah. Back to the reference of the non-cosmetic use section. Just saying that heart of palm is the edible part of the apical meristem of Euterpe oleracea and Euterpe edulis, both of those species. Is that sufficient for food use relating to all of the ingredients that are being used?

DR. BELSITO: Well, the other ingredients that are being used are the seed powder. The juice of the fruit is consumed. You can see food uses for that. The seed powder is what we asked for.

MR. JOHNSON: Method of manufacture.

DR. BELSITO: Right.

DR. KLAASSEN: Which isn't used.

DR. LIEBLER: So heart of palm, according to the reference you cite -- Wilbur, reference 42 -- of the apical meristem of both oleracea and edulis is considered a gourmet vegetable.

MR. JOHNSON: Right.

DR. LIEBLER: So, will that clear the fruit and juice of edulis?

MS. EISENMANN: I'm sure we'll be able to find another reference for those.

DR. BELSITO: The fruit and juice are used as foods as well.

DR. LIEBLER: Okay. That reference might not be sufficient, but there are others that are gettable by some internet searching, following the links to see if you get to citable material. We don't need to do more of that here. It's just a waste of time.

Sounds like we can bring those all in on terms of food safety and that we will mitigate our concern about the 28-day dermal. So, that gets rid of that. Then what do we have left, concerns with these guys?

DR. BELSITO: Well, we still need method of manufacturing, skin sensitization, or the edulis fruit extract and juice extract. And we need method of manufacture for the seed powder and the hydrolyzed Euterpe oleracea fruit. And we need sensitization, irritation for the palm extract.

But we have sufficient data for oleracea fruit extract, oleracea juice, and oleracea pulp powder as safe as used. So, three of them safe as used and the rest still as listed except that the genotox goes away for one of them. Right? I have genotox going away for -- whatever the one we asked for genotox.

DR. SNYDER: Fruit extract.

DR. BELSITO: Yeah. So the fruit extract and the juice extract, we no longer need genotoxicity or confirmation that they're ingredients in food. We need manufacture and skin sensitization.

DR. LIEBLER: I flagged the Euterpe oleracea fruit oil, which isn't one of the ingredients in this report. But I thought it might be a useful weight of evidence although not a cosmetic ingredient. The oil would be high in constituents of concern. And if the oil was clean on sensitization we could bring that in. That may not suffice for our current deficiency. We've only got pulp powder HRIPT.

DR. BELSITO: I think you lost me.

DR. LIEBLER: Okay. We only have the pulp powder, but we don't have any of the other oleracea ingredients for sensitization.

DR. BELSITO: No. We have the fruit extract and the fruit juice are clear. So, the oleracea fruit extract, the juice and the pulp powder are safe as used. We have those three.

DR. LIEBLER: Was that in Wave 2? Did I miss it?

MS. EISENMANN: What kind of oil were you talking about? Because they have reviewed the triglyceride oil from the Euterpe oleracea Fruit Oil. That's in the 2017 plant oil reports.

DR. LIEBLER: Yeah, no. Fruit extract, are you talking about the in vitro data?

DR. BELSITO: Yeah, the in vitro data.

DR. LIEBLER: The in vitro data. So, we have no in vivo data?

DR. BELSITO: But we have two out of three, right?

DR. LIEBLER: Right. So, we have the KeratinoSens and DPRA on the fruit extract pulp powder. Oh, I know. My note was that we could use the food oil -- it's already in the report -- as weight of evidence in the discussion.

DR. BELSITO: For what?

DR. LIEBLER: Because the fruit oil contains --

DR. BELSITO: But the weight of evidence to clear what?

DR. LIEBLER: For sensitization. I guess you feel like you don't need it.

DR. BELSITO: No, I don't need it.

DR. LIEBLER: You just don't need it? Okay. Then we delete that section, the Euterpe Oleracea Fruit Oil in the italics.

DR. BELSITO: The current approach to assessment of hazard for sensitization is if two of the three tests are negative. That is DPRA, KeratinoSens, and then either the LuSens or the MUSST for lymphocyte activation. And this already clears two of the three. So, it doesn't represent, theoretically, a sensitization hazard.

DR. LIEBLER: Okay. That's fine.

MS. FIUME: Now, this doesn't represent a sensitization hazard itself. Typically, in botanicals, the caveat is when formulated to be non-irritating and non-sensitizing because of possible cumulative exposure.

DR. BELSITO: Right. And there we can use the oils to see whether there are any sensitizers of concern.

MS. FIUME: So, then, is that not needed in this conclusion?

DR. BELSITO: No, I think it's needed in all the botanicals.

MS. FIUME: Okay. That's what I thought. I just wanted to make sure that that was a part of the conclusion.

MS. EISENMANN: I don't know if you saw the request from CIR SSC to add the common names to that title; because palm, they don't want it to be confused with palm that's used for palm oil.

DR. LIEBLER: Yeah. I was okay with that.

MS. EISENMANN: What?

DR. LIEBLER: I was okay with that suggestion.

DR. BELSITO: What's the different between palm and palm that's used as palm oil?

MS. EISENMANN: Palm is elaeis guineensis, however you say it. It's a completely different genus and species.

DR. BELSITO: Okay. I don't care.

MR. JOHNSON: In your comment, you mentioned changing the title to "Palm (Acai and Jucara)-Derived Ingredients." So, that's fine?

MS. EISENMANN: Yeah. That's fine with me if it's okay with the panel.

DR. LIEBLER: That's fine.

DR. BELSITO: Why were they concerned that it would be confused with palm oil?

MS. EISENMANN: Because there's issues about palm, about growing it in an environmentally friendly way. So they don't want it to be tied in with this because it's completely different.

DR. BELSITO: I wasn't aware of that. Palm oil isn't grown in an environmentally friendly way?

MS. EISENMANN: Sometimes. Sometimes there have been issues with sourcing palm oil.

DR. BELSITO: Sourcing it?

MS. EISENMANN: Um-hmm.

DR. LIEBLER: Yeah. They hack down a rainforest and plant palm.

MS. EISENMANN: Right. That's all there is. So, they're putting a pushback on using palm. Well, this isn't the same palm, it's a different palm.

DR. BELSITO: Ah-ha. You want the tree-huggers off your back, including environmental working group, the Women's Voices for the Earth.

MS. EISENMANN: Well, it's correct though.

DR. BELSITO: It's okay. I'm a tree hugger.

DR. LIEBLER: I just hope nobody got their palm greased over this.

DR. BELSITO: No. I use canola oil and olive oil.

MR. JOHNSON: Dr. Belsito, other than the changes with respect to data needs, should there be any other changes or additions to the discussion section as written?

DR. BELSITO: No.

MR. JOHNSON: Okay.

DR. BELSITO: Are we done with that?

DR. SNYDER: Yes.

Marks Team - September 16, 2019

DR. MARKS: This is a draft tentative report on palm tree-derived ingredients. There were 8 ingredients and an insufficient data announcement was issued in April of this year. The needs were outlined in the August 22nd memo by Wilbur. A 28-day dermal and for several of the fruit extract, the juice extract, a number of requirements. I won't read all those down that we asked for. To date, we haven't received a Wave 3 or 4 on these ingredients. There's been no new data, no response.

So, Ron and Tom? Your comments? Do we move forward with a tentative report with an insufficient conclusion and the needs as outlined below that's on this memo?

DR. SLAGA: Is there HRIPT data?

DR. BERGFELD: We got nothing.

DR. SLAGA: Huh?

DR. MARKS: Nothing.

DR. BERGFELD: Nothing on this.

DR. SHANK: Okay. The needs include sensitization data at maximum use concentrations for Euterpe edulis fruit extract and juice extract. but they're not used so there is no maximum use concentration. So, that needs to be clarified. For the same group, the fruit extract and the juice extract, confirmation that these ingredients are foods. If they are foods, then we don't need genotoxicity data, so those should be tied together.

And for Euterpe oleracea palm heart extract, the last need says skin irritation and sensitization at maximum use concentration. The maximum use concentration is 0.001 percent. It is a food, so do we really need sensitization data, I don't think so. And then I had lots of comments on the tables.

DR. MARKS: Okay. Sensitization for EOU (phonetic) fruit extract and pulp powder was okay and that wasn't required.

MR. ANSELL: We would also agree that for the 3-oleracea fruit juice and pulp, that they are foods. That there is a 90-day rat study with a NOAEL of 40 grams. And there's also a 16-week anti-carcinogenicity study, which I continually object to that title, but found no evidence of toxicity.

So, we would also argue, consistent with the past procedures with these materials, that the 3-oleracea fruits, oleracea juice, and oleracea pulp powder be concluded to be safe -- or safe when formulated to be non-sensitizing. And that the oleracea palm seed and hydrolyzed materials continue to progress as insufficient.

DR. MARKS: Repeat that again. The ones that are foods, Oleracea --

MR. ANSELL: Oleracea fruit, oleracea juice, and oleracea pulp powder.

DR. MARKS: Because that was one of the questions last meeting, which ones are foods. So, these are foods?

MR. ANSELL: As well as some tox data.

DR. MARKS: Ron? Tom?

DR. SLAGA: I didn't find anything.

DR. MARKS: Fruits, extract, and pulp powder. And I have the sensitization for the pulp powder to be okay. Let me take a look.

MS. FIUME: Dr. Marks, I believe that was Wave 2 last meeting. The summary is on PDF Page 30 of the current report.

DR. MARKS: Yes. So, if that's a food, I would agree that that would be a safe. I'm not sure we even need to have when formulated to be non-sensitizing, although we often do that with botanicals.

MR. JOHNSON: I have a question. Is this saying -- what is the basis for saying that this is food? Do you have a reference for that?

DR. MARKS: Yeah, that was my question to Jay, and then Ron was looking it up, are these really foods? Which, the ones that we can identify as foods for sure, then we are not as concerned about the systemic toxicity and we have some other data to support the lack of systemic toxicity. What's your take on this, Ron Shank?

DR. SHANK: If they're foods, then the systemic tox is not needed.

DR. MARKS: Pardon?

DR. SHANK: Oh, sorry. Those ingredients which are foods don't require systemic toxicology data, only skin data if not present already.

DR. MARKS: Jay, is there any documentation how these are food? How do you know these are foods?

MR. ANSELL: Carol told me. I'll have to ask Carol for the references.

DR. MARKS: Oh, okay. And it was just those three that she confirmed were foods? The fruit, the juice, and the pulp powder?

MR. ANSELL: Correct. The oleracea.

DR. MARKS: Yeah. The oleracea fruit.

MR. ANSELL: But not oleracea palm or oleracea seed.

DR. MARKS: Right. Just the oleracea fruit, juice, and pulp powder. So, I think it'll be -- we can confirm that with Carol. Maybe, Wilbur, she an give you a reference to that effect that could be included. Comments?

You know, it's kind of interesting because, with the brown algae, there were so many ingredients that Priya started this table. I kind of like the idea for any of these ingredients that potentially are foods, we have similar tables so you go down and check.

Okay, this is food. Do we have sensitization? Yes or no. This is a food. This is not a food. We need systemic tox. So, Wilbur -- maybe Ron, if you and Tom concur, you could create a little table to that effect.

DR. SLAGA: That would be good.

DR. MARKS: Then maybe moving forward, when we have botanicals in which -- unless all of them are GRAS and it's a no-brainer, we actually create a table and it makes it easier to scan. Yeah. That would be nice, Wilbur.

MR. JOHNSON: Now, repeat what that table you want?

DR. MARKS: Basically a table just like Priya did for the brown algae, where you have which ones are foods and which ones -- the big issue with them was sensitization, irritation. And when we had data on both, then we could come to a conclusion with those, particularly they were a safe like many of the brown algae. And the same with these.

From what we now know with oleracea fruit, juice, and pulp powder, we could move that they are safe when formulated to be non-sensitizing. And the remainders are insufficient for the request below, other than -- as Ron, you pointed out -- the Edulis fruit extract and the juice extract. Either they're not used so we aren't going to get a maximum concentration, so we should remove that. And then the oleracea palm heart extract, there's low concentration of use so that we really need sensitization on that.

Okay. So, we'll be seconding a tentative report tomorrow. We'll suggest -- as you have pointed out, Jay -- that the oleracea fruit, juice, and pulp powder are foods. And if we have a conclusion, safe when formulated to be non-sensitizing, we could move forward with a safe for those three and insufficient for the other remaining ingredients. That would be five. Does that sound reasonable, Tom and Ron?

DR. SLAGA: Yep.

DR. SHANK: Yes.

DR. MARKS: Sorry. Could you hear me clear enough in the back there? We'll take a 10-minute break.

DR. BELSITO: So, at the 2019 meeting we had issued an insufficient data announcement for 28-day dermal tox and all the ingredients. For the edulis fruit extract and juice extract, method of manufacture, skin sensitization and maximum use concentration, genotoxicity, confirmation that there were foods; for the oleracea seed powder and hydrolyzed oleracea fruit, method of manufacture, and for the palm heart extract, skin irritation and sensitization.

And there have been no data that were provided other than I did do a review, and both of these are foods and have food uses. So we can dismiss, I thought, the 28-day dermal. The oleracea, in fact, is the main source for heart of palm.

So, I thought that we would then be at the point where the oleracea fruit extract and oleracea juice and the oleracea pulp powder are safe as used. And the others are insufficient for sensitization and irritation. And the seed powder and the hydrolyzed oleracea fruit for method of manufacture.

DR. MARKS: We basically second that. We also thought the oleracea fruit juice, pulp and powder were foods. We added the caveat, formulated to be non-sensitizing since with botanicals we add that if there were multiple botanicals put together. And then the other five are insufficient.

DR. BERGFELD: Is that agreeable?

DR. BELSITO: Yes.

DR. BERGFELD: And that's sort of a summary of what you said?

DR. BELSITO: Um-hmm.

DR. BERGFELD: All right. Any other discussion regarding the insufficiencies of Palm? Seeing none, this was going to go a tentative final -- insufficient? Tentative insufficient?

DR. MARKS: No, tentative report with a conclusion safe and insufficient. It's a split conclusion.

DR. BERGFELD: All right, call the question, all those in favor please indicate by raising your hand. Thank you, unanimous. Did you capture everything Wilbur?

MR. JOHNSON: Yes I did, Dr. Bergfeld, thank you.

DR. BERGFELD: Okay. All right, moving on to the next ingredient then with the Sulfites, it's Dr. Marks presenting.

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DR. BELSITO: Okay. So, at the September meeting we issued a tentative report that the fruit extract, the juice, the pulp powder was safe in cosmetics in the present practice of use and concentration when formulated to be non-sensitizing. And that the data were insufficient for five of the ingredients for different reasons.

For the edulis fruit extract and edulis juice extract, manufacturing, skin irritation and sensitization. For the seed powder and fruit, method of manufacture. And for the palm heart extract, skin irritation and sensitization.

DR. SNYDER: Hydrolyzed fruit. The hydrolyzed fruit, right?

DR. BELSITO: Hydrolyzed fruit, yeah. The seed powder in hydrolyzed fruit. We need method of manufacture and we didn't get any of these.

And so, Dan, you combined a bunch of stuff before on the first one that took us an hour to get through, whatever one that was. Do you want to say --

DR. SNYDER: Pomegranate.

DR. BELSITO: Yeah, pomegranate. Do you want to say we don't need something here? Or are our conclusions from last time fine?

DR. LIEBLER: I don't think our conclusions from last time were any different. We didn't get any new data, right?

DR. BELSITO: No. But we didn't get any new data on pomegranate except for bleaching and --

DR. LIEBLER: No, I don't have any miraculous -- I don't have a rabbit to pull out of a hat here. I actually have one little deletion of a reference in a table, simply because I think the data are no good. And that's on PDF 26, under Euterpe edulis fruit extract.

Under composition impurities, the very first item there. In that little paragraph, composition has been characterized using gas chromatography mass spectrometry.

I looked actually at that, because I thought the data numbers looked funny. And I looked at the paper, and I realized they were using a method that is kind of a, sort of a machine learning -- a really crude machine learning association of possible chemical constituents; and then reporting them as actual analytical identifications. And I think that's just bogus.

I would just delete that reference and that table, because we already have two more paragraphs of data for that ingredient anyway. So, it doesn't address the question you had, Don, but that's one thing that needed doing there, just dump that.

DR. BELSITO: What is this here?

DR. LIEBLER: Under Euterpe edulis fruit extract composition impurities, the very first little paragraph, two sentences. The data are no good and shouldn't be used in this report. But I don't think we have --

DR. BELSITO: What page are you on? I'm sorry.

DR. LIEBLER: I'm on PDF 26, under composition impurities.

MR. JOHNSON: But the table is on PDF 37.

DR. LIEBLER: And the table is -- yeah.

DR. BELSITO: So, what are you saying? I'm sorry.

DR. LIEBLER: The data in that reference, that are in Table 3 and discussed in these two little sentences, those data are not good. The method is inappropriate to assign those identifications of those chemicals in it.

DR. BELSITO: So, the first paragraph under composition and impurities in Table 3 you want deleted?

DR. LIEBLER: Correct.

DR. BELSITO: And the method was not good because?

DR. LIEBLER: Because it didn't clearly identify the compounds listed as being present. They provided some sorts of crude estimates of probabilities that they were present, but that's not up to snuff. I mean, we can exactly identify molecules using GCMS, if it's done right, and they just didn't do it the right way, so it's not good.

DR. SNYDER: So, in our introduction, we say that the ingredient group -- under the second paragraph -- was formed based on the supposition that ingredients from a given genus and species, and a closely related species, for example, edulis and oleracea, would have common constituents. And we list these constituents in common. So, why aren't we using it as a read-across -- the edulis as a read-across for the oleracea?

Because we have the oleracea, fruit extract juice and pulp powder are safe as used, non-sensitizing. But then we're saying for the edulis fruit extract, edulis juice extract and those two, why can't we read-across for those two?

Because basically, when we consider the method of manufacture to be similar, and we still say we want irritation and sensitization, but we said non-sensitizing for the oleracea.

So, couldn't we read across and clear those two and then just leave the oleracea seed powder, hydrolyze oleracea fruit and oleracea palm heart extract? Or could we use it to clear everything?

Because we're saying they have constituents in common, so we don't need composition, right? And what would we get -- would there be something in the method of manufacture that -- what we know about the oleracea that would be different from the edulis? Because it seems to be -- the method of manufacture seems to be the weak link there. Because we have plenty of composition on both of them, both species.

DR. LIEBLER: I think you got a good point, Paul. And we should be consistent about this. We have enough data, other than method of manufacture for Euterpe, that we could make, I think, a reasonable assumption that extraction processes that generate the Euterpe equivalent ingredients are going to be similar. They have similar -- well, they don't have many uses, do they? There's hardly any uses for the Euterpe.

DR. SNYDER: No uses.

MS. EISENMANN: Or the edulis.

DR. SNYDER: Yeah, they're all Euterpe.

DR. LIEBLER: Oh, they're Euterpe -- edulis. Yeah, the edulis stuff.

DR. BELSITO: We don't have much. We have composition for the fruit extract, and impurities for the juice extract.

DR. LIEBLER: The composition --

DR. BELSITO: And we have composition for the oleracea fruit extract in juice.

DR. SNYDER: It actually says at the top on the composition it says, characterized with different polarities extraction hexane, ethyl acetate, and chloroform.

DR. LIEBLER: Yeah, that's that reference I just --

DR. SNYDER: That's the one -- oh, the one you're leaving out?

DR. LIEBLER: Yeah. I don't think that the data are reliable.

DR. SNYDER: Okay. I mean, otherwise, I think we have to change that introductory statement. Because we say, in the introduction, that a given genus and species are closely related, would have the same constituent in common. And we list those constituents.

DR. LIEBLER: I mean, the oleracea -- Table 7 has a lot of data on oleracea. You know, it goes on for, gosh, more than two pages -- almost two full pages. And it's mostly flavonoids and related small molecule polyphenolics, monophenolics.

And so we have that for the oleracea. And then for the edulis we have similar data listing similar constituents on PDF 26, right below that paragraph I just had deleted. So, I think -- I was just looking for that to see if I could justify, with analytical data, the assertion that these are compositionally similar. And I think you can certainly justify that with the data that we have in the report.

Does that make sense, Wilbur?

MR. JOHNSON: I see what you're saying.

DR. LIEBLER: Okay. So, if you take the paragraph descriptions on PDF 26 for edulis fruit extract, and then you've got Table 4 which has some constituents, and then you got Table 7 for the oleraceas, I think you list a lot of ingredients in common, suggesting that these are similar; even though we don't have method of manufacture for the edulis. We just have the composition, which says they're similar, and one could reasonably expect that method of manufacture is analogous. So, that's a roundabout answer to your point, Paul.

DR. SNYDER: And then the seed powder versus the pulp powder? So is that different?

Because we're clearing the pulp powder, but we're not clearing the seed powder; for method of manufacture, again, and the same thing with the fruit.

We were clearing the hydrolyzed fruit. We're clearing the oleracea fruit extract, but we're not clearing the hydrolyzed oleracea fruit for method of manufacture.

I just didn't know if there was anything in the -- you would anticipate in the method of manufacture of these that would be of concern. Because it seems kind of odd that it's only -- it's not impurities, it's just the method of manufacture, because we're saying the constituents are similar across all of them.

DR. LIEBLER: I'm trying to look at the description of where the palm seed is with respect to the --

DR. SNYDER: Pulp.

DR. LIEBLER: -- pulp. If the seed is contained within the --

So, the pulp surrounds the kernel. So, the structure is similar to like an avocado. That's what I'm thinking is that you've got the kernel, which I don't know if that's what they mean by the seed.

MR. JOHNSON: Well now, Table 2 has the definitions of those plant parts, the seed.

DR. LIEBLER: So, the definition of the seed is a propagating sexual structure resulting from the fertilization of an ovule, formed by embryo, endosperm or seed coat. That doesn't help us too much.

What I'm wondering is the seed the hard, middle part as opposed to the pulp, which is the part that surrounds it? I mean, I'm looking at diagrams on the web there. And it looks a lot like an avocado. In fact, an avocado is one of the structures. And we can easily identify with that. I just don't know if it's accurate.

If you have an avocado, you take the avocado part and you throw the seed away. I don't know if they take the seed and grind that up to make the ingredient we're talking about here, in which case pulp and seed don't clear each other. I'm trying to get the question that Paul raised.

DR. SNYDER: Yeah. And then the pulp says it's formed by the fruit wall, or the placenta. So, that would say that it would be within the fruit, right? Extract. If it's formed by the fruit wall for the pulp. And the palm heart is edible, right? That's the edible portion of the palm.

DR. BELSITO: Right.

DR. LIEBLER: Inner core of the stem. So, it's not the -- the palm heart is a separate part of the plant. It's part of the stem. So, if you cut the tree down to get to the inside of the trunk, that's where the heart is. But the seeds are kind of hanging off the leaves.

DR. SNYDER: No, I'm just going back to where the palm heart extract, because I think that's the edible part. So, we can clear that because it's a food.

DR. LIEBLER: Right.

MS. FIUME: For systemic tox, but not irritation and sensitization?

DR. SNYDER: No, we were saying -- we've already caveated the ones -- the three we've cleared already, that they have to be non-sensitized.

MS. FIUME: So, this is where it comes in where it's that gray area. It's not non-sensitizing for the ingredient itself. If refers more to -- in the formulations because of other botanicals can be in the same formulation and it's --

DR. SNYDER: Right.

DR. BELSITO: Additive.

MS. FIUME: -- cumulative, yes.

DR. SNYDER: But what sensitization data do we have then? Do we have sensitization on any?

MR. JOHNSON: Yes, PDF page 32.

DR. BELSITO: We have in vitro predictive models.

DR. SNYDER: Well, with fruit extract and the pulp powder, we don't have juice.

DR. BELSITO: So, we essentially have a negative DPRA and we have a negative KeratinoSens. So, we have two out of three negative, which would predict that it's negative.

DR. SNYDER: Oh, yeah. I was going to lean towards we could clear them all, but --

DR. BELSITO: Well, that's fruit extract. And then we have -- in humans we have pulp powder for an HRIPT. So, we have the fruit extract that can clear with in vitro and the pulp powder, we can clear with an HRIPT.

DR. SNYDER: Yeah, I just don't think the seed clears.

DR. BELSITO: And then we have the seed extract that we got data on. And so, the seed extract clears with new data. So, we have seed extract, we have juice and we have pulp. What more do you need? Can you read across from those?

DR. SNYDER: Well, Dan says he's a little uncomfortable with the seed.

DR. BELSITO: What's your concern with the seed now?

DR. SNYDER: Seed powder.

DR. LIEBLER: I think we do have composition and impurities on the seed. It's brief, but it's there. It's the seed powder, excuse me. We have a couple of seed powders on PDF 27. You're got pulp powder. PDF 27 is very brief. We do have a method of manufacture for pulp powder, it's just it appears that pulp and seed are different. And then we have sensitization data on seed?

DR. BELSITO: Yep.

DR. LIEBLER: Yep, we're good there. And pulp?

DR. BELSITO: Yep.

DR. LIEBLER: We're good there.

DR. BELSITO: And fruit.

DR. LIEBLER: And fruit?

DR. BELSITO: Um hmm.

DR. LIEBLER: So, we're okay.

DR. BELSITO: So, safe as used.

DR. LIEBLER: Yeah, I think so.

DR. KLAASSEN: Go for it.

DR. BELSITO: So, this one safe as used when formulating to be non-sensitizing. I just don't see any additive sensitizing material. And there are things like quercetin, but I mean, this is a food.

The amount you would obtain from a food would be much more than you would from a -- I mean, you certainly don't want to say, when formulated to not be sensitizing, because I don't see any sensitizing materials. I mean, if anything, you'd be concerned about quercetin, right?

DR. KLAASSEN: Well, not as a sensitizer, I don't think.

DR. BELSITO: No, not as a sensitizer, no. I'm saying, if you were concerned, I'm not seeing any sensitizing endpoints to be concerned about. Is there is anything you're concerned about otherwise?

DR. KLAASSEN: Oh. No.

DR. BELSITO: So, just safe as used?

DR. KLAASSEN: Yes.

MS. FIUME: I'm sorry. I missed why heart of palm moved to the safe category.

DR. BELSITO: Because we have palm pulp.

DR. SNYDER: I mean, the heart of palm is the edible portion; so I mean, is that the correct definition we have in the table? It's the edible portion we should put in the table. The definition is the edible portion of the palm plant. That's my understanding; it's the heart of palm, unless there's a different definition.

MS. FIUME: The definitions in Table 1 come strictly from the dictionary. I don't know if it's up further in any of the definitions. But usually systemic tox versus sensitization and irritation are two separate categories.

So, was trying to see why it was cleared for sensitization and irritation, just so that we have it as Wilbur formulates the discussion.

DR. SNYDER: Like I said, again, it's the gray zone where we don't know where there's overlap. It means different parts of the plant.

DR. BELSITO: The palm heart is used at 0.001 percent in a spray, 0.001 percent in leave-on and rinse-off. And we just have a reported use where we don't have composition. So we don't really know what's in it. I guess that's Monice's point. We don't have composition, how can we read across for sensitization and irritation?

MS. FIUME: It wasn't -- the outstanding use was irritation, right. So -- yeah.

DR. BELSITO: Right. How can we read across if we don't have composition?

MS. FIUME: And it's fine. It's just that Wilbur needs to be able to formulate a discussion.

DR. BELSITO: Yeah. And it's the edible portion, which suggests that it is different. Otherwise, you'd eat the leaf or the shell or the --

DR. LIEBLER: And you're talking about the heart?

DR. BELSITO: Yes.

DR. LIEBLER: We don't have any other ingredient that's from that same part of the plant.

DR. BELSITO: Right.

DR. LIEBLER: So we can't really --

DR. BELSITO: Yeah. So, sensitization. It's -- all of them are safe as used, the fruit, the juice, the pulp, the seed, but the palm heart is insufficient for sensitization and irritation.

DR. SNYDER: Or composition.

DR. BELSITO: Or composition. So, composition, if significantly different, sensitization and irritation.

DR. SNYDER: Sensitization at 0.001 percent.

MS. EISENMANN: Which I know you're not going to get, because the supplier has stopped making it so they're getting out of that. That's what they're --

DR. BERGFELD: Microphone.

MS. KOWCZ: Just to repeat, the supplier is not making this material anymore.

DR. BELSITO: Okay. So, the palm-derived ingredients are all safe as used, except for the palm heart is insufficient for composition, and of significant difference, sensitization, irritation, and we probably won't get that. But it's not used anymore.

DR. SNYDER: It's not being supplied so it can't be used.

MS. KOWCZ: Well, they can't get it. No.

MR. JOHNSON: Now, my question is --

DR. BELSITO: Too expensive?

MS. KOWCZ: There have been a lot of issues with the palm tree oil.

MS. EISENMANN: It's different palm.

MS. KOWCZ: Okay. A different palm. So, now they're just not making it, not a need for it.

MR. JOHNSON: For those ingredients that you have grouped and said that they are safe when formulated to be non-sensitizing, what is the basis for saying that all of those are similar enough to come under that conclusion?

DR. BELSITO: Because they contain material -- they typically -- it's a botanical that contains a material that is a fragrance and could be combined or -- it contains materials that are known sensitizers. And the data we have on the material itself, that we're looking at, would clear the safety.

However, if combined with X, Y and Z, that also contains more geranial, the final finished product could end up exceeding standards where you would cause sensitization.

When you look at the composition of palm, there's nothing that comes up as a dermal sensitizer. Which is why I asked were there any other ingredients that were of concern for other tox endpoints. And the other members said no.

So, it's like pomegranate. There was nothing that came up to suggest that there were any materials in pomegranate that we would need to be concerned about, so we didn't say, safe as used when formulated to be non-sensitizing.

It's only when we have indications that there could be other materials -- that there are materials in this botanical product that could cause issues from a tox standpoint, that we remind them that there are other things out there with similar ingredients.

MR. JOHNSON: So when you look at all of those that you grouped together, there are no issues with respect to constituents, so that's why you can have one conclusion with those?

DR. BELSITO: Right, just safe as used.

Okay. Are we done with palm?

DR. KLAASSEN: Yes.

DR. BELSITO: Okay. Capryloyl salicylic acid.

MR. JOHNSON: One other question, Dr. Belsito.

DR. BELSITO: Um hmm.

MR. JOHNSON: We've identified common constituents. When you talk about similarities, are you just talking about the common constituents or are you talking about common chemical classes of constituents?

In other words, you may have other ingredients that are similar to those that are constituents. Because there are a lot of constituents that are listed in those tables, and those are just a few that have been identified.

DR. BELSITO: Yeah, but when you go through them, you're not -- when I'm thinking about sensitizers, I'm looking at terpenes in particular. And I'm not seeing any terpenes here. So I'm not seeing things that would concern me about causing dermal sensitization.

MR. JOHNSON: Okay.

DR. BELSITO: So, I'm not seeing pinenes. I'm not seeing any of those.

MR. JOHNSON: Okay. Thank you.

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DR. MARKS: Okay. So, we're up to palm. I like palm. So, Wilbur, in his November 15th memo of this year, sent us a draft final report on palm tree derived ingredients. At the September 16th meeting of this year, we found E. Oleracea fruit extract, the juice, the pulp powder safe in the present practices and use and concentration, when formulated to be non-sensitizing.

And Lisa, I think I mentioned earlier, but the idea of this formulated to be non-sensitizing is, when you take a number of botanicals and put them together, there may be components and a botanical which is sensitizing or has some toxic effect. And as individually, within palm, it's okay. But if you mix palm with three other botanicals, you may get above the NOEL level.

Okay. Let me see. "Conclude that the available data were insufficient to support the conclusion of the five other ingredients, and they're listed there. And there was no response to data request.

So I would think, based on our reasoning in the last meeting, we would move to a final report, safe for three when formulated to be non-sensitizing. Insufficient for five. And the conclusion is on page 35. And the insufficient needs are there, also, Wilbur, right before the conclusion. Ron, Tom, comments?

DR. SHANK: No, good.

DR. SLAGA: Same. I agree.

DR. SHANK: A couple editorial things.

DR. MARKS: Lisa, any comments?

DR. PETERSON: No. I just had some editorial things.

DR. MARKS: Editorial, should we mention those now? Ron, do you want to so Wilbur can -- ?

DR. SHANK: Okay, in the abstract on Page 25, it says the five ingredients. I would list the five ingredients in the abstract, rather than just saying five. What are the five? And then on Page 34, in the discussion, the second paragraph is a repeat of the -- that paragraph is repeated twice in the discussion.

MR. JOHNSON: Which one, doctor?

DR. SHANK: Okay. Page 34. The second paragraph: "The Expert Panel expressed concern." And then it's again on the top of Page 35, the same paragraph. "The Panel also expressed concern about pesticides."

MR. JOHNSON: Okay.

DR. MARKS: I won't mention these tomorrow if they're captured. Is that okay, Ron?

DR. SHANK: Sure. Sure.

DR. MARKS: And Lisa, you had?

DR. PETERSON: I didn't understand the unit in Table 3, on Page 35, when you say, principal compounds and then there's a number there. The numbers add up to more than a hundred -- there were no units, I guess.

And the numbers added more to a hundred, so I didn't think they were percents. So, I just was curious what the units were.

MR. JOHNSON: What page are you on, doctor?

DR. PETERSON: 37, Table 3.

DR. HELDRETH: I think, if I understood the reference correctly, those weren't percentages of the constituent that you expected. But that was the percent probability of finding that constituent there at all.

DR. MARKS: Ohh. Yeah, that's a --

DR. PETERSON: Oh. Can you -- I think then the -- it should be the probability percent of finding it. Because when you say "principle compounds" in that second column, and then "percent probability." I would say "percent probability."

I don't know how I'd change the title, but it's confusing to me. It's not clear.

DR. HELDRETH: Okay. We can change that and make it a lot more clear.

DR. PETERSON: Maybe say exactly, "percent probability."

DR. ANSELL: Yeah. Principle component that's only going to be found 20 percent of the time.

DR. HELDRETH: Right.

DR. ANSELL: It's hard to see that's principle.

DR. PETERSON: Twenty percent is principle. I don't have trouble with the numbers, per se. It's just the designation of the column.

DR. MARKS: Yeah. And even the table could be probability -- composition probability data or something like that.

DR. PETERSON: Yeah, yeah, yeah. Something like that.

DR. MARKS: Because it says composition data. Actually, while you were editorializing, Ron and Lisa, I went back. Obviously, I always focus on the conclusions since, particularly on this one, I'm making the motion. It's 35, right? Something like that.

And this is nitpicking because it doesn't change anything. But the first part of the conclusion, the three ingredients which are safe when formulated to be non-sensitizing, that almost -- in the past, I know we've divided up in paragraphs.

So, I wonder if there would be -- not bullets -- but as you have the five ingredients which are unsafe -- or insufficient, I should say, not unsafe -- that as a separate paragraph. And it won't get confused with the three. Because if you were to read this through quickly, maybe you might misinterpret and say the five down below are insufficient.

That's a minor point. But just visually, to me, it would be nice to put the three standout as safe, and then the five as insufficient. So, it's a minor edit, minor thing. It doesn't change the conclusion, just the way it's formatted.

DR. SHANK: That's good.

DR. MARKS: Okay. I won't mention that tomorrow. But, Wilbur, you understood what I was talking about there.

MR. JOHNSON: Um hmm.

DR. MARKS: Yeah, and you could do the same thing, the safety for the following ingredients, and the safe would be the following three ingredients and then list them, just in different paragraphs. I think then it makes it clear which is safe and which is -- okay.

So again, tomorrow I'll move final report safe for these three ingredients when they're formulated to be non-sensitizing. That's the E. Oleracea fruit extract, juice and pulp powder. And the other five ingredients are insufficient. Okay.

Full Panel –December 10, 2019

DR. MARKS: So, this is a final report on palm tree-derived ingredients. At the September meeting of this year the E. oleracea fruit extract, juice, and pulp powder. The conclusion was these were safe in cosmetics in the present practices of use and concentration described in the safety assessment, when formulated to be non-sensitizing.

The panel further concluded that the available data are insufficient to support the conclusion for safety of five ingredients, and they're listed in the conclusion on Page 35.

So, our team moves to issue a final report with that conclusion, safe for three when formulated to be non-sensitizing, and insufficient for five. And the insufficient needs are elucidated on Page 35.

DR. BERGFELD: Belsito Team?

DR. BELSITO: Actually, we thought that all were safe except for the palm heart, which was insufficient for composition. And if it was different from the others for sensitization and irritation, I'll let Dan address these. But he felt that the data for the fruit and the juice and seed could be used to read across where there was data missing for those. And that the edulis and oleracea were essentially the same.

DR. LIEBLER: Yeah, I think we had data for the -- hang on, I'm going back up. We do have composition impurities data for the seed, seed powder, and the pulp powder. We also have a fair amount of data for the fruit extract, which really, I think, covers us for the fruit.

And so, what we don't have in detail is method of manufacture for -- let's see -- the seed in the text under method of manufacture. But the seed powder, it seems evident enough that it would be produced by essentially grinding up the seed.

So, the only thing that we didn't have really documented was the palm heart, which is from an entirely different part of the plant. It's from the stem trunk of the tree.

DR. MARKS: So, the data we had requested at this point, then you don't feel there's a significant different between the species? We had the fruit extract for the oleracea, but the E. edulis fruit extract and juice extract, we felt we could read across from the E. oleracea, Dan?

DR. LIEBLER: Yeah, the table, Table 3, which has a lot of the data for the edulis, in terms of the components, the flavonoids and other related small molecules. And then, Table 7, which I think one of them is very extensive and has the data for the oleracea, lists a lot of similar ingredient. You know, I don't think that these are different enough to feel that they couldn't both be covered by the data, one from the data for the other, so.

DR. MARKS: So I'll withdraw my motion. Don, would you propose the motion that your team felt that you had more -- we didn't get any new data, so I figured -- our team we would just move on as was said in the last meeting.

DR. BELSITO: All of them are safe as used excepted for the palm heart, which is insufficient for composition; and if the composition is significantly different than the other parts, then sensitization and irritation.

DR. MARKS: Okay, so sensitization and irritation if different, composition.

DR. BERGFELD: Is that a second?

DR. MARKS: Second.

DR. BERGFELD: I have to ask a question. Jim had added formulated to be non-sensitizing; you've not added that to yours?

DR. BELSITO: No, because I didn't see any specific ingredients that were necessarily allergens. And this is not like some of the other plants where we're looking at geraniol, isoeugenol, eliminating things that things that are in there but just were not listed. So, I do not see anything to worry about that would be compounded.

DR. BERGFELD: Okay. Wilbur?

MR. JOHNSON: Given what has been said, should the discussion be revised in any way?

DR. BELSITO: Of course; I mean, it has to say that we feel that we can read across the species. And the other read across elements that Dan had pointed out.

MR. JOHNSON: Now, there is some information in there regarding a clinical study evaluating the sensitization potential; should that language remain?

DR. BELSITO: Could you tell me what page you're on, Wilbur?

MR. JOHNSON: It's on PDF Page 34; the paragraph is the fourth paragraph.

DR. BELSITO: PDF Page 34?

MR. JOHNSON: Yes.

DR. BELSITO: Third paragraph.

MR. JOHNSON: Fourth paragraph; in the discussion.

DR. KLAASSEN: Only in the discussion?

MR. JOHNSON: Yes.

DR. BELSITO: No, I think that's fine. I mean, again I don't think that in this case we need that sentence, "because final product formulations may contain multiple botanicals." Because I don't see any other thing in this that could be combined to cause issues.

DR. BERGFELD: Any other?

MR. JOHNSON: No, that's fine.

DR. BERGFELD: Okay.

DR. LIEBLER: Wilbur, that second paragraph in the discussion, "the expert panel express concern regarding pesticide." You've got that elsewhere further down in the discussion.

DR. BELSITO: Yeah, it's redundant.

DR. LIEBLER: So, I just deleted the first occurrence of it.

MR. JOHNSON: Okay, sure.

DR. BELSITO: Oh, I deleted the second. Don't delete both of them Wilbur.

MR. JOHNSON: Okay. One will be left in.

DR. LIEBLER: Okay. So, be on the lookout for that, please.

MR. JOHNSON: Okay, thank you.

DR. BERGFELD: Any other discussion?

DR. HELDRETH: I just wanted to mention a bit on procedure for this one. So, even though this conclusion is technically less restrictive than the previous conclusion, there appears to be, to me, some substantial changes to the discussion and the rationale that Wilbur will be drafting for this report. So, I think it would be appropriate for this to go back out for public comment, once more, and come back to the panel for approval of the revised discussion section.

DR. BELSITO: You're the boss.

DR. MARKS: I concur.

DR. BERGFELD: So, that's acceptable?

DR. BELSITO: Um-hmm.

DR. BERGFELD: All right, call the question, and all those in favor of this conclusion? Thank you, unanimous.

Safety Assessment of Palm Tree (açaí and juçara)-derived Ingredients as Used in Cosmetics

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ABSTRACT: The Expert Panel for Cosmetic Ingredient Safety (Panel) reviewed the safety of 8 palm tree (*Euterpe edulis* (juçara) and *Euterpe oleracea* (açaí)-derived ingredients in cosmetic products; these ingredients are reported to function mostly as skin conditioning agents. The Panel reviewed relevant data relating to the safety of these ingredients in cosmetic formulations. Industry should continue to use good manufacturing practices to limit impurities. The Panel concluded that Euterpe Edulis Fruit Extract, Euterpe Edulis Juice Extract, Euterpe Oleracea Fruit Extract, Euterpe Oleracea Juice, Euterpe Oleracea Pulp Powder, Euterpe Oleracea Seed Powder, and Hydrolyzed Euterpe Oleracea Fruit are safe in the present practices of use and concentration. The Panel further concluded that that the available data are insufficient to support a conclusion of safety for Euterpe Oleracea Palm Heart Extract under intended conditions of use in cosmetic formulations.

INTRODUCTION

The safety of the following 8 palm tree (açaí and juçara)-derived ingredients, as used in cosmetics, is reviewed in this safety assessment.

Euterpe Edulis Fruit Extract
Euterpe Edulis Juice Extract
Euterpe Oleracea Fruit Extract
Euterpe Oleracea Juice
Euterpe Oleracea Palm Heart Extract
Euterpe Oleracea Pulp Powder
Euterpe Oleracea Seed Powder
Hydrolyzed Euterpe Oleracea Fruit

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), the palm tree-derived ingredients are reported to function mostly as skin conditioning agents in cosmetic products (See Table 1).[1] Euterpe Oleracea Pulp Powder and Euterpe Oleracea Seed Powder also are reported to function as abrasives and exfoliants in cosmetics.

The ingredient group that is being reviewed in this safety assessment (*Euterpe oleracea* (açaí)- and *Euterpe edulis* (juçara)-derived ingredients) was formed based on the supposition that ingredients from a given genus and species, and on a closely related species (i.e., *edulis* and *oleracea*), would have constituents in common. For example, both species have the following constituents in common: catechin, chlorogenic acid, cyanidin-3-glucoside, cyanidin-3-rutinoside, ellagic acid, ferulic acid, gallic acid, pelargonidin-3-glucoside, and peonidin-3-rutinoside.[2-14]

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A list of the typical search engines and websites used, sources explored, and endpoints that the Panel evaluates, is available on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/ supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Botanicals, such as *Euterpe edulis*- or *Euterpe oleracea*-derived ingredients, may contain hundreds of constituents. In this assessment, the Panel is reviewing the potential toxicity of each of the botanical ingredients as a whole, complex mixture. The Panel is not reviewing the potential toxicity of the individual constituents.

Because the safety of *Euterpe oleracea*-derived ingredients is being reviewed in this safety assessment, it should be noted that the Panel published a safety assessment on Euterpe Oleracea Fruit Oil (and other plant-derived fatty acid oils) in 2017.[15] Based on the available data, the Panel concluded that the ingredients included in that report are safe in the present practices of use and concentration described in the safety assessment. Given some similarities in composition (based on the available data) between different parts of *Euterpe oleracea*, data on components that are not the names of cosmetic ingredients that are being reviewed in this safety assessment are included. Data on a component of *Euterpe edulis* (*Euterpe edulis* fruit oil) that is not among the names of cosmetic ingredients that are being reviewed are also included.

It is often not known how the substance being tested in a study compares to the ingredient that is being used in cosmetics. In the report text, if it is known that the material being tested is a cosmetic ingredient, the *Dictionary* naming convention will be used (i.e., the names of cosmetic ingredients are capitalized, without italics (e.g., Euterpe Edulis Fruit Extract)). If it is not known that the test substance is that same as the cosmetic ingredient, then the taxonomic naming conventions will be used (i.e., with genus and species name, italicized (e.g., a *Euterpe edulis* fruit extract)).

CHEMISTRY

Definition and General Characterization

The definitions and reported functions in cosmetics of these ingredients, according to the *Dictionary*, are presented in Table 1.[1]

The palm species *Euterpe edulis* Martius, popularly known as juçara (or jussara) and açaídosol, is a native tree of the Atlantic Forest (South American forest).[16] The juçara palm produces a spherical purple fruit. *Euterpe oleracea* Martius (açaí), is a native species of tree in the Amazon rainforest.[17] *Euterpe oleracea* produces a spherical fruit (berry) that contains a single seed in the center.[18] Heart of palm (vegetable) is composed of the apical meristem of the palm plus part of the young or immature leaves emerging from the meristem.[19] Plant part definitions are presented in Table 2.[1]

Method of Manufacture

Euterpe Oleracea Fruit Extract

The method of manufacture for a Euterpe Oleracea Fruit Extract trade name mixture (98% Euterpe Oleracea Fruit Extract and 2% *Lactobacillus* ferment) provided by a supplier is as follows:[20] *Euterpe oleracea* fruit is processed (mechanical grinding/milling). This process is followed by aqueous extraction (at specific pH and temperature) for a specified duration. The aqueous fruit extract is then subjected to tangential flow filtration to isolate the desired components. Addition of *Lactobacillus* ferment is the next step, and batch adjustments are made if needed (refiltration). A sample is then subjected to quality control, after which the material is packed and sampled for microbiological analysis prior to shipment.

Euterpe Oleracea Juice

According to one manufacturer of a *Euterpe oleracea* juice, for use in foods, this juice is obtained by cold pressing the thin pulp of the ovoidal fruit (berry) of *Euterpe oleracea* Mart.[21]

The method of manufacture for Euterpe Oleracea Juice (undiluted, freeze dried), provided by a supplier, is as follows:[22] *Euterpe oleracea* is cold-pressed for juice. This process is followed by filtration to remove unnecessary plant matter. The filtrate is then freeze dried, and batch adjustments are made, if necessary. A sample is then subjected to quality control, after which the material is packed. The packed material is then sampled for microbiological analysis prior to shipment, and it is reconstituted with water for use.

Euterpe Oleracea Pulp Powder

In one production method, the fruit pulp obtained from *Euterpe oleracea* fruit harvested in Brazil was frozen.[23] Samples of spray-dried pulp were obtained using an industrial scale spray dryer system and anionic maltodextrin DE10 was used as a carrier agent.

Composition/Impurities

Euterpe Edulis Fruit Extract

The composition of a *Euterpe edulis* fruit extract has been characterized using gas chromatography-mass spectrometry and solvents with different polarities (hexane, ethyl acetate, or chloroform) for extraction. These data are presented in Table 3.[24]

According to research investigating the major anthocyanins (type of flavonoid) and non-anthocyanin phenolic compounds in a *Euterpe edulis* fruit extract, high amounts of anthocyanins, approximately 26 mg/g dry weight basis (dwb), of a total of 31 mg/g dwb of phenolic compounds, were detected.[2] Cyanidin-3-*O*-rutinoside was the most abundant anthocyanin (73% of the total phenolic content). It should be noted that an analysis of *Euterpe edulis* fruit for phenolics yielded a value of 4087 mg/100 g dwb for soluble phenolics in pulp from fruits collected in southeastern Brazil.[3] However, a lower value of 1695 mg/100 g dwb for soluble phenolics in this fruit (from Minas Gerais State, a state in the north of Southeastern Brazil) has also been reported.[4] Furthermore, *Euterpe edulis* fruit is rich in oleic and palmitic fatty acids.[16]

Additional data on the composition of Euterpe Edulis Fruit Extract, as well as data on the following other components of *Euterpe edulis* component extracts, are presented in Table 4: *Euterpe edulis* fruit, *Euterpe edulis* pulp extract, and *Euterpe edulis* pulp.[2-8] Though not cosmetic ingredients, composition data on these 3 materials are included because they contain constituents that may also be present in Euterpe Edulis Fruit Extract. Furthermore, data in Table 4 indicate that Euterpe Edulis Fruit Extract and one or more of the 3 fruit parts/extract have constituents in common.

Euterpe Edulis Fruit Extract and Euterpe Edulis Juice Extract

In the absence of impurities data on Euterpe Edulis Fruit Extract and Euterpe Edulis Juice Extract, data on heavy metal/mineral constituents of *Euterpe edulis* fruit and *Euterpe edulis* pulp, and ash residue for each, are found in Table 5.[4]

Euterpe Oleracea Fruit Extract

The heavy metals content of Euterpe Oleracea Fruit Extract (powder) has been described as follows: arsenic (< 0.1 ppm), cadmium (< 0.01 ppm), mercury (< 0.005 ppm), lead (< 0.05 ppm), and copper (0.3 ppm).[25] A supplier reported that a Euterpe Oleracea Fruit Extract trade name mixture contains 98% Euterpe Oleracea Fruit Extract and 2% *Lactobacillus* ferment.[14] This supplier has certified that this product does not contain the 26 allergenic chemical substances that are restricted by the European Union, nor does it contain pesticides exceeding the limitations established by the US Environmental Protection Agency.[14,26] Heavy metals, lead, arsenic, microbial content, yeast and mold, and gram negative bacteria are below detection limits.

Euterpe Oleracea Fruit Extract (test material Euterpe oleracea *fruit)*

Euterpe oleracea Martius, as a native fruit of the Amazon rainforest, has been described as highly contaminated in microbiological terms.[17] The fruit is said to be subject to natural microbiological contamination and one of the main sources of this contamination is water, considering that more than 50% of the municipalities located in the Brazilian Amazon do not use chlorinated water. *Euterpe oleracea* fruit from Brazil and the United States (US) were analyzed for 174 different pesticides, using liquid chromatography-tandem mass spectrometry (LC-MS/MS) and gas chromatography-tandem mass spectrometry (GC-MS/MS).[27] *Euterpe oleracea* fruit that was harvested and lyophilized in Brazil had no detectable pesticides. There also were no detectable pesticides in 7 out of 12 samples of *Euterpe oleracea* fruit in the US. However, the

following pesticides were detected in the 5 other samples of *Euterpe oleracea* fruit in the US: methoxyfenozide (0.2 ng/g), metalaxyl (0.2 ng/g), boscalid (2.6 - 3 ng/g), imidacloprid (0.9 ng/g), bifenazate (1.6 - 2.5 ng/g), carbendazim (0.9 ng/g), hexythiazox (0.6 ng/g), and pyraclostrobin (0.1 ng/g).

The following heavy metals have been detected in *Euterpe oleracea* fruit: lead, cadmium, mercury, and arsenic.[10] Additionally, the following elements have been detected in *Euterpe oleracea* fruit: potassium, magnesium, phosphorus, calcium, sodium, zinc, iron, and copper. Ash residue in the amount of 1.68 ± 0 g/100 g (dwb) remained after the combustion of *Euterpe oleracea* fruit.[28]

Euterpe Oleracea Fruit Extract and Euterpe Oleracea Juice

Composition data on Euterpe Oleracea Fruit Extract (various extractants used) relating to phenolic compounds content (anthocyanins included) are presented in Table 6.[28,29] As a food product, this material is reported to be a thin hygroscopic powder that is water-soluble.[17]

It has been reported that total phenolic yields for a *Euterpe oleracea* pulp (freeze-dried and mixed with ethyl acetate) ranged from 132.6 to 391.2 mg gallic acid equivalent (GAE)/100 g fresh weight (FW).[30] Also, the total anthocyanin yield ranged from 4.2 to 90.0 mg/100 g FW. Data on the composition of *Euterpe oleracea fruit*, *Euterpe oleracea* fruit powder extract, *Euterpe oleracea* juice extract, Euterpe Oleracea Juice, and *Euterpe oleracea* pulp are presented in Table 7.[9-14] Taking into consideration the INCI names that represent the ingredients that are being reviewed in this safety assessment, except for Euterpe Oleracea Juice, these are not cosmetic ingredient names. Composition data on 4 *Euterpe oleracea*-derived botanicals are included because they contain chemicals that are also present in Euterpe Oleracea Fruit Extract (see Table 6 and Table 7). Particularly, data on *Euterpe oleracea* pulp are included because Euterpe Oleracea Pulp Powder is a cosmetic ingredient.

According to a supplier's specification for a Euterpe Oleracea Fruit Extract trade name mixture (98% Euterpe Oleracea Fruit Extract and 2% *Lactobacillus* ferment), the ferulic acid content ranges from 4% to 5%. This material is a clear to slightly hazy liquid.[14]

Euterpe Oleracea Seed Powder

Composition data on *Euterpe oleracea* seed are presented in Table 8.[28] It should also be noted that when *Euterpe oleracea* seeds were extracted with a solution of 95% ethanol/1.5 N hydrochloride (85:15, v/v), the content of phenolic compounds was reported as a total only (3602 ± 88 mg GAE/100 g (dwb; chemical names not stated), and anthocyanins (content not stated) were among the types of phenolic compounds that were represented in the total.

*Euterpe Oleracea Pulp Powder (*Euterpe oleracea *pulp)*

Ash residue in the amount of 3.78 ± 0.06 g/100 g (dwb) remained after the combustion of *Euterpe oleracea* pulp.[28]

*Euterpe Oleracea Seed Powder (*Euterpe oleracea *seed)*

Ash residue in the amount of 1.44 ± 0.01 g/100 g (dwb) remained after the combustion of *Euterpe oleracea* seed.[28]

USE

Cosmetic

The safety of palm tree-derived ingredients 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.[31] 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.[32]

According to 2020 VCRP data, Euterpe Oleracea Fruit Extract is reported to be used in 469 cosmetic products (328 leave-on products, 137 rinse-off products, 4 products that are diluted for (bath) use).[31] Of the palm tree-derived ingredients 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 Euterpe Oleracea Pulp Powder is being used at maximum use concentrations up to 3% in leave-on products (face and neck products [not spray]) and maximum use concentrations up to 0.6% in rinse-off products (paste masks [mud packs]).[32] These are the highest use concentrations in leave-on and rinse-off products that are being reported for the palm tree-derived ingredients that are being reviewed in this safety assessment. Further use data are presented in Table 9.

According to VCRP and Council survey data, the following 3 ingredients are not being used in cosmetic products: Euterpe Edulis Fruit Extract, Euterpe Edulis Juice Extract, and Euterpe Oleracea Seed Powder.

Cosmetic products containing palm tree-derived ingredients may be applied to the skin or, incidentally, may come in contact with the eyes (e.g., Euterpe Oleracea Fruit Extract). Euterpe Oleracea Fruit Extract, Euterpe Oleracea Juice, Euterpe Oleracea Palm Heart Extract, and Euterpe Oleracea Pulp Powder are ingredients that are used in products that come in contact with mucous membranes during product use (ingredient use concentrations: 0.0000083 - 0.3%). Additionally, Euterpe Oleracea Fruit Extract and Euterpe Oleracea Pulp Powder could be incidentally ingested (at maximum use concentrations up to 0.025% [lipstick] and 0.3% [lipstick], respectively). Products containing palm tree-derived ingredients

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 following palm tree-derived ingredients are being used in products that are sprayed: Euterpe Oleracea Fruit Extract (0.001% in pump hair spray), Euterpe Oleracea Palm Heart Extract (0.001% in colognes and toilet waters), and Euterpe Oleracea Pulp Powder (0.015% in colognes and toilet waters). In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm, compared with pump sprays.[33,34,35,36] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[33,34] The only use of palm tree-derived ingredients in powders is being reported for Euterpe Oleracea Juice, which is being used at concentrations up to 0.01% in face powders. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[37,38,39]

The palm tree-derived ingredients reviewed in this safety assessment are are not restricted from use in any way under the rules governing cosmetic products in the European Union.[40]

Non-Cosmetic Use

Euterpe oleracea extract is not the name of any of the ingredients that are being reviewed in this safety assessment, but has the same CAS number (879496-95-4) as the following ingredients that are being reviewed: Euterpe Oleracea Fruit, Euterpe Oleracea Palm Heart Extract, Euterpe Oleracea Pulp Powder, Euterpe Oleracea Pulp Powder, and Euterpe Oleracea Seed Powder Extract. However, it should be noted that *Euterpe oleracea* extract (also known as acai berry extract) is a food flavoring agent or adjuvant.[41] According to another source, *Euterpe oleracea* extract is a hydroalcoholic (ethanol and water) extract of *Euterpe oleracea* berry stones (pits).[42] Because the safety of Euterpe Oleracea Palm Heart Extract is being reviewed in this report, it is also important to note that heart of palm is the edible part of the apical meristem of palms (*Euterpe oleracea* and *Euterpe edulis*) and is considered a gourmet vegetable.[43] Furthermore, it should be noted that both *Euterpe oleracea* and *Euterpe edulis* fruits are typically consumed in the Amazon region of Brazil.[44]

TOXICOKINETIC STUDIES

Dermal Penetration

Data on the dermal penetration of the palm tree-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted. Dermal penetration data were not expected to be found because each botanical ingredient is a mixture of hundreds of constituents.

Absorption, Distribution, Metabolism, and Excretion

Human

Oral

Euterpe Oleracea Juice and Euterpe Oleracea Pulp Powder (test material Euterpe oleracea pulp)

An acute 4-way crossover clinical trial that involved oral dosing with the following was performed using 12 subjects: Euterpe Oleracea Juice, *Euterpe oleracea* pulp, applesauce (control), and a non-antioxidant beverage (control).[45] An oral dose of Euterpe Oleracea Juice or *Euterpe oleracea* pulp (7 mL/kg) was administered after a washout phase and overnight fast, and plasma was repeatedly sampled over 12 h. Urine was sampled over a 24-h period after dosing. Plasma anthocyanin (antioxidant) concentrations were determined over a period of 0 - 12 h. Noncompartmental pharmacokinetic analysis of total anthocyanins, quantified as cyanidin-3-*O*-glucoside, indicated maximum plasma concentration (C_{max}) values of 2321 and 1138 ng/L at maximum concentration times (t_{max}) of 2.2 and 2.0 h, and area under the concentration-time curve (AUC_{last}; last refers to AUC up to the last measurable concentration) values of 8568 and 3314 ng h/L for *Euterpe oleracea* pulp and Euterpe Oleracea Juice, respectively. Nonlinear mixed effect modeling identified dose volume as a significant predictor of relative oral bioavailability in a negative nonlinear relationship for *Euterpe oleracea* pulp and Euterpe Oleracea Juice. Additionally, after consumption of *Euterpe oleracea* pulp, applesauce, and Euterpe Oleracea Juice, plasma antioxidant capacity was statistically significantly increased ($P < 0.01$) when compared to the non-antioxidant control beverage. Individual increases in plasma antioxidant capacity of up to 2.3- and 3-fold for Euterpe Oleracea Juice and *Euterpe oleracea* pulp, respectively, were observed. Both applesauce and *Euterpe oleracea* pulp induced statistically significantly higher plasma antioxidant activities than Euterpe Oleracea Juice ($P < 0.05$). The non-oxidant control beverage also caused an increase in the antioxidant capacity of the plasma when compared to the baseline, which may have resulted from its fructose content. The antioxidant capacity in the urine, generation of reactive oxygen species, and uric acid concentrations in plasma were not significantly altered by the treatments. The results of this study indicate that anthocyanins from *Euterpe oleracea* are bioavailable in human subjects after consumption of Euterpe Oleracea Juice and *Euterpe oleracea* pulp in moderate amounts.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

Euterpe Oleracea Juice (test material Euterpe oleracea pulp-enriched fruit and berry juice)

The acute toxicity of a *Euterpe oleracea* pulp-enriched fruit and berry juice (fortified with glucosamine) was evaluated in accordance with Organization for Economic Co-operation and Development (OECD) test guideline (TG) 423.[46] The juice is described as afunctional beverage containing 19 fruits and berries. The concentration of *Euterpe oleracea* pulp (predominant ingredient in the juice) in the juice was not stated. Two groups of Wistar rats (Crl:(WI) BR strain; 5 males and 5 females per group) received single oral doses by gavage of 5 g/kg and 20 g/kg, respectively. Dosing was followed by a 14-day observation period and gross necropsy was performed on day 15. None of the animals died and there were no treatment-related clinical or behavioral signs. For female rats, the mean body weight gain (on days 1 and 2 and during the last week) in the 20 g/kg dose group was statistically significantly lower when compared to the 5 g/kg group. However, the total body weight gain of females in the 20 g/kg dose group was not statistically significantly different when compared to the 5 g/kg dose group. At necropsy (both dose groups) on day 15, there was no evidence of gross lesions in any organ, and all organs were free of gross pathological changes. It was concluded that the acute oral LD_{50} for the test substance was > 20 g/kg.

Short-Term Toxicity Studies

Oral

Euterpe oleracea fruit oil

The short-term oral toxicity of *Euterpe oleracea* fruit oil was evaluated using groups of 6 Wistar rats.[47] *Euterpe oleracea* fruit oil (doses of 30 mg/kg, 100 mg/kg, or 300 mg/kg) in 1% Tween 80 was administered by gavage daily (at 24-h intervals) for 14 consecutive days. At the dose of 300 mg/kg, but not at lower doses, some animals began to display signs of toxicity, such as diarrhea and bristling of the hair. Information on mortalities or microscopic changes was not reported.

Subchronic Toxicity Studies

Oral

Euterpe Oleracea Juice (test material Euterpe oleracea pulp-enriched fruit and berry juice)

The subchronic oral toxicity of *Euterpe oleracea* pulp-enriched fruit and berry juice (fortified with glucosamine) was evaluated using groups of 40 Wistar rats (SPF Hsd.Brl.Han strain; 20 males and 20 females per group).[46] The juice is described as a functional beverage containing 19 fruits and berries. The concentration of *Euterpe oleracea* pulp (predominant ingredient in the juice) in the juice was not stated. The test substance was administered daily by gavage for 90 days to 3 groups at doses of 10, 20, and 40 g/kg, respectively. Necropsy was performed on day 91. The vehicle control group was dosed with saline, and there was also an untreated control group. When compared to the control groups, there were no treatment-related, statistically significant changes in the following in surviving animals of all 3 dose groups: body weight, food and water consumption, ophthalmology, organ weights, urinalysis, hematological and clinical chemistry, or gross pathology. Three animals died during the study (1 female at 10 g/kg; 1 male at 20 g/kg; and 1 male at 40 g/kg). The animals that died did not have clinical symptoms prior to death. With the exception of signs of suffocation/aspiration congestion (due to problems with the gavage administration of the test substance; not considered test substance-related), there was no evidence of histopathological lesions or injury to tissues or organs. The only statistically significant difference (not clinically meaningful) observed was in mean adrenal weight (values not stated) relative to the brain weight in the 20 mg/kg dose group when compared to untreated female controls. Whether or not the change in adrenal weight in treated animals was an increase or decrease when compared to controls was not stated. However, this statistically significant difference was not biologically significant. The no-observed-adverse-effect-level (NOAEL) was determined to be 40 g/kg/day for male and female rats.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Data on the developmental and reproductive toxicity of palm tree-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

GENOTOXICITY STUDIES

The genotoxicity studies on palm tree-derived ingredients are summarized below and described in Table 10.

In Vitro

Euterpe edulis fruit pulp (9% in water) was genotoxic (at 25 to 250 µg/plate, but not at higher doses), without (but not with) metabolic activation, in one *Salmonella typhimurium* strain (TA97) in the Ames test.[24] In the same test, the authors noted a clear trend for the genotoxicity of this test substance in strains TA98 and TA100 at doses ranging from 25 to 250 µg/plate without metabolic activation. *Euterpe edulis* fruit pulp (9% in water) was also genotoxic in the micronucleus assay (RAW264.7 mouse macrophage-like cells; genotoxic at the entire range of concentrations tested (0.27 to 10.8 mg/ml)).[24] *Euterpe edulis* fruit oil was non-genotoxic in the cytokinesis-block micronucleus assay (human peripheral blood lymphocytes

and HepG2 human hepatoma cells; concentrations up to 1000 µg/ml) or in the comet assay (human peripheral blood lymphocytes and HepG2 human hepatoma cells; concentrations up to 1000 µg/ml).[48]

An Euterpe Oleracea Fruit Extract trade name mixture (98% Euterpe Oleracea Fruit Extract and 2% *Lactobacillus* ferment) was non-genotoxic, with and without metabolic activation, in the Ames test (*S. typhimurium* strains and an *Escherichia coli* strain; doses up to 5000 µg/plate).[49] A *Euterpe oleracea* pulp-enriched fruit and berry juice (fortified with glucosamine) was non-genotoxic, with and without metabolic activation, in the Ames test (*S. typhimurium* strains; doses up to 5 µg/plate), and non-genotoxic, with and without metabolic activation, in the chromosomal aberration assay (Chinese hamster lung cells; concentrations up to 5000 µg/ml) and in the L5178Y/TK+/- mouse lymphoma assay (concentrations up to 500 µg/ml).[46] The juice is described as afunctional beverage containing 19 fruits and berries. The concentration of *Euterpe oleracea* pulp (predominant ingredient in the juice) in the juice was not stated.

In Vivo

Euterpe edulis fruit pulp extract (9% in water) was genotoxic in a micronucleus assay using bone marrow erythrocytes from rats that were dosed with up to 180 mg/kg by gavage for 3 days.[24] However, in a second study using the same protocol and doses, *Euterpe edulis* fruit pulp extract (9% in water) was non-genotoxic.[24] Negative results were also obtained in the comet assay (single cell gel electrophoresis [SCGE] test) using this test article involving randomly selected cells in blood from rats receiving doses (by gavage) up to 180 mg/kg, and in another Comet assay involving randomly selected cells in human blood that was drawn after oral ingestion of 300 ml/day for 5 days.

Euterpe oleracea pulp-enriched fruit and berry juice (fortified with glucosamine) was non-genotoxic in the micronucleus assay (mouse bone marrow erythrocytes from mice receiving daily oral or intraperitoneal (i.p.) doses of 100 µg/150 µl saline).[46] The juice is described as afunctional beverage containing 19 fruits and berries. The concentration of *Euterpe oleracea* pulp (predominant ingredient in the juice) in the juice was not stated. *Euterpe oleracea* fruit pulp was non-genotoxic in the micronucleus assay (mouse bone marrow erythrocytes and peripheral blood erythrocytes from mice receiving either single or 14 days of oral doses up to 16.67 g/kg), and was non-genotoxic in the comet assay involving mouse peripheral blood erythrocytes, liver cells, and kidney cells from mice orally receiving doses up to 16.67 mg/kg for 1 or 14 days.[50] In rats dosed (by gavage) with *Euterpe oleracea* fruit oil (doses up to 300 mg/kg), there was no significant induction of DNA strand breaks in the comet assay (peripheral blood, bone marrow, liver cells, and testicle cells), but there was minor DNA damage in a few nucleoids (after dosing with 300 mg/kg).[47] *Euterpe oleracea* fruit oil was non-genotoxic in the micronucleus assay (bone marrow erythrocytes from rats receiving doses up to 300 mg/kg by gavage for 14 days).

CARCINOGENICITY STUDIES

Data on the carcinogenicity of palm tree-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

ANTI-CARCINOGENICITY STUDIES

Euterpe Oleracea Fruit Extract

The anti-tumorigenicity of Euterpe Oleracea Fruit Extract (hydroalcoholic extract) was evaluated using 2 groups of 40 female Wistar rats.[42] Twenty rats were dosed orally (200 mg/kg, by gastric intubation) with a saline solution of the fruit extract for 16 consecutive weeks. The control group (20 rats) was dosed with saline according to the same procedure. One day after starting dosing with Euterpe Oleracea Fruit Extract, mammary carcinogenesis was induced in all animals by subcutaneous (s.c.) injection of 25 mg/kg of 7,12-dimethylbenz[a]anthracene (DMBA) in the mammary gland. The animals were palpated in the mammary gland once per week to detect the presence of breast tumors. At the end of the treatment period, the animals were killed and tumor tissues as well as heart, liver, and kidney samples were examined histologically. Survival analysis indicated that Euterpe Oleracea Fruit Extract increased survival ($P = 0.0002$, long-rank test) and reduced the number of deaths ($P = 0.0036$, Chi-square test). Cumulative survival periods of 15.15 weeks and 12.75 weeks were reported for test and control animals, respectively. The mortality rate in the control group was 65% (13 deaths), and the mortality rate was 15% (3 deaths) after dosing with Euterpe Oleracea Fruit Extract. There was no evidence of toxicity of the extract, based on food consumption, body weight, and activity levels, when compared to results for the 20 control rats. Histopathological results for the liver and kidneys indicated a protective effect of Euterpe Oleracea Fruit Extract, because, in the control group, there was an increase in fibrosis, atypical cells, and hemorrhagic microenvironment. There were no morphological differences in heart tissue between test and control rats.

In the control group, the tumor incidence rate was 100%. However, in the group dosed with Euterpe Oleracea Fruit Extract, the tumor incidence rate was markedly reduced to 50%. In both groups, mammary tumors displayed adhesions and a cystic pattern near the site of tumor induction. However, there was no significant difference in tumor volume (control: 4.151 ± 0.8 mL; Euterpe Oleracea Fruit Extract: 3.971 ± 1.3 mL) and tumor weight (control: 3.012 ± 0.5 g; Euterpe Oleracea Fruit Extract: 2.52 ± 0.7 g). It was concluded that Euterpe Oleracea Fruit Extract (hydroalcoholic extract) exhibited anti-tumorigenic activity in DMBA-induced breast cancer.[42]

Euterpe Oleracea Pulp Powder

A study was performed to investigate the protective effect of Euterpe Oleracea Pulp Powder (spray-dried) intake on colon carcinogenesis induced by 1,2-dimethylhydrazine.[51] Four groups of 10 rats received 4 s.c. injections of

1,2-dimethylhydrazine (40 mg/kg) for 4 weeks (twice a week), for initiation of colon carcinogenesis. A fifth group (5 rats) received similar injections of ethylenediaminetetraacetic acid (EDTA; 1,2-dimethylhydrazine vehicle). The groups were then fed a standard diet containing 2.5% or 5.0% Euterpe Oleracea Pulp Powder, or a diet containing 0.2% *N*-acetylcysteine (antioxidant and anti-carcinogenic agent) for 10 weeks, using aberrant crypt foci (ACF) as the endpoint. Additionally, two groups were fed a standard diet or a diet containing 5.0% Euterpe Oleracea Pulp Powder for 20 weeks, using colon tumors as the endpoint. In the assay using ACF as the endpoint, a reduction in the number of aberrant crypts and ACF were observed in the groups fed 5.0% Euterpe Oleracea Pulp Powder (37% aberrant crypts and 47% ACF inhibition, $P = 0.036$) and 0.2% *N*-acetylcysteine (39% aberrant crypts and 41% ACF inhibition, $P = 0.042$). In the assay using colon tumors as the endpoint, a reduction in the number of invasive tumors ($P < 0.005$) and tumor multiplicity ($P = 0.001$) was observed in the group fed with 5.0% Euterpe Oleracea Pulp Powder. Also, a reduction in tumor Ki-67 (human protein strictly associated with cell proliferation) cell proliferation ($P = 0.003$) and net growth index ($P = 0.001$) was observed in the group fed 5.0% Euterpe Oleracea Pulp Powder. It was concluded that the results of this study indicate that Euterpe Oleracea Pulp Powder feeding may reduce the development of chemically-induced rat colon carcinogenesis.

Another study was performed to evaluate whether feeding with Euterpe Oleracea Pulp Powder attenuates the initiation step of chemically-induced mouse colon carcinogenesis.[23] *Euterpe oleracea* fruit pulp was frozen and samples of spray-dried pulp (powder) were obtained. The production method for this powder is stated in the Method of Manufacture section of this report. This study involved male Swiss mice (3 groups of 15 (Groups 1 - 3); 1 group of 5 (Group 4)). Group 1 was fed a low-fat diet and Groups 2 and 3 were fed a low-fat diet containing 2.5% and 5% Euterpe Oleracea Pulp Powder, respectively, during weeks 1 to 4. The positive control group (Group 4) was fed a low-fat diet containing 0.1% indole-3-carbinol during weeks 1 to 3. All groups received an i.p. injection of the colon carcinogen azoxymethane (AOM) at week 3. Some mice from groups 1 to 3 and all mice from group 4 ($n = 5$ mice per group) were killed 24 h after the first injection of AOM at week 3 ($n = 5$ mice/group) and liver samples were collected for immunohistochemical and glutathione analysis. The remaining mice (Groups 1-3; $n = 10$ mice/group) received a second i.p. injection of AOM at week 4 and were fed a high-fat diet to accelerate the development of preneoplastic ACF until week 14. At week 3, both dietary Euterpe Oleracea Pulp Powder doses (2.5% or 5.0%) reduced ($P < 0.001$) peripheral blood cell DNA damage induced by AOM. Also, 5.0% Euterpe Oleracea Pulp Powder increased ($P = 0.002$) hepatic total glutathione. At week 14, 5.0% Euterpe Oleracea Pulp Powder reduced ($P < 0.05$) ACF multiplicity. These findings indicate that feeding with Euterpe Oleracea Pulp Powder attenuates chemically-induced mouse colon carcinogenesis by increasing total glutathione and attenuating DNA damage and preneoplastic lesion development.

OTHER RELEVANT STUDIES

Effect on Mast Cell Activation

Euterpe Oleracea Pulp Powder (test material Euterpe oleracea *pulp)*

The pretreatment of immunoglobulin E (IgE)-sensitized mouse primary cultured mast cells with *Euterpe oleracea* pulp caused dramatic suppression of antigen-induced degranulation in a dose-dependent manner (1 to 1000 ng/ml).[52] Furthermore, *Euterpe oleracea* pulp suppressed IgE-mediated degranulation and transcription of the cytokine genes from a cultured mast cell line of rat basophilic leukemia (RBL)-2H3 cells. The results also suggest that *Euterpe oleracea* pulp could selectively inhibit a high affinity IgE receptor (FcεRI) signaling pathways, and indicate that the FcεRI-mediated complementary signaling pathway was suppressed by *Euterpe oleracea* pulp. The authors noted that these results demonstrate that *Euterpe oleracea* Pulp is a potent inhibitor of IgE-mediated mast cell activation.

Cytotoxicity

Euterpe Oleracea Fruit Extract

A cellular viability assay was performed to assess the potential for a Euterpe Oleracea Fruit Extract trade name mixture (98% Euterpe Oleracea Fruit Extract and 2% *Lactobacillus* ferment) to increase cellular metabolic activity in human dermal fibroblasts cultured for 24 h with concentrations of 0.01%, 0.1%, and 1% (in Dulbecco's modified eagle medium).[53] In this assay, resazurin (nonfluorescent dye) is converted to resorufin, a fluorescent dye, in response to chemical reduction of growth medium from cell growth and by respiring mitochondria. Healthy cells in a proliferative state will be able to easily convert resazurin to resorufin without harming the cells. A proliferative cellular state is indicated by an increase in the signal generated by resazurin conversion. When compared to the control (unnamed), all concentrations of the Euterpe Oleracea Fruit Extract trade name mixture increased cellular metabolism. The increase in the fluorescent signal indicated an increase in cellular metabolism and viability after incubation with the trade name mixture.

The anti-carcinogenicity potential of Euterpe Oleracea Fruit Extract (hydroalcoholic extract) was evaluated in vitro in a study using cell viability as the toxicity endpoint.[54] The malignant cell lines derived from human mammary adenocarcinoma (MCF-7 and MDA-MB-468 cells) and human colon adenocarcinomas (Caco-2 and HT-29) were treated with 10, 20, and 40 µg/ml Euterpe Oleracea Fruit Extract for 24 h and 48 h. After treatment, cell viability was measured using 3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays, and cell morphological features were observed by light and transmission electron microscopy. The data were analyzed statistically. Of all the cell lines tested, MCF-7 was the only line that responded to Euterpe Oleracea Fruit Extract treatment (cytotoxic effect). Significant reduction ($P < 0.01$) in cell viability and altered cell morphological features (by inducing the appearance of autophagic vacuoles) was noted at all concentrations. It was concluded that Euterpe Oleracea Fruit Extract possesses anti-tumorigenic potential in the MCF-7 cell line.

Euterpe Oleracea Pulp Extract

The antiproliferative activity of a *Euterpe oleracea* pulp extract (polyphenolic extract, concentrations ranging from 0.04 to 12 µg of gallic acid equivalents (GAE)/mL) was evaluated in a cell culture model using HT-29 colon carcinoma cell viability as the endpoint.[55] Cell numbers were determined after 48 h of incubation. Total cell numbers were indicative of the proliferative activity of HT-29 cells and the cytotoxic effect of *Euterpe oleracea* pulp extract. The extract caused significant ($P < 0.01$) decreases in total cell numbers in a concentration-dependent manner.

DERMAL IRRITATION AND SENSITZATION STUDIES

Irritation

In Vitro

Euterpe Oleracea Fruit Extract

The skin irritation potential of a Euterpe Oleracea Fruit Extract trade name mixture (98% Euterpe Oleracea Fruit Extract and 2% *Lactobacillus* ferment) was evaluated using the EpiDerm™ model (reconstructed human epidermis) assay.[56] The test substance was applied to tissue inserts, which were incubated for 60 minutes. Tissue viability was measured by dehydrogenase conversion of MTT, present in mitochondria, into blue formazan salt. Skin irritation potential of the test substance is dictated by the reduction in tissue viability of exposed tissues when compared to the negative control (sterile Dulbecco's phosphate buffered saline). Sodium dodecyl sulfate (5%) served as the positive control. An irritant is predicted if the mean relative tissue viability of the 3 tissues exposed to the test substance is reduced by 50% of the mean viability of the negative controls, and a non-irritant's viability is > 50%. The trade name mixture was classified as a non-irritant in this assay.

Sensitization

In Vitro/In Chemico

Euterpe Oleracea Fruit Extract

The in vitro skin sensitization antioxidant/electrophile response element (ARE)-nuclear factor (erythroid-derived 2; Nrf2) luciferase test method was used to evaluate the sensitization potential of a Euterpe Oleracea Fruit Extract trade name mixture (98% Euterpe Oleracea Fruit Extract and 2% *Lactobacillus* ferment).[57] This test method (validated by independent peer review by the European Union Reference Laboratory for Alternatives to Animal Testing (EURL)-European Center for the Validation of Alternative Methods (ECVAM)) addresses the induction of genes that are regulated by AREs by skin sensitizers. The sensitization assay in this study utilizes the KeratinoSens™ method. Collectively, an immortalized adherent human keratinocyte cell line (HaCaT) was incubated for 48 h with 12 concentrations of the trade name mixture ranging from 0.98 µM to 2000 µM. Cinnamic aldehyde (4 µM to 64 µM) and 1% dimethyl sulfoxide served as positive and negative controls, respectively. There was no statistically significant increase in luciferase expression, and the Euterpe Oleracea Fruit Extract trade name mixture was not predicted to be a skin sensitizer.

The skin sensitization potential of a Euterpe Oleracea Fruit Extract trade name mixture (98% Euterpe Oleracea Fruit Extract and 2% *Lactobacillus* ferment) was evaluated using the direct peptide reactivity assay (DPRA, an in chemico method).[58] This assay is designed to mimic the covalent binding of electrophilic chemicals to nucleophilic centers in skin proteins by quantifying the reactivity of chemicals towards the model synthetic peptides containing cysteine and lysine. The mean percent depletion of cysteine and lysine was 3.20%, interpreted as minimal reactivity in the assay and yielding a prediction of no sensitization.

Human

Euterpe Oleracea Pulp Powder

A human repeated insult patch test (HRIPT) involving a face and neck product containing 3% Euterpe Oleracea Pulp Powder was performed using 214 subjects.[59] Testing occurred over a 6-week period. During induction, a 2 cm x 2 cm occlusive patch containing the product (0.2 ml or 0.2 g) was applied for 24 h to the infrascapular area of the back (to the right or left of midline) or to the upper arm. This procedure was repeated for a total of 9 induction applications, and sites were evaluated at 48-h intervals. For 24-h patch applications on Fridays, sites were evaluated on the following Monday (i.e., 72 h after patch application). The evaluation of sites after the 9th patch application was followed by a 10- to 15-day non-treatment period, after which (at week 6) the challenge phase was initiated. A challenge patch was applied for 24 h to a new test site, and reactions were scored at 24 h, 48 h, and 72 h after patch application. Definite erythema and damage to the epidermis, but no edema, were observed (at 5th induction evaluation) in 1 subject. Thereafter, the product was applied to a new site and reactions were not observed for the remainder of the induction period or during the challenge phase. The authors concluded that there was no evidence of sensitization to the product tested in this study.

OCULAR IRRITATION STUDIES

In Vitro

Euterpe Oleracea Fruit Extract

The EpiOcular™ model (human corneal epithelial model) assay was used to evaluate the irritation potential of a Euterpe Oleracea Fruit Extract trade name mixture (98% Euterpe Oleracea Fruit Extract and 2% *Lactobacillus* ferment).[56] The test substance was applied to tissue inserts and incubated for 30 min. Tissue viability was measured by dehydrogenase conversion of MTT, present in the cell mitochondria, into blue formazan salt. Ocular irritation potential of the test substance is dictated by the reduction in tissue viability of exposed tissues when compared to the negative control (sterile deionized water). Methyl acetate served as the positive control. An irritant is predicted if the mean relative tissue viability of the 2 tissues exposed to the test substance is reduced by 60% of the mean viability of the negative controls, and a non-irritant's viability is > 40%. The trade name mixture was classified as a non-irritant in this assay.

SUMMARY

The safety of 8 palm tree (*Euterpe edulis* (juçara) and *Euterpe oleracea* (açaí))-derived ingredients as used in cosmetics is reviewed in this safety assessment. According to the *Dictionary*, these ingredients function mostly as skin conditioning agents in cosmetic products. Euterpe Oleracea Pulp Powder and Euterpe Oleracea Seed Powder also function as abrasives and exfoliants in cosmetics.

Information on the method of manufacture of a Euterpe Oleracea Fruit Extract trade name mixture (98% Euterpe Oleracea Fruit Extract and 2% *Lactobacillus* ferment) from a supplier indicates that the process involves the aqueous extraction of Euterpe Oleracea Fruit. Additionally, this trade name mixture and Euterpe Oleracea Juice have been analyzed for the 26 fragrance allergens that are required to be listed on the product label in the European Union if they exceed a certain concentration. Both were found not to contain these allergenic flavors or fragrances, neither directly nor through cross contamination. The same supplier's impurities specifications for a Euterpe Oleracea Fruit Extract trade name mixture (98% Euterpe Oleracea Fruit Extract and 2% *Lactobacillus* ferment) include the following: heavy metals (< 20 ppm), lead (< 10 ppm), arsenic (< 2 ppm), microbial content (< 100 cfu/g; no pathogens), yeast and mold (< 100 cfu/g), and gram-negative bacteria (0 cfu/g). Data provided by the same supplier indicate that pesticides present in this trade name mixture do not exceed the EPA's limits.

According to 2020 VCRP data, Euterpe Oleracea Fruit Extract is reported to be used in 469 cosmetic products (328 leave-on products, 137 rinse-off products, and 4 products that are diluted for (bath) use). Of the palm tree-derived ingredients 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 Euterpe Oleracea Pulp Powder is being used at maximum use concentrations up to 3% in leave-on products (face and neck products [not spray]) and maximum use concentrations up to 0.6% in rinse-off products (moisturizing products [not spray] and paste masks [mud packs]). These are the highest use concentrations in leave-on and rinse-off products that are being reported for the palm tree-derived ingredients that are being reviewed in this safety assessment. According to VCRP and Council survey data, the following 3 ingredients that are being reviewed are not being used in cosmetic products: Euterpe Edulis Fruit Extract, Euterpe Edulis Juice Extract, and Euterpe Oleracea Seed Powder.

The results from a clinical trial involving 12 subjects who consumed an oral dose (7 ml/kg) of Euterpe Oleracea Juice or *Euterpe oleracea* pulp indicated that anthocyanins from *Euterpe oleracea* are bioavailable in human subjects after consumption of Euterpe Oleracea Juice and *Euterpe oleracea* pulp in moderate amounts.

The acute toxicity of a *Euterpe oleracea* pulp-enriched fruit and berry juice (fortified with glucosamine) was evaluated using 2 groups of 10 Wistar rats that received single oral doses of 5 g/kg and 20 g/kg, respectively. The acute oral LD_{50} was reported as > 20 g/kg.

In groups of 6 Wistar rats, *Euterpe oleracea* fruit oil (doses of 30 mg/kg, 100 mg/kg, or 300 mg/kg) in 1% Tween 80 was administered by gavage daily for 14 consecutive days. At the dose of 300 mg/kg, but not at lower doses, some of the animals had signs of toxicity such as diarrhea and bristling of the hair. In a 16-week study involving 20 Wistar rats dosed orally with Euterpe Oleracea Fruit Extract and s.c. with DMBA, there was no evidence of toxicity of the extract, based on food consumption, body weight, and activity levels. There were no morphological differences in heart tissue between test and control rats.

The subchronic oral toxicity of *Euterpe oleracea* pulp-enriched fruit and berry juice (fortified with glucosamine) was evaluated using groups of 40 Wistar rats. The test substance was administered daily for 90 days to 3 groups at oral doses of 10, 20, and 40 g/kg, respectively. There were no treatment-related, statistically significant changes in the following in surviving animals of all 3 dose groups: body weight, food and water consumption, ophthalmology, organ weights, urinalysis, hematological and clinical chemistry, or gross pathology. The 3 animals that died during the study did not have clinical symptoms prior to death, and there was no evidence of histopathological lesions or injury to tissues or organs. An NOAEL of 40 g/kg/day was reported.

Components of *Euterpe edulis* and *Euterpe oleracea* were evaluated in in vitro genotoxicity tests. *Euterpe edulis* fruit pulp (9% in water) was genotoxic without metabolic activation in one *S. typhimurium* strain in the Ames test, and in the in vitro micronucleus assay. In the Ames test on *Euterpe edulis* fruit pulp (9% in water), there was also a clear trend for genotoxicity in strains TA98 and TA100 at doses ranging from 25 to 250 µg/plate without metabolic activation. *Euterpe*

edulis fruit oil was non-genotoxic in the cytokinesis-block micronucleus assay and in the comet assay. A Euterpe Oleracea Fruit Extract trade name mixture (98% Euterpe Oleracea Fruit Extract and 2% *Lactobacillus* ferment) was non-genotoxic, with and without metabolic activation, in the Ames test (*S. typhimurium* strains and an *E. coli* strain). *Euterpe oleracea* pulp-enriched fruit and berry juice (fortified with glucosamine) was non-genotoxic in the Ames test, the chromosomal aberration assay, and in the L5178Y/TK+/- mouse lymphoma assay.

In vivo genotoxicity test results for components of *Euterpe edulis* and *Euterpe oleracea* have also been reported. *Euterpe edulis* fruit pulp (9% in water) was genotoxic in one micronucleus assay (dosing by gavage), but was non-genotoxic in another micronucleus assay using the same procedure or in comet assays. *Euterpe oleracea* pulp-enriched fruit and berry juice (fortified with glucosamine, daily oral or i.p. doses) was non-genotoxic in the micronucleus assay. *Euterpe oleracea* fruit pulp was non-genotoxic in the micronucleus assay and in the comet assay. Results for *Euterpe oleracea* fruit oil in the comet assay indicated no significant induction of DNA strand breaks, but there was minor DNA damage in a few nucleoids. *Euterpe oleracea* fruit oil was also non-genotoxic in the micronucleus assay.

The anti-tumorigenicity of Euterpe Oleracea Fruit Extract has been demonstrated both in vivo (rats, breast cancer study) and in vitro (human mammary adenocarcinoma cell line). In vivo anti-carcinogenic activity of Euterpe Oleracea Pulp Powder has been demonstrated in colon cancer studies involving rats. In another study, the antiproliferative activity of *Euterpe oleracea* pulp extract was evaluated in a cell culture model using colon carcinoma cells, and a significant decrease in total cell numbers was reported.

When compared to the control (details not provided), a Euterpe Oleracea Fruit Extract trade name mixture increased cellular metabolism and viability at all test concentrations (0.01%, 0.1%, and 1%) in human dermal fibroblasts in vitro. In an in vitro study in which IgE-sensitized mouse mast cells were treated with *Euterpe oleracea* pulp, the test material was found to be a potent inhibitor of IgE-mediated mast cell activation.

A Euterpe Oleracea Fruit Extract trade name mixture (98% Euterpe Oleracea Fruit Extract and 2% *Lactobacillus* ferment) was classified as a non-irritant when skin irritation was evaluated using the EpiDerm™ model (reconstructed human epidermis) assay.

The in vitro skin sensitization ARE-Nrf2 luciferase test method was used to evaluate the sensitization potential of a Euterpe Oleracea Fruit Extract trade name mixture (98% Euterpe Oleracea Fruit Extract and 2% *Lactobacillus* ferment). This test method involved incubation of the HaCaT cell line with concentrations ranging from 0.98 µM to 2000 µM, and the trade name mixture was not predicted to be a skin sensitizer. The same trade name mixture was evaluated for sensitization potential using the DPRA and was predicted to be a non-sensitizer.

An HRIPT involving a face and neck product containing 3% Euterpe Oleracea Pulp Powder was performed using 214 subjects. The authors concluded that there was no evidence of sensitization to the product tested in this study.

The EpiOcular™ model (human corneal epithelial model) assay was used to evaluate the ocular irritation potential of a Euterpe Oleracea Fruit Extract trade name mixture (98% Euterpe Oleracea Fruit Extract and 2% *Lactobacillus* ferment). The trade name mixture was classified as a non-irritant in this assay.

DISCUSSION

The ingredient group reviewed in this safety assessment (*Euterpe edulis* (juçara) and *Euterpe oleracea* (açaí)-derived ingredients) was formed based on the supposition that ingredients from a given genus and species, and on a closely related species (i.e., *edulis* and *oleracea*), would have constituents in common. For example, both species have the following constituents in common: catechin, chlorogenic acid, cyanidin-3-glucoside, cyanidin-3-rutinoside, ellagic acid, ferulic acid, gallic acid, pelargonidin-3-glucoside, and peonidin-3-rutinoside. Except for Euterpe Oleracea Palm Heart Extract, for which composition data are absent, the Panel agreed that the available data indicate that the compositions of the two species are similar.

The Panel discussed the issue of incidental inhalation exposure from powders and hair sprays. The Council survey results indicate that Euterpe Oleracea Fruit Extract is being used in pump hair sprays at concentrations up to 0.001%. Also, Euterpe Oleracea Juice is being used at concentrations up to 0.01% in face powders. The Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

The skin sensitization potential of a face and neck product containing 3% Euterpe Oleracea Pulp Powder was evaluated in a study involving 214 subjects, and the results were classified as negative. However, definite erythema and damage to the epidermis (but no edema) were observed in 1 subject at the 5th induction evaluation. No other effects were observed when the induction site was moved, or after the challenge application. The test concentration evaluated in this study is the highest maximum use concentration in leave-on products that is reported in this safety assessment. These are the only human skin sensitization data that are included and, also, the in vitro/in chemico sensitization data on Euterpe Oleracea Fruit Extract are classified as negative. Additionally, the Panel noted that the available composition data do not indicate the presence of any sensitizing constituents.

The Panel also expressed concern about pesticide residues, heavy metals, and other plant species that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

Finally, the Panel determined that the available data are insufficient to arrive at a conclusion on the safety of Euterpe Oleracea Palm Heart Extract. The data needs on this ingredient include:

- Composition data; if the composition of this ingredient is found to be significantly different from the other ingredients in this group, skin irritation and sensitization data would be needed

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 7 palm tree (*Euterpe edulis* (juçara) and *Euterpe oleracea* (açaí)-derived ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Euterpe Edulis Fruit Extract*
Euterpe Edulis Juice Extract*
Euterpe Oleracea Fruit Extract
Euterpe Oleracea Juice
Euterpe Oleracea Pulp Powder
Euterpe Oleracea Seed Powder*
Hydrolyzed Euterpe Oleracea Fruit

* *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.*

The Panel further concluded that the available data are insufficient to make a determination of safety for Euterpe Oleracea Palm Heart Extract under the intended conditions of use in cosmetic formulations.

TABLES

Table 1. Definitions and functions of the ingredients in this safety assessment.[1]

Ingredient CAS No.	Definition & Structures	Function(s)
Euterpe Edulis Fruit Extract	Euterpe Edulis Fruit Extract is the extract of the fruit of *Euterpe edulis*.	Skin-Conditioning Agents - Miscellaneous
Euterpe Edulis Juice Extract	Euterpe Edulis Juice Extract is the extract of the sap of *Euterpe edulis*.	Skin-Conditioning Agents - Miscellaneous
Euterpe Oleracea Fruit Extract 879496-95-4 (generic) 906351-38-0 (generic)	Euterpe Oleracea Fruit Extract is the extract of the fruit of *Euterpe oleracea*.	Hair Conditioning Agents
Euterpe Oleracea Juice 879496-95-4 (generic) 906351-38-0 (generic)	Euterpe Oleracea Juice is the juice expressed from the fruit of *Euterpe oleracea*.	Skin-Conditioning Agents - Miscellaneous
Euterpe Oleracea Palm Heart Extract 879496-95-4 (generic) 906351-38-0 (generic)	Euterpe Oleracea Palm Heart Extract is the extract of the palm heart of *Euterpe oleracea*.	Skin-Conditioning Agents - Emollient
Euterpe Oleracea Pulp Powder 879496-95-4 (generic) 906351-38-0 (generic)	Euterpe Oleracea Pulp Powder is the powder obtained from the dried, ground pulp of *Euterpe oleracea*.	Abrasives; Antioxidants; Exfoliants; Skin-Conditioning Agents - Miscellaneous
Euterpe Oleracea Seed Powder 879496-95-4 906351-38-0	Euterpe Oleracea Seed Powder is the powder obtained from the dried, ground seeds of *Euterpe oleracea*.	Abrasives; Exfoliants
Hydrolyzed Euterpe Oleracea Fruit	Hydrolyzed Euterpe Oleracea Fruit is the hydrolysate of the fruit of *Euterpe oleracea* derived by acid, enzyme, or other method of hydrolysis.	Skin-Conditioning Agents - Miscellaneous

Table 2. Generic plant part definitions as they apply to palm tree-derived ingredients.[1]

Plant Part	Definition
Fruit	Mature, ripened ovary of flowering plant, containing seeds.
Palm heart	Inner core of the stem of various palm species (Arecaceae).
Pulp	A soft, fleshy part of a fleshy fruit, often formed by the fruit wall or the placenta.
Sap	The fluid transported through the vascular system of a plant
Seed	A propagating sexual structure resulting from the fertilization of an ovule, formed by embryo, endosperm, or seed coat.

Table 3. Composition data on Euterpe Edulis Fruit Extract (various extractants).[24]

Components	Probability of constituent presence(%)*
Hexane Extract	
bis(2-methylpropyl)-1,2-benzenedicarboxylic acid ester (diisobutyl phthalate)	20
hexadecanamide	54
9-(Z)-octadecenamide	61
phenethyl alcohol	25
squalene	20
Ethyl Acetate Extract	
1,6-anhydro-β-D-glucopyranose,	43
hexadecanamide	72
9-(Z)-octadecenamide	54
Chloroform Extract	
2,4-(E,E)-decadienal	23
(Z)-2-hepten-1-al	29
naphthalene	35
phenethyl alcohol	55

*The chemical constituents of the extracts were identified by comparing their retention indices and making computer matches with the National Institute of Standards and Technology library provided by the computer controlling the gas chromatography-mass spectrometry system.

Table 4. Content of Ingredients/Fruit Parts derived from *Euterpe edulis*.[2-8]

Components	Euterpe Edulis Fruit Extract	*Euterpe edulis* fruit	*Euterpe edulis* pulp extract	*Euterpe edulis* pulp
Carotenoids (µg/100 g fresh weight)				
apocarotenoid		undetectable		
all-*trans*-α-carotene		60.2 ± 6.0		
all-*trans*-β-carotene		266.5 ± 41.5		
all-*trans*-α-cryptoxanthin		undetectable		
all-*trans*-β-cryptoxanthin		undetectable		
all-*trans*-lutein		292.7 ± 3.3		
all-*trans*-neochrome		undetectable		
all-*trans*-zeaxanthin		5.4 ± 2.4		
all-*trans*-zeinoxanthin		7.7 ± 0.4		
cis-antheraxanthin		undetectable		
9-*cis*-β-carotene		37.8 ± 3.5		
13-*cis*-β-carotene		15.8 ± 1.9		
15-*cis*-β-carotene		9.2 ± 0.3		
9-*cis*-β-cryptoxanthin		undetectable		
9'-*cis*-β-cryptoxanthin		undetectable		
13-*cis*-β-cryptoxanthin		undetectable		
13'-*cis*-β-cryptoxanthin		undetectable		
15-*cis*-β-cryptoxanthin		undetectable		
cis-lutein		12.6 ± 1.3		
9-*cis*-violaxanthin		5.5 ± 0.4		
13-*cis*-violaxanthin		6.5 ± 4.3		
9-*cis*-neoxanthin		13.2 ± 4.2		
5,8-epoxy-β-carotene		undetectable		
5,6-epoxy-β-cryptoxanthin		undetectable		
5,8-epoxy-β-cryptoxanthin		undetectable		
phytoene		undetectable		

Table 4. Content of Ingredients/Fruit Parts derived from *Euterpe edulis*.[2-8]

Components	Euterpe Edulis Fruit Extract	*Euterpe edulis* fruit	*Euterpe edulis* pulp extract	*Euterpe edulis* pulp
Nutrients (%)				
Carbohydrate		85.7 ± 0.4		42.5 ± 0.1
Dietary fiber		71.8 ± 0.6		27.1
Lipid		6.9 ± 0.3		46.6
Moisture		51.9 ± 0.3		83.8 ± 0.5
Protein		5 ± 0.3		7.5 ± 0.1
Anthocyanins (expressed as mg cyanidin 3-glucoside (C3G)/100 g fresh matter or as gallic acid equivalents (GAE)/100 g)				
cyanidin-3-*O*-glucoside	Amount not stated			
cyanidin 3-glucoside	Not assayed	47.93 ± 1.52	Amount not stated	
cyanidin 3-glucoside	Not assayed	51.4 ± 3.1 (as GAE)	Amount not stated	
cyanidin 3,5-hexose pentose	Not assayed	1.43 ± 0.05	Not assayed	
cyanidin 3-rhamnoside	Not assayed	0.30 ± 0.01	Not assayed	
cyanidin-3-*O*-rutinoside	73% of total phenolic content	Not assayed	Not assayed	
cyanidin 3-rutinoside	Not assayed	179.60 ± 5.77	Amount not stated	
cyanidin 3-rutinoside	Not assayed	141 ± 8.5 (as GAE)	Amount not stated	
cyanidin-3-sambubioside	Not assayed	Not assayed	Amount not stated	
delphinidin-3-glucoside	Not assayed	Not assayed	Amount not stated	
pelargonidin-3-*O*-glucoside	Amount not stated	Not assayed	Not assayed	
pelargonidin-3-glucoside	Not assayed	1.66 ± 0.05	Amount not stated	
pelargonidin 3-rutinoside	Not assayed	2.87 ± 0.09	Not assayed	
peonidin-3-rutinoside	Not assayed	3.59 ± 0.11	Amount not stated	
Other Phenolic Compounds (expressed as gallic acid equivalents (GAE)/100 g)				
apigenin	Amount not stated	Not assayed		
apigenin deoxyhexosidehexoside	Not assayed	25.4 ± 1.5		
apigenin dihexoside	Not assayed	11.06 ± 0.9		
apigenin hexoside	Not assayed	13.2 ± 1		
caffeic acid	Not assayed	Amount not stated		
catechin	Amount not stated	Not assayed		
chlorogenic acid	Not assayed	Amount not stated		
chrysoeriol deoxyhexosylhexoside	Not assayed	22.5 ± 0.7		
m-coumaric acid	Not assayed	Amount not stated		
p-coumaric Acid	Not assayed	Amount not stated		
dihydroluteolin deoxyhexosylhexoside	Not assayed	12.7 ± 0.5		
4,5-dicaffeoylquinic acid	Amount not stated	Not assayed		
dihydrokaempferol acetyl-hexoside	Not assayed	2.8 ± 0.01		
dihydrokaempferol hexoside	Not assayed	66.4 ± 2.6		
3,4-dihydroxyphenylacetic acid	Not assayed	Amount not stated		
ellagic acid	Amount not stated	Not assayed		
ferulic acid	Not assayed	Amount not stated		
gallic acid	Not assayed	Amount not stated		
gallic acid hexoside	Not assayed	1.7 ± 0.04		
p-hydroxybenzoic acid	Not assayed	Amount not stated		
4-hydroxyphenylacetic acid	Not assayed	Amount not stated		
kaempferol	Amount not stated	Not assayed		
kaempferol deoxyhexosylhexoside	Not assayed	7.21 ± 0.9		
kaempferol-3-*O*-rutinoside	Amount not stated	Not assayed		
luteolin	Amount not stated	Not assayed		
luteolin deoxyhexosylhexoside	Not assayed	37.6 ± 1.9		
myricetin	Amount not stated	Not assayed		
protocatechuic acid	Not assayed	Amount not stated		
quercetin	Amount not stated	Not assayed		
rutin	Amount not stated	Not assayed		
sinapinic acid	Not assayed	Amount not stated		
syringic acid	Not assayed	Amount not stated		
taxifolin hexoside	Not assayed	13.3 ± 0.4		
trans-cinnamic acid	Not assayed	Amount not stated		
vanillic acid	Not assayed	Not assayed		

Table 5. Heavy Metal/Mineral Constituents of *Euterpe edulis* Fruit and *Euterpe edulis* Pulp and Ash Residue for Each.[4]

Constituents (mg/100 g)	***Euterpe edulis* fruit**	***Euterpe edulis* pulp**
Calcium	63.8 ± 3.3	76.4 ± 2.9
Copper	0.3 ± 0	0.5 ± 0
Iron	1.67 ± 0.4	4.3 ± 0.6
Magnesium	32.1 ±4.2	47.4 ± 4.2
Manganese	2.8 ± 0.9	3 ± 0
Nickel	0.5 ± 0	1 ± 0.1
Phosphorus	69.2 ± 12.2	41.2 ± 1.4
Potassium	361 ± 42	419.1 ± 26.9
Sodium	21.8 ± 2.5	17.3 ± 0.1
Sulfur	26.9 ± 2.9	35.4 ± 4.9
Zinc	0.6 ± 0.1	0.9 ± 0
Constituents (µg/100g)		
Cadmium	1.1 ± 0.2	1.2 ± 0
Cobalt	13.6 ± 1.9	7.1 ± 0.2
Selenium	1 ± 0.1	0.5 ± 0.1
Residue after combustion (%)		
Ash	2.5	3.4

Table 6. Composition data on Euterpe Oleracea Fruit Extract (various extractants).[29,28]

Components	**Amount (mg GAE/100g [dwb])***
Sequential extraction with ethyl acetate, methanol, and methanol/water, yielding anthocyanins	
cyanidin-di-*O*-glycoside	Not stated
cyanidin-3-glucoside	Not stated
cyanidin-3-rutinoside	Not stated
pelargonidin-3-glucoside	Not stated
peonidin-3-glucoside	Not stated
peonidin-3-rutinoside	Not stated
Extraction with solution of ethanol and aqueous hydrochloric acid	
Total phenolic compounds	2370 ± 177
Total anthocyanins	81.62 ± 12.89

*dwb = dry weight basis

Table 7. Content of Ingredients/Components Derived from *Euterpe oleracea*.[9-14]

Components	***Euterpe oleracea* fruit**	***Euterpe oleracea* fruit powder extract**	***Euterpe oleracea* juice extract**	**Euterpe Oleracea Juice (data on the pulp [contains juice] identified as pulp below)**
Anthocyanins				
cyanidin 3-acetyl hexose	Amount not stated			
cyanidin-3-arabinoside	Amount not stated			
cyanidin-3-glucoside	Not assayed		Amount not stated	
cyanidin-3-*O*-glucoside	Amount not stated			
cyanidin-3-rutinoside	Not assayed		Amount not stated	
cyanidin-3-*O*-rutinosíde	Amount not stated			
cyanidin 3-sambubioside	Amount not stated			
peonidin 3-glucoside	Amount not stated			
peonidin 3-rutinoside	Amount not stated			

Table 7. Content of Ingredients/Components Derived from *Euterpe oleracea*.[9-14]

Components	*Euterpe oleracea* fruit	*Euterpe oleracea* fruit powder extract	*Euterpe oleracea* juice extract	Euterpe Oleracea Juice (data on the pulp [contains juice] identified as pulp below)
Flavonoids (mg/100 g dry matter of juice extract; µg/g dry weight of juice)				
apigenin	Amount not stated			
apigenin 6,8-di-*C*-hexoside	Not assayed		Amount not stated	
apigenin-*O*-hexoside-*C*-hexoside	Not assayed		Amount not stated	
apigenin 6-*C*-hexoside-8-*C*-pentoside	Not assayed		Amount not stated	
apigenin 6-*C*-pentoside-8-*C*-hexoside	Not assayed		Amount not stated	
apigenin 8-*C*-(2"-*O*-pentosyl) hexoside	Not assayed		Amount not stated	
astilbin	Amount not stated			
caffeic acid	Not assayed		Amount not stated	Amount not stated
catechin	Amount not stated			5.20 ± 1.08
(+)-catechin	Not assayed		8.14 ± 0.80	
chrysoeriol	Amount not stated		1.03 ± 0.03	
crisoeirol	Amount not stated			
(+)-dihydrokaempferol	Not assayed		2.18 ± 0.02	
(2R,3R)-dihydrokaempferol	Amount not stated			
5,4'-dihydroxy-7, 3', 5'-trimethoxy flavone	Amount not stated			
epicatechin	Amount not stated			
(-)-epicatechin	Not assayed		4.43 ± 0.28	
homoorientin	Not assayed		71.56 ± 5.81	
isoorientin	Amount not stated			89.74 ± 5.32
isovitexin	Amount not stated		Amount not stated	
kaempferol rhamnoside	Amount not stated			
kaempferol rutinoside	Amount not stated			
kaempherol-3-rutinoside	Not assayed		Amount not stated	
luteolin	Not assayed		Amount not stated	
luteoline diglicoside	Amount not stated			
orientin	Amount not stated		55.19 ± 0.76	189.49 ± 13.56
procyanidin dimeric	Amount not stated			
protoanthocyanidin	Amount not stated			
quercetin	Amount not stated		1.77 ± 0.03	
quercetin arabinopyranoside	Amount not stated			
quercetin-3-glucoside	Not assayed		1.57 ± 0.04	
quercetin rhamnoside	Amount not stated			
quercetin rutinoside	Amount not stated			
rutin	Amount not stated		3.95 ± 0.07	
scoparin	Amount not stated		4.71 ± 0.12	
taxifolin	Not assayed		Amount not stated	1.57 ± 0.25
taxifolin deoxyhexose	Amount not stated			
taxifolin deoxyhexose (or isomer)	Not assayed		Amount not stated	
Other Phenolic Compounds (µg/g dry weight of juice)				
benzoic acid	Amount not stated			
chlorogenic acid	Amount not stated			4.23 ± 0.86
p-coumaric acid	Not assayed			4.67 ± 0.93
p-coumarinic acid	Amount not stated			
dihydrokaempferol	Amount not stated			
(+)-dihydrokaempferol	Not assayed			
4-hydroxybenzoic acid	Not assayed			13.38 ± 1.50
3,4-dihydroxybenzoic acid	Not assayed			Amount not stated
ellagic acid	Amount not stated			
eriodictyol	Not assayed		Amount not stated	

Table 7. Content of Ingredients/Components Derived from *Euterpe oleracea*.[9-14]

Components	*Euterpe oleracea* fruit	*Euterpe oleracea* fruit powder extract	*Euterpe oleracea* juice extract	Euterpe Oleracea Juice (data on the pulp [contains juice] identified as pulp below)
escoparine	Amount not stated			
ferulic acid	Amount not stated			27.95 ± 2.48
gallic acid	Amount not stated			
glycoside ellagic acid	Amount not stated			
p-hydroxybenzoic acid	Amount not stated			
3-hydroxy-1-(4-hydroxy-3,5-dimetoxyphenil)-1-propanonadihydroconiferyl alcohol	Amount not stated			
isovitexin	Not assayed		7.07 ± 0.53	
lariciresinol	Amount not stated			
pinoresinol	Amount not stated			
pirocatéquic acid	Amount not stated			
protocatechuic acid	Not assayed		Amount not stated	
syringaresinol	Amount not stated			
syringic acid	Not assayed			0.69 ± 0.09
vanillic acid	Amount not stated		Amount not stated	55.61 ± 5.26
velutine	Amount not stated			
vitexin	Not assayed		6.26 ± 0.48	
Simple Benzenoids				
dihydroconiferyl alcohol	Amount not stated			
3,4′-dihydroxy-3′-methoxypropiophenone	Amount not stated			
3-hydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanone	Amount not stated			
protocatechuic acid methyl ester	Amount not stated			
Benzoquinone				
2,6-dimethoxy-1,4-benzoquinone	Amount not stated			
Monoterpenoids				
(E,Z)-2,6-dimethyl-2,6-octadiene-1,8-diol	Amount not stated			
(E,E)-2,6-dimethyl-2,6-octadiene-1,8-diol	Amount not stated			
(S)-menthiafolic acid	Amount not stated			
Norisoprenoids				
(4R)-4-[(1E)-3-Hydroxy-1-butenyl]-3,5,5-trimethyl-2-cyclohexen-1-one	Amount not stated			
(-)-loliolide	Amount not stated			
Saturated Fatty Acids (g/100g [dwb])				
behenic	Amount not stated			
butyric	Amount not stated			
caproic	Amount not stated			
caprylic	Amount not stated			
capric	Amount not stated			
eicosanoic	Amount not stated			
lauric	Amount not stated			
liognoceric	Amount not stated			
margaric	Amount not stated			
myristic	Amount not stated			
nonadecanoic	Amount not stated			
palmitic	Not assayed			7.64 (pulp)
pentadecanoic	Amount not stated			
stearic	Amount not stated			0.36 (pulp)

Table 7. Content of Ingredients/Components Derived from *Euterpe oleracea*.[9-14]

Components	*Euterpe oleracea* fruit	*Euterpe oleracea* fruit powder extract	*Euterpe oleracea* juice extract	Euterpe Oleracea Juice (data on the pulp [contains juice] identified as pulp below)
tricosanoic	Amount not stated			
tridecanoic	Amount not stated			
undecanoic	Amount not stated			
Monounsaturated Fatty Acids (g/100g [dwb])				
elaidic	Amount not stated			
erucic	Amount not stated			
gadoleic	Amount not stated			
margaroleic	Amount not stated			
myristoleic	Amount not stated			
nervonic	Amount not stated			
oleic	Amount not stated			18.20 (pulp)
palmitoleic	Amount not stated			1.82 (pulp)
pentadecenoic	Amount not stated			
tridecanoic	Amount not stated			
Polyunsaturated Fatty Acids (g/100g [dwb])				
arachidonic	Amount not stated			
docosadienoic	Amount not stated			
docosahexaenoic	Amount not stated			
eicosadienoic	Amount not stated			
eicosapentaenoic	Amount not stated			
eicosatrienoic	Amount not stated			
linoleic	Amount not stated			3.64 (pulp)
linolenic	Amount not stated			
α-linolenic acid	Not assayed			0.36 (pulp)
gamma linolenic	Amount not stated			
homogamma linolenic	Amount not stated			
Sterols				
campesterol	Amount not stated			
beta-sitosterol	Amount not stated			
stigmasterol	Amount not stated			
Amino Acids				
alanine	Amount not stated			
arginine	Amount not stated			
aspartic acid	Amount not stated			
cysteine	Amount not stated			
glutamic acid	Amount not stated			
glycine	Amount not stated			
histidine	Amount not stated			
hydroxyproline	Amount not stated			
isoleucine	Amount not stated			
leucine	Amount not stated			
lysine	Amount not stated			
methionine	Amount not stated			
phenylalanine	Amount not stated			
proline	Amount not stated			
serine	Amount not stated			
threonine	Amount not stated			
tryptophan	Amount not stated			

Table 7. Content of Ingredients/Components Derived from *Euterpe oleracea*.[9-14]

Components	*Euterpe oleracea* fruit	*Euterpe oleracea* fruit powder extract	*Euterpe oleracea* juice extract	Euterpe Oleracea Juice (data on the pulp [contains juice] identified as pulp below)
tyrosine	Amount not stated			
valine	Amount not stated			
Sugars				
fructose	Amount not stated			
glucose	Amount not stated			
lactose	Amount not stated			
maltose	Amount not stated			
sucrose	Amount not stated			
Lignans				
(-)-(7R,8S)-dihydrodehydroconiferyl alcohol	Amount not stated			
erythro-1-(4-hydroxy-3-methoxyphenyl)-2-[4-(3-hydroxypropyl)-2-methoxy-phenoxy]-1,3-propanediol	Amount not stated			
(+)-isolariciresinol	Amount not stated			
(+)-(6R,7S,8S)-isolariciresinol	Amount not stated			
(+)-lariciresinol (8)	Amount not stated			
(+)-(7S,8R,8′R)-lariciresinol	Amount not stated			
(+)-(7R,8S)-5-methoxydihydrodehydroconiferyl alcohol	Amount not stated			
(+)-5-methoxy-isolariciresinol	Amount not stated			
(+)-(6R,7S,8S)-5-methoxyisolariciresinol	Amount not stated			
(+)-pinoresinol	Amount not stated			
(+)-syringaresinol	Amount not stated			
threo-1-(4-Hydroxy-3-methoxyphenyl)-2-[4-(3-hydroxypropyl)-2-methoxyphenoxy]-1,3-propanediol	Amount not stated			
Neolignan glucosides				
(–)-(7R,8S)-7′,8′-dihydroxy-dihydrodehydroconiferyl alcohol-9-*O*-β-D-glucopyranoside		Amount not stated		
(+)-(7S,8R)-7′,8′-dihydroxy-dihydrodehydroconiferyl alcohol-9-*O*-β-D-glucopyranoside		Amount not stated		
4-hydroxy-2-methoxyphenyl 1-*O*-[6-(hydrogen 3-hydroxy-3-methylpentanedioate)]-β-D-glucopyranoside		Amount not stated		
Carotenoids				
α-carotene	Amount not stated			
ß-carotene	Amount not stated			
chlorophyll	Amount not stated			
lutein	Amount not stated			
tocopherols A, B, C, and D	Amount not stated			
Vitamins				
vitamin A	Amount not stated			
vitamin B1	Amount not stated			
vitamin B2	Amount not stated			
vitamin B3	Amount not stated			
vitamin B5	Amount not stated			
vitamin C	Amount not stated			
vitamin E	Amount not stated			
vitamin K	Amount not stated			

Table 8. Composition Data on *Euterpe oleracea* Seed.[28]

Components	**Amount (g/100 g [wwb])***
Moisture	38.57 ± 0.07
Protein	3.95 ± 0.03
Lipid	1.04 ± 0.03
Carbohydrates	55.55
Fatty Acid Composition	**Amount (g/100 g [dwb])**
Saturated	0.085 total
capric acid	0.16
myristic acid	0.39
palmitic acid	0.28
stearic acid	0.02
Monounsaturated	0.46 total
oleic acid	0.44
palmitoleic acid	0.02
Polyunsaturated	0.31 total
linoleic acid	0.29
α-linolenic	0.02
Other Fatty Acids	0.08

*wwb = wet weight basis

Table 9. Frequency (2020) and Concentration of Use (2017) According to Duration and Type of Exposure.[31,32]

	Euterpe Oleracea Fruit Extract		**Euterpe Oleracea Juice**		**Euterpe Oleracea Palm Heart Extract**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals*	**469**	**0.0000001-0.38**	**1**	**0.04**	**3**	**0.001**
Duration of Use						
Leave-On	*328*	*0.0000083-0.04*	*1*	*0.01-0.04*	*2*	*0.001*
Rinse off	*137*	*0.0000001-0.38*	*NR*	*NR*	*1*	*0.001*
Diluted for (bath) Use	*4*	*0.0005*	*NR*	*NR*	*NR*	*0.001*
Exposure Type						
Eye Area	4	NR	NR	NR	NR	NR
Incidental Ingestion	7	0.0000083-0.025	1	NR	NR	NR
Incidental Inhalation - Sprays	10;196[a];79[c]	0.001; 0.00003- 0.001[a]	NR	NR	1	0.001
Incidental Inhalation - Powders	79[c]	0.0001-0.01[b]	NR	0.01	NR	0.001[b]
Dermal Contact	402	0.0000001-0.83	NR	0.01-0.04	3	0.001
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	57	0.00000075-0.001	NR	NR	NR	0.001
Hair-Coloring	1	0.38	NR	NR	NR	NR
Nail	1	0.04	NR	NR	NR	NR
Mucous Membrane	68	0.0000083-0.025	1	NR	1	0.001
Baby Products	NR	NR	NR	NR	NR	NR

	Euterpe Oleracea Pulp Powder		**Hydrolyzed Euterpe Oleracea Fruit**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	**11**	**0.003-3**	**1**	**NR**
Duration of Use				
Leave-On	*9*	*0.033-3*	*NR*	*NR*
Rinse off	*2*	*0.003-0.6*	*1*	*NR*
Diluted for (bath) Use	*NR*	*NR*	*NR*	*NR*
Exposure Type				
Eye Area	NR	NR	NR	NR
Incidental Ingestion	NR	0.033-0.3	NR	NR
Incidental Inhalation - Sprays	5; 1[c]	0.015	NR	NR
Incidental Inhalation - Powders	NR;1[c]	0.015-3[b]	NR	NR
Dermal Contact	9	0.015-3	NR	NR
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	2	0.003-0.3	NR	NR
Hair-Coloring	NR	NR	1	NR
Nail	NR	NR	NR	NR
Mucous Membrane	NR	0.033-0.3	NR	NR
Baby Products	NR	NR	NR	NR

* 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.
NR = Not Reported
[a]It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays
[b]It is possible that these products may be powders, but it is not specified whether the reported uses are powders
[c]Not specified that these products are sprays or powders, but it is possible the use can be as a spray or powder, therefore the information is captured in both categories

Table 10. Genotoxicity Studies on Palm Tree-derived ingredients and Related Components of *Euterpe edulis* and *Euterpe oleracea*

Ingredient	Strain/cell type	Assay	Dose/Concentration	Results
		In Vitro		
Euterpe Oleracea Fruit Extract trade name mixture (98% Euterpe Oleracea Fruit Extract and 2% *Lactobacillus* ferment) in sterile distilled water	*S. typhimurium* strainsTA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2uvrA.	Ames test, with and without metabolic activation.	Doses up to 5000 µg/plate	Non-genotoxic, with and without metabolic activation in all bacterial strains tested.[49]
Euterpe edulis fruit pulp (9% in water)	*S. typhimurium* strains: TA97, TA98, TA100, and TA102	Ames test, with and without metabolic activation.	Doses up to 500 µg/plate	Genotoxic in strain TA97 at doses ranging from 25 to 250 µg/plate without metabolic activation. Clear trend for genotoxicity in strains TA98 and TA100 at doses ranging from 25 to 250 µg/plate without metabolic activation. Genotoxicity with metabolic activation was not reported for any strain tested.[24]
Euterpe edulis fruit pulp (9% in water)	RAW264.7 cells (mouse macrophage-like cells).	Micronucleus assay	Concentrations of 0.027, 0.108, 0.27, 0.54, and 1.08 mg per plate (0.27, 1.08, 2.7, 5.4, and 10.8 mg/ml, respectively)	Cytotoxic effect, suggested by a decrease in the mitotic index and survival rates, observed at all concentrations. When compared to negative control (sodium chloride), genotoxicity was significantly higher at all doses tested .[24]
Euterpe edulis fruit oil	Human peripheral blood lymphocytes and HepG2 (human hepatoma) cell line	Cytokinesis-block micronucleus assay	Concentrations up to 1000 µg/ml	Absence of significant DNA and chromosome damage in human lymphocytes and HepG2 cells.[48]
Euterpe edulis fruit oil	Human peripheral blood lymphocytes and HepG2 (human hepatoma) cell line	Comet assay	Concentrations up to 1000 µg/ml in both assays	Absence of significant DNA and chromosome damage in human lymphocytes and HepG2 cells.[48]
Euterpe oleracea pulp-enriched fruit and berry juice (fortified with glucosamine)	*S. typhimurium* strains: TA98, TA100, TA1535, TA1537. *Eschericia coli* strain: WP2 (uvrA)	Ames test, with and without metabolic activation	Doses up to 5 µg/plate	Non-genotoxic, with and without meta-bolic activation.[46]
Euterpe oleracea pulp-enriched fruit and berry juice (fortified with glucosamine)	Chinese hamster lung cells	Chromosomal aberration assay, with and without metabolic activation (OECD TG 473)	Concentrations up to 5000 µg/ml	Structural chromosome aberrations not observed with or without metabolic activation. Non-clastogenic.[46]
Euterpe oleracea pulp-enriched fruit and berry juice (fortified with glucosamine)	L5178Y/TK+/- mouse lymphoma cells	L5178Y/TK+/- mouse lymphoma assay, with and without metabolic activation (OECD TG 476)	Concentrations up to 500 µg/ml	Non-genotoxic, with and without metabolic activation.[46]
		In Vivo		
Euterpe edulis fruit pulp extract (9% in water)	4 groups of 5 male Wistar rats	Micronucleus assay (OECD TG 474). After dosing period, animals were killed and bone marrow smears prepared. Ratio of polychromatic to normochromatic erythrocytes (PCE/PCE + NCE x 100) calculated based on an evaluation of 2000 erythrocytes per slide (1000 per animal).	4 groups received doses (by gavage) of 22.5, 45, 90, and 180 mg/kg, respectively, for 3 consecutive days.	Significant increase ($P < 0.05$) in frequency of micronucleated polychromatic erythrocytes in bone marrow, at daily doses of 45 to 180 mg/kg.[24]

Table 10. Genotoxicity Studies on Palm Tree-derived ingredients and Related Components of *Euterpe edulis* and *Euterpe oleracea*

Ingredient	Strain/cell type	Assay	Dose/Concentration	Results
Euterpe edulis fruit pulp extract (9% in water)	4 groups of 5 male Wistar rats	Micronucleus assay. Peripheral blood (500 µl) drawn from rats dosed according to preceding test procedure, and whole blood smears prepared. Frequency of lymphocytes with micronuclei per total lymphocytes determined using sample sized of 1000 lymphocytes per animal	Doses same as in preceding test	No statistically significant positive results for micronucleus frequency observed. Dose-related increase in mitotic index ($P > 0.05$) detected (at 90 to 180 mg/kg), suggesting induction of proliferation alongside acceptable survival rates of >80%.[24]
Euterpe edulis fruit pulp extract (9% in water)	4 groups of 5 male Wistar rats	Comet assay (Single cell gel electrophoresis (SCGE) test). Blood drawn from rats dosed according to same test procedure (stated above). Slides prepared and extent and distribution of DNA damage evaluated by examining at least 200 randomly selected and non-overlapping cells.	Same doses	The SCGE score did not indicate significant DNA lesions, such as single or double breakages.[24]
Euterpe edulis fruit pulp (9%)	5 human subjects	Comet assay. Subjects ingested single dose on 5 consecutive days. Peripheral blood drawn and slides prepared. Extent and distribution of DNA damage evaluated by examining at least 200 randomly selected and non-overlapping cells.	300 ml/day	SCGE score did not indicate significant DNA lesions, such as single or double breakages. No statistically significant positive genotoxicity response identified.[24]
Euterpe oleracea pulp-enriched fruit and berry juice (fortified with glucosamine) in saline	Groups of 16 BALB/c mice (8 males, 8 females) and 12 BALB/c mice (6 males, 6 females)	Micronucleus assay. Group divided into mice dosed orally or intraperitoneally daily for 7 days. Animals then killed, and bone marrow analyzed for micronuclei in poly-chromatic erythrocytes. Cytogenetic analysis performed by direct method of rinsing marrow of the femur and tibia.	Daily doses of 100 µg/150 µl	No increase in frequency of micronuclei in bone marrow polychromatic erythrocytes.[46]
Euterpe oleracea fruit pulp	Bone marrow cells and peripheral blood polychromatic erythrocytes (male Swiss albino mice)	Micronucleus assay. Assay performed using bone marrow cells and peripheral blood polychromatic erythro-cytes. Number of micro-nucleated polychromatic erythrocytes in 2000 polychromatic erythrocytes per animal recorded.	Single (acute) oral doses (gavage) or daily oral doses (gavage) (14 days) of 3.33 g/kg, 10 g/kg, and 16.67 g/kg were administered to groups of male Swiss albino mice (number per dose not stated).	No statistically significant differences ($P > 0.05$), between the negative control and groups treated with doses of the test substance, in the frequency of micronucleated polychromatic erythrocytes in bone marrow or blood. No genotoxic effects in this assay.[50]
Euterpe oleracea fruit pulp	Bone marrow cells and peripheral blood polychromatic erythrocytes (male Swiss albino mice)	Comet assay (DNA damage assay). Peripheral blood collected from mice and cellular suspensions prepared. Liver and kidney cells also collected (100 cells in each tissue visually scored)	Swiss albino mice dosed with test substance (same doses in acute and subacute dosing procedures in both micronucleus assays immediately above)	Absence of increased DNA damage (in peripheral blood, liver, and kidney cells) in mice dosed orally (all doses). Non-genotoxic.[50]

Table 10. Genotoxicity Studies on Palm Tree-derived ingredients and Related Components of *Euterpe edulis* and *Euterpe oleracea*

Ingredient	Strain/cell type	Assay	Dose/Concentration	Results
Euterpe oleracea fruit oil	Groups of 6 Wistar rats	Comet assay. Doses administered by gavage (at 24-h intervals) for 14 consecutive days. At 24 h after last dose, peripheral blood from tail collected. Animals were killed and liver, bone marrow (from femur), and testicle cells also collected. DNA damage evaluated by examining at least 100 randomly selected and non-overlapping cells (50 cells per coded slide) per animal in blind analysis.	Doses of 30, 100, or 300 mg/kg in 1% Tween 80	No significant induction of DNA strand breaks observed in tissues from any dose group. In the few nucleoids (after dosing with 300 mg/kg) with DNA damage (also observed with vehicle control), damage was considered minor.[47]
Euterpe oleracea fruit oil	Groups of 6 Wistar rats	Micronucleus assay. Doses and dosing procedure used in preceding test. Slides of bone marrow (femur) smears prepared and 2000 polychromatic Erythrocytes (PCE) per animal scored to determine clastogenic and/or aneugenic property of test substance. Clastogenic/aneugenic damage investigated by analyzing micronuclei formation in bone marrow PCE.	Doses of 30, 100, or 300 mg/kg in 1% Tween 80	No significant increase in the micronucleus frequency in bone marrow cells, as well as no significant difference/increase in the PCE/NCE ratio ($P < 0.05$).[47]

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2020 FDA VCRP Data

Euterpe Edulis Fruit Extract - No Data

Euterpe Edulis Juice Extract - No Data

Euterpe Oleracea Fruit Extract

2A-Bath Oils, Tablets, and Salts	1
2B-Bubble Baths	2
2D-Other Bath Preparations	1
3D-Eye Lotion	1
3F-Mascara	1
3G-Other Eye Makeup Preparations	2
4E-Other Fragrance Preparation	10
5A-Hair Conditioner	20
5E-Rinses (non-coloring)	3
5F-Shampoos (non-coloring)	22
5G-Tonics, Dressings, and Other Hair Grooming Aids	8
5I-Other Hair Preparations	4
6H-Other Hair Coloring Preparation	1
7C-Foundations	2
7E-Lipstick	7
7F-Makeup Bases	1
7I-Other Makeup Preparations	4
8G-Other Manicuring Preparations	1
10A-Bath Soaps and Detergents	46
10E-Other Personal Cleanliness Products	11
12A-Cleansing	28
12C-Face and Neck (exc shave)	60
12D-Body and Hand (exc shave)	19
12F-Moisturizing	181
12G-Night	2
12H-Paste Masks (mud packs)	6
12I-Skin Fresheners	2
12J-Other Skin Care Preps	20
13A-Suntan Gels, Creams, and Liquids	1
13B-Indoor Tanning Preparations	1
13C-Other Suntan Preparations	1
Total	**469**

Euterpe Oleracea Juice

07E - Lipstick	1
Total	**1**

Euterpe Oleracea Palm Heart Extract

Other Fragrance Preparation	1
Bath Soaps and Detergents	1
Body and Hand (exc shave)	1

Total	3

Euterpe Oleracea Pulp Powder

Hair Conditioner	1
Shampoos (non-coloring)	1
Other Makeup Preparations	1
Face and Neck (exc shave)	1
Body and Hand (exc shave)	4
Moisturizing	1
Other Skin Care Preps	2
Total	**11**

Euterpe Oleracea Seed Powder - No Data

Hydrolyzed Euterpe Oleracea Fruit

06F - Hair Lighteners with Color	1
Total	**1**

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: December 3, 2019

SUBJECT: Draft Final Report: Safety Assessment of Palm Tree (açai and juçara)-Derived Ingredients as Used in Cosmetics (draft prepared for the December 2019 CIR Expert Panel meeting)

The Personal Care Products Council respectfully submits the following comments on the draft final report, Safety Assessment of Palm Tree (açai and juçara)-Derived Ingredients as Used in Cosmetics.

Abstract; Conclusion - It is not clear what is meant by "under intended conditions of use", especially for ingredients with no uses reported.

Anti-Carcinogenicity, Euterpe Oleracea Pulp Powder - In the description of the study cited to reference 23, the timing between the injection of azoxymethane (at week 3) and sacrifice (killed at week 3) is not clear.

Discussion - Although the original grouping of ingredients may have been based on "supposition" of constituents in common, based on the composition information in the report, the Discussion should be revised to be more conclusive that there is common composition for these ingredients.

It is not clear what is meant by "chemical and biological properties of these ingredients." Perhaps for complex mixtures from plants, such as the ingredients included in this report, the composition should be considered when inhalation safety is discussed.

Table 2 - As a number of plant parts are not relevant to this report, e.g., kernel, sap, straw (this is only for grasses), it is not clear why they are included in Table 2 which is titled "Generic plant part definitions as they apply to palm tree-derived ingredients".

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 14, 2020

SUBJECT: Revised Tentative Report: Safety Assessment of Palm Tree (açai and juçara)-Derived Ingredients as Used in Cosmetics (release date: December 13, 2019)

The Personal Care Products Council respectfully submits the following comments on the revised tentative report, Safety Assessment of Palm Tree (açai and juçara)-Derived Ingredients as Used in Cosmetics.

Key Issues

The conclusion in the Abstract needs to be corrected to reflect the language as presented in the Conclusion section. The Conclusion (and post-meeting announcement) says "safe in cosmetics in the present practices of use and concentration described in the safety assessment." In contrast, the Abstract includes the qualification of "when formulated to be non-sensitizing".

Is the CIR Expert Panel aware that Euterpe Edulis Juice Extract is defined as an "extract of the sap"? In contrast, Euterpe Oleracea Juice is a more traditional juice, "expressed from the fruit".

Additional Considerations

Abstract; Conclusion - The meaning of "intended conditions of use" for Euterpe Oleracea Palm Heart Extract is not clear.

Composition, Euterpe Oleracea Fruit Extract (test material *Euterpe oleracea* fruit) - Potassium, magnesium, phosphorus, calcium and sodium are not considered "trace" elements.

Cosmetic Use - Although it is correct that a use concentration of 0.6% Euterpe Oleracea Pulp Powder was reported for both moisturizing products and paste masks, only paste masks are considered rinse-off products. Moisturizing products are generally considered to be leave-on products.

Non-Cosmetic Use - Since the paragraph in this section states that "*Euterpe oleracea* extract is not the name of any of the ingredients that are being reviewed in this safety assessment but has the same CAS number (879496-95-4) as the following ingredients..." it would be helpful to include the CAS definition for *Euterpe oleracea* extract.

Discussion - As there is much information in the report about composition, perhaps inhalation safety should be based on composition rather than "chemical and biological properties of these ingredients".