Safety Assessment of Palm Tree-Derived Ingredients as Used in Cosmetics

Status: Draft Tentative Report for Panel Review
Release Date: August 22, 2019
Panel Date: September 16-17, 2019

The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst.

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1620 L STREET, NW, SUITE 1200 ◊ WASHINGTON, DC 20036-4702 ◊ PH 202.331.0651 ◊ FAX 202.331.0088 ◊ CIRINFO@CIR-SAFETY.ORG

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Memorandum

To: CIR Expert Panel Members and Liaisons

From: Wilbur Johnson, Jr.
Senior Scientific Analyst

Date: August 22, 2019

Subject: Draft Tentative Report on Palm Tree-Derived Ingredients

Enclosed is a draft tentative report on 8 palm tree-derived ingredients. This ingredient family comprises cosmetic ingredients that are derived from two palm tree species, *Euterpe edulis* and *Euterpe oleracea*. An insufficient data announcement (IDA) was issued at the April 8-9, 2019 Panel meeting, with the following data needs:

For all of 8 ingredients
- 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

To date, there has been no response to the Panel's IDA on palm tree-derived ingredients.

The attached draft tentative report (*palmtr092019rep*) has been revised to include an HRIPT on a face and neck product containing 3% Euterpe Oleracea Pulp Powder that was reviewed at the April Panel meeting. Report comments (*palmtr092019pcpc1*) that were received from the Council prior to that meeting have been addressed, and a draft Discussion has been added for the Panel's review; any changes or additions to the draft Discussion should be identified.

Furthermore, a request from the Council (*palmtr092019pcpc2*) that the title of this safety assessment be changed to Palm (acai and juçara)-Derived Ingredients was received after the April Panel meeting . This request needs to be addressed by the Panel.

Also included in this package for your review are the CIR report history (*palmtr092019hist*), flow chart (*palmtr092019flow*), literature search strategy (*palmtr092019strat*), ingredient data profile (*palmtr092019prof*), 2019 FDA VCRP data (*palmtr092019fda*), and minutes from the April 8-9, 2019 Panel meeting (*palmtr092019min*).

After reviewing these documents, if the available data remain insufficient, the Panel should issue a tentative report with an insufficient data conclusion, specifying the data needs in the Discussion. However, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a tentative report with a safe as used, safe with qualifications, or unsafe conclusion.

1620 L Street, NW, Suite 1200, Washington, DC 20036
(Main) 202-331-0651 (Fax) 202-331-0088
(Email) cirinfo@cir-safety.org (Website) www.cir-safety.org

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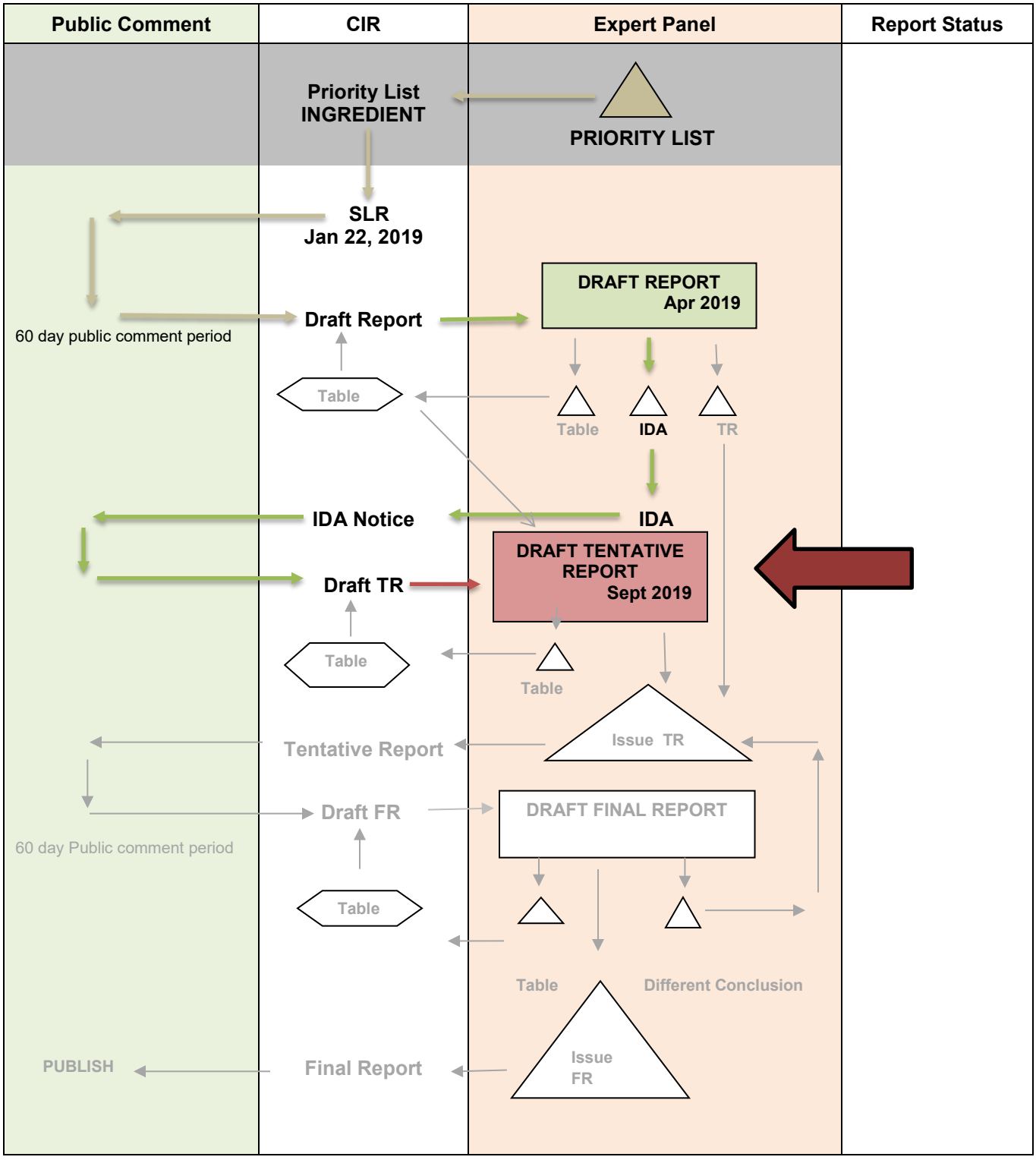
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Palm Tree-derived ingredients

MEETING September 2019



CIR 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.

Palm Tree-Derived Ingredients Data Profile* –September 16-17, 2019 – 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]

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	

Search Strategy

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

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

LINKS

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

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

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

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

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

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

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

April 8-9, 2019 CIR Expert Panel Meeting – Dr. Belsito's Team

Palm Tree-derived Ingredients

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.

April 8-9, 2019 CIR Expert Panel Meeting – Dr. Marks' Team

Palm Tree-derived Ingredients

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

April 8-9, 2019 CIR Expert Panel Meeting – Full Panel

Palm Tree-derived Ingredients

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.

Safety Assessment of Palm Tree-Derived Ingredients as Used in Cosmetics

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The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst.

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1620 L STREET, NW, SUITE 1200 ◊ WASHINGTON, DC 20036-4702 ◊ PH 202.331.0651 ◊ FAX 202.331.0088 ◊ CIRINFO@CIR-SAFETY.ORG

ABSTRACT: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the safety of 8 palm tree (*Euterpe edulis* and *Euterpe oleracea*)-derived ingredients in cosmetic products; these ingredients are reported to function mostly as skin conditioning agents in cosmetic products. The Panel reviewed relevant data relating to the safety of these ingredients in cosmetic formulations and concluded that …[to be determined].

INTRODUCTION

The safety of the following 8 palm tree-derived ingredients, as used in cosmetics, is reviewed in this Cosmetic Ingredient Review (CIR) 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

The ingredient group that is being reviewed in this safety assessment (*Euterpe oleracea*- and *Euterpe edulis*-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.[1-13] 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 Table1).[14] Euterpe Oleracea Pulp Powder and Euterpe Oleracea Seed Powder also are reported to function as abrasives and exfoliants in cosmetics.

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 CIR evaluates, is available on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Botanicals, such as *Euterpe edulis*- or *Euterpe oleracea*-derived ingredients, may contain hundreds of constituents, some of which may have the potential to cause toxic effects. In this assessment, CIR is reviewing the potential toxicity of each of the botanical ingredients as a whole, complex mixture. CIR 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 CIR Expert Panel (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 these ingredients are safe in the present practices of use and concentration described in the safety assessment. Though the safety of Euterpe Oleracea Fruit Oil is not being reviewed in this report on palm tree-derived ingredients, human repeated insult patch test (HRIPT) data on this ingredient from the published safety assessment are included in *italicized text* within the report text for the Panel's consideration. 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 are presented in Table1.[14]

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

(açai), 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 merisem.[19] Plant part definitions are presented in Table2.[14]

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.[1] 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.[2] 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.[3] 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.[1-7] 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 presented in Table 5.[3]

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'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 colony forming unit (cfu)/g; no pathogens), yeast and mold (< 100 cfu/g), and gram negative bacteria (0 cfu/g).[13] Data provided by the same supplier indicate that pesticides present in this trade name mixture do not exceed the Environmental Protection Agency's (EPA's) limits.[26] These data on pesticide levels are presented in Table 6.

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

Açai (*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.[9] Additionally, the following trace 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 Table7.[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 8.[8-13] 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 Table7 and Table8). 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.[13]

Euterpe Oleracea Seed Powder

Composition data on *Euterpe oleracea* seed are presented in Table 9.[28] It should also be noted that when *Euterpe oleracea* seeds were extracted with a solution of 95% ethanol/1.5 N HCl (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 2019 VCRP data, Euterpe Oleracea Fruit Extract is reported to be used in 430 cosmetic products (297 leave-on products, 129 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 (moisturizing products [not spray] and 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 Table10.

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 not included on the European Union's list of substances that are restricted or list of substances that are prohibited in cosmetic products.[40] A list of allergenic constituent limitations for a Euterpe Oleracea Fruit Extract trade name mixture (98% Euterpe Oleracea Fruit Extract and 2% *Lactobacillus* ferment) and organic Euterpe Oleracea Juice (undiluted, freeze dried) do not contain, regardless of direct or cross contamination, are presented in Table 11.[22,26] This trade name mixture and the juice have been analyzed for these 26 fragrance allergens that are required to be listed on the product label in the European Union if they exceed certain concentrations.

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] 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.[42]

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).[43] 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.[44] The concentration of *Euterpe oleracea* pulp 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.[45] *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).[44] 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 12.

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. 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).[46]

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) .[47] 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).[44]

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. 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 up to 180 mg/kg, and in another Comet assay involving randomly selected cells in human blood that was drawn after a 300 ml dose.

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).[44] *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.[48] In rats dosed 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).[45] *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.[49] 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.[49]

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.[50] 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 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 GSH 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 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).[51] 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 FcεRI (high affinity IgE receptor) 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).[52] 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.[53] 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-dimethylthiazol-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.[54] 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

In addition to the in vitro and in chemico sensitization data that are summarized in this section, human skin sensitization data on Euterpe Oleracea Fruit Oil that are summarized in the CIR safety assessment on Euterpe Oleracea Fruit Oil and other plant-derived fatty acid oils[15] are included in the Sensitization section below for the Panel's consideration.

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.[55] The test substance was applied to tissue inserts and incubated for 60 minutes. Cell viability was measured by dehydrogenase conversion of MTT, present in the cell 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).[56] 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 (DMSO) 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).[57] 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

An HRIPT involving a face and neck product containing 3% Euterpe Oleracea Pulp Powder was performed using 214 subjects.[58] 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.

Euterpe Oleracea Fruit Oil

The skin sensitization potential of 0.5% Euterpe Oleracea Fruit Oil in an eye treatment was evaluated using 104 subjects. The test substance (150 µl) was applied under semi-occlusive conditions in an HRIPT. It was concluded that the test substance was neither a dermal irritant nor a sensitizer in this study.[15]

OCULAR IRRITATION STUDIES

In Vitro

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).[55] The test substance was applied to tissue inserts and incubated for 30 min. Cell 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-derived ingredients as used in cosmetics is reviewed in this CIR 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 2019 VCRP data, Euterpe Oleracea Fruit Extract is reported to be used in 430 cosmetic products (297 leave-on products, 129 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 in one *S. typhimurium* strain in the Ames test, and in the micronucleus assay. *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, but was non-genotoxic in another micronucleus assay 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.

DRAFT DISCUSSION

The following discussion items are pending Panel approval. Additional discussion items may be added.

The ingredient group that is being reviewed in this safety assessment (*Euterpe oleracea*- and *Euterpe edulis*-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.

The Panel noted the availability of specifications relating to the potential presence of heavy metal, microbial, and pesticide impurities in some of these palm tree-derived ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit these impurities.

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.

Finally, 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

CONCLUSION

To be determined.

TABLES

Table 1. Definitions and functions of the ingredients in this safety assessment.[14; *CIR Staff*]

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.[14]

Plant Part	Definition
Bran	The outer hard layers of the grain formed by the fused fruit and seed wall in grains and cereals.
Endosperm	Energy storage tissue inside seeds.
Germ	The embryo in a seed; the part of a seed that can develop into new plant.
Grain	Dry one-seeded fruits produced by grasses, e.g. cereals such as wheat.
Kernel	The grain of a grass.
Leaf	Flattened photosynthetic organs, attached to stems.
Pericarp	Fruit wall.
Seed	A propagating sexual structure resulting from the fertilization of an ovule, formed by embryo, endosperm, or seed coat.
Seed coat	Seed wall; testa; protective outer layer of seed, formed from the outer layers of the ovule
Sprout	Seedling; germinating seed; any new growth of a plant from a stem such as a new branch or a bud
Stem	A slender or elongated structure that supports a plant or a plant part or plant organ.
Straw	The stem of a grass or related families

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

Components	Principles Compound (Probability (%))*
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
phenethylalcohol	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*.[1-7]

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*.[1-7]

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 compounds 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		

Table 4. Content of Ingredients/Fruit Parts derived from *Euterpe edulis*.[1-7]

Components	Euterpe Edulis Fruit Extract	*Euterpe edulis* fruit	*Euterpe edulis* pulp extract	*Euterpe edulis* pulp
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.[3]

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. List of Pesticides In Euterpe Oleracea Fruit Extract* That Do Not Exceed the EPA's Limits.[26]

Pesticide	EPA's Limit (mg/kg)**
Alachlor	< 0.02
Aldrin and Dieldrin	< 0.05
Azinphos-methyl	< 1.00
Bromopylate	< 3.00
Chlordane (cis and trans)	< 0.05
Chlorfenvinphos	< 0.50
Chlorpyrifos	< 0.20
Chlorpyrifos-methyl	< 0.10
Cypermethrin	< 1.00
DDT	< 1.00
Deltamethrin	< 0.50
Diazinon	< 0.50
Dichlorvos	< 1.00
Dithiocarbamates	< 2.00
Endosulfan	< 3.00
Endrin	< 0.05
Enthion	< 2.00
Fenitrothion	< 0.50
Fenvalerate	< 1.50
Fonofos	< 0.05
Heptachlor	< 0.05
Hexachlorobenzene	< 0.10
Hexachlorocyclohexane	< 0.30
Lindane	< 0.60
Malathion	< 1.00
Methidathion	< 0.20
Parathion	< 0.50
Parathion-methyl	< 0.20
Permethrin	< 1.00
Phosalone	< 0.10
Piperonyl butoxide	< 3.00
Pirimiphos-methyl	< 4.00
Pyrethrins	< 3.00
Quintozene (sum of 3 items)	< 1.00

*Trade name mixture containing 98% Euterpe Oleracea Fruit Extract and 2% *Lactobacillus* ferment

**Each value reported is a limit of detection.

Table 7. 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 hydrochloric acid	
Total phenolic compounds	2370 ± 177
Total anthocyanins	81.62 ± 12.89

*dwb = dry weight basis

Table 8. Content of Ingredients/Components Derived From *Euterpe oleracea*.[8-13]

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			
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			

Table 8. Content of Ingredients/Components Derived From *Euterpe oleracea*.[8-13]

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)
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	
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	

Table 8. Content of Ingredients/Components Derived From *Euterpe oleracea*.[8-13]

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)
laricіresinol	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)
tricosanoic	Amount not stated			

Table 8. Content of Ingredients/Components Derived From *Euterpe oleracea*.[8-13]

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)
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			
tridecenoic	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			

Table 8. Content of Ingredients/Components Derived From *Euterpe oleracea*.[8-13]

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)
methionine	Amount not stated			
phenylalanine	Amount not stated			
proline	Amount not stated			
serine	Amount not stated			
threonine	Amount not stated			
tryptophan	Amount not stated			
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			

Table 8. Content of Ingredients/Components Derived From *Euterpe oleracea*.[8-13]

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)
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 9. 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 10. Frequency (2019) 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*/Conc. Range**	**430**	**0.0000001-0.38**	**1**	**0.04**	**3**	**0.001**
Duration of Use						
Leave-On	*297*	*0.0000083-0.04*	*1*	*0.01-0.04*	*2*	*0.001*
Rinse off	*129*	*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	3	NR	NR	NR	NR	NR
Incidental Ingestion	7	0.0000083-0.025	1	NR	NR	NR
Incidental Inhalation - Sprays	259[a]	0.001; 0.00003- 0.001[a]	NR	NR	1	0.001
Incidental Inhalation - Powders	NR	0.0001-0.01[b]	NR	0.01	NR	0.001[b]
Dermal Contact	373	0.0000001-0.83	NR	0.01-0.04	3	0.001
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	48	0.00000075-0.001	NR	NR	NR	0.001
Hair-Coloring	1	0.38	NR	NR	NR	NR
Nail	NR	0.04	NR	NR	NR	NR
Mucous Membrane	66	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

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

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

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

[c]Not specified 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

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

Table 11. Allergens Limited in Euterpe Oleracea Fruit Extract* or organic Euterpe Oleracea Juice *Freeze Dried).[22,26]

Allergen	CAS Number	European Union Limit (ppm)**
Alpha-IsoMethyl Ionone	127-51-5	< 0.02
Amyl Cinnamal	122-40-7	< 0.10
Anise Alcohol	105-13-5	< 0.00
Benzyl Alcohol	100-61-69	< 0.01
Benzyl Benzoate	120-51-4	< 0.09
Benzyl Cinnamate	103-41-3	< 0.30
Benzyl Salicylate	118-58-1	< 0.06
Butylphenyl Methylpropional	80-54-6	< 0.50
Cinnamal	104-55-2	< 0.01
Cinnamyl Alcohol	104-54-1	< 0.30
Citral	5392-40-5	<1.00
Citronellol	106-22-9	< 1.00
Coumarin	91-64-5	< 0.00
Eugenol	97-53-0	< 0.70
Farnesol	4602-84-0	< 0.04
Geraniol	106-24-1	< 0.08
Hexyl Cinnamal	101-86-0	< 0.40
Hydroxycitronellal	107-75-5	< 1.00
Hydroxymethylpentyl 3-Cyclohexene Carboxaldehyde	31906-04-4	< 0.00
Isoeugenol	97-54-1	< 0.06
Limonene	5989-27-5	< 0.05
Linalool	78-70-6	< 0.00
Methyl 2-Octynoate	111-12-6	< 0.20
Evernia prunastri	90028-68-5	< 0.00
Evernia furfuracea	90028-67-4	< 0.00
Amylcinnamyl Alcohol	101-85-9	< 1.00

*Trade name mixture containing 98% Euterpe Oleracea Fruit Extract and 2% *Lactobacillus* ferment
**Each value reported is a limit of detection.

Table 12. 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.[47]
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.[46]
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.[46]

Table 12. 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 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.[44]
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.[44]
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.[44]
		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]
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. 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.	Single dose of 300 ml	SCGE score did not indicate significant DNA lesions, such as single or double breakages. No statistically significant positive genotoxicity response identified.[24]

Table 12. 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 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.[44]
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.[48]
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.[48]
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 with DNA damage (also observed with vehicle control), damage was considered minor.[45]
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 ($P < 0.05$).[45]

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2019 FDA VCRP Data

Euterpe Edulis Fruit Extract - No Data

Euterpe Edulis Juice Extract - No Data

Euterpe Oleracea Fruit Extract

02A - Bath Oils, Tablets, and Salts	1
02B - Bubble Baths	2
02D - Other Bath Preparations	1
03D - Eye Lotion	1
03F - Mascara	1
03G - Other Eye Makeup Preparations	1
04E - Other Fragrance Preparation	10
05A - Hair Conditioner	18
05E - Rinses (non-coloring)	1
05F - Shampoos (non-coloring)	21
05G - Tonics, Dressings, and Other Hair Grooming Aids	5
05I - Other Hair Preparations	3
06H - Other Hair Coloring Preparation	1
07C - Foundations	2
07E - Lipstick	7
07F - Makeup Bases	1
07I - Other Makeup Preparations	4
10A - Bath Soaps and Detergents	44
10E - Other Personal Cleanliness Products	11
12A - Cleansing	27
12C - Face and Neck (exc shave)	42
12D - Body and Hand (exc shave)	19
12F - Moisturizing	176
12G - Night	2
12H - Paste Masks (mud packs)	6
12I - Skin Fresheners	2
12J - Other Skin Care Preps	18
13A - Suntan Gels, Creams, and Liquids	1
13B - Indoor Tanning Preparations	1
13C - Other Suntan Preparations	1
Total	**430**

Euterpe Oleracea Juice

07E - Lipstick	1
Total	**1**

Euterpe Oleracea Palm Heart Extract

04E - Other Fragrance Preparation	1
10A - Bath Soaps and Detergents	1
12D - Body and Hand (exc shave)	1
Total	**3**

Euterpe Oleracea Pulp Powder

05A - Hair Conditioner	1
05F - Shampoos (non-coloring)	1
07I - Other Makeup Preparations	1
12C - Face and Neck (exc shave)	1
12D - Body and Hand (exc shave)	4
12F - Moisturizing	1
12J - 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**

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: March 27, 2019

SUBJECT: Draft Report: Safety Assessment of Palm Tree-Derived Ingredients as Used in Cosmetics (draft prepared for the April 8-9, 2019 CIR Expert Panel meeting)

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

Key Issues

The Introduction suggests that these ingredients have constituents in common. Although some constituent information is presented in tables, it would be helpful to include a discussion as to which constituents these species have in common. If the species do not have constituents in common, they should not be reviewed together. As safety data identified in the report are all on açai-derived ingredients, perhaps the *Euterpe edulis*-derived ingredients should be deleted from the report.

Although the memo indicates that a cellular viability assay on Euterpe Oleracea Fruit Extract is not relevant, this study is presented in the Summary of the report. Because the study was completed in human dermal fibroblasts, it should be included in the CIR report and presented in the Cytotoxicity section.

Additional Considerations

Composition, Euterpe Oleracea Fruit Extract and Juice; Table 6 - Table 6, indicating the 26 fragrance allergens that are required to be on the label if they are above a certain concentration is not necessary. The text should simply state that they are not present.

Impurities - Stating that "ash has been detected" suggests that there is lack of understanding of what ash means. Ash is what is left after the ingredient is burned.

Non-Cosmetic - Please look at the FEMA GRAS designation again (reference 39) with Acai berry extract they also state: "Assai palm; Fats and glyceridic oil, *Euterpe oleracea*". FEMA also uses the CAS number 861902-11-6. In the Dictionary, this CAS number is only associated with Euterpe Oleracea Fruit Oil (which is not being reviewed in this report). Although there is a trade name mixture name acai berry extract (listed as Euterpe

Oleracea Fruit Extract, propylene glycol and water), it should not be associated with the material considered GRAS by FEMA.

Genotoxicity, In Vitro - In which strain was *Euterpe edulis* fruit pulp positive?

Summary - In the Summary it should be made clear that the Euterpe Oleracea Fruit Extract and Juice were analyzed for the 26 fragrance allergens required to be on the label in the EU if they exceed a certain concentration. (It currently states that they have not been found to contain "many of the allergenic flavors or fragrances that have been identified in the published literature.")

In addition to the industry submitted cell viability study, the Summary also includes a description of a study in mouse mast cells treated with *Euterpe oleracea* pulp that is not described earlier in the report. This study should be included in the report as mast cell activation is responsible for immediate-type sensitization reactions.

Table 1 - As no structures are shown in Table 1, "idealized structures" needs to be deleted from the title of the table.

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Personal Care Products Council
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Memorandum

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

FROM: CIR Science and Support Committee of the Personal Care Products Council

DATE: May 16, 2019

SUBJECT: CIR report on Palm (açai and juçara)-Derived Ingredients

The CIR Science and Support Committee (CIR SSC) appreciates the opportunity to comment on the CIR report on palm (açai and juçara)-derived ingredients.

To avoid confusion with the species of palm (*Elaeis guineensis*) used to derive palm oil, we request that the title of the report be changed to "Safety Assessment of Palm (açai and juçara)-Derived Ingredients as Used in Cosmetics".

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