Safety Assessment of *Carica papaya* (Papaya) - Derived Ingredients as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	February 16, 2021
Panel Meeting Date:	March 11 - 12, 2021

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. Previous Panel member involved in this assessment: James G. Marks, Jr., M.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Alice Akinsulie, former Scientific Analyst/Writer, and Priya Cherian, Scientific Analyst/Writer, CIR.

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Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

From: Priya Cherian, Scientific Analyst/Writer, CIR

Date: February 16, 2021

Subject: Safety Assessment of *Carica papaya* (Papaya)-Derived Ingredients as Used in Cosmetics

Enclosed is the Draft Final Report of the Safety Assessment of *Carica papaya* (Papaya)-Derived Ingredients as Used in Cosmetics (*papaya032021rep*). The 5 ingredients included in the report are Carica Papaya (Papaya) Fruit, Carica Papaya (Papaya) Fruit Extract, Carica Papaya (Papaya) Fruit Juice, Carica Papaya (Papaya) Fruit Water, and Carica Papaya (Papaya) Leaf Extract.

At the December 2020 meeting, the Expert Panel for Cosmetic Ingredient Safety (Panel) issued a Final Report with the conclusion that the available data are insufficient to make a determination of safety for the 5 *Carica papaya* (papaya)-derived ingredients. In order to come to a conclusion of safety for Carica Papaya (Papaya) Fruit, Carica Papaya (Papaya) Fruit Extract, Carica Papaya (Papaya) Fruit Juice, and Carica Papaya (Papaya) Fruit Water, the Panel requested phototoxicity/photosensitization data. In lieu of these data, the Panel would also accept a clarification on the specific ingredients of the SPF 50 lotion in the existing phototoxicity/photosensitization assays. Genotoxicity data, irritation and sensitization at maximum use concentration, and phototoxicity/photosensitization data are needed to come to a conclusion of safety for Carica Papaya (Papaya) Leaf Extract.

Since the December 2020 meeting, data regarding a UV profile of a mixture containing 0.006 Carica Papaya (Papaya) Fruit Extract was provided from Council (*papaya032021data*). There were no spectral peaks in the UVA or UVB for this test substance, and there was not enough information to determine the absorbance wavelength of a peak in the UVC.

Comments on the Tentative Report were received and addressed (*papaya032021pcpc*). Also included in this package for your review are the report history (*papaya032021hist*), flow chart (*papaya032021flow*), minutes (*papaya032021min*), literature search strategy (*papaya032021strat*), data profile (*papaya032021prof*). In addition, 2021 FDA VCRP have been received and incorporated into the report (*papaya032021FDA*). Compared to 2020 FDA VCRP data, Carica Papaya (Papaya) Fruit Extract, the ingredient with the highest number of uses in this ingredient group, has decreased in the total number of uses (from 349 to 172 formulations).

The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Report.

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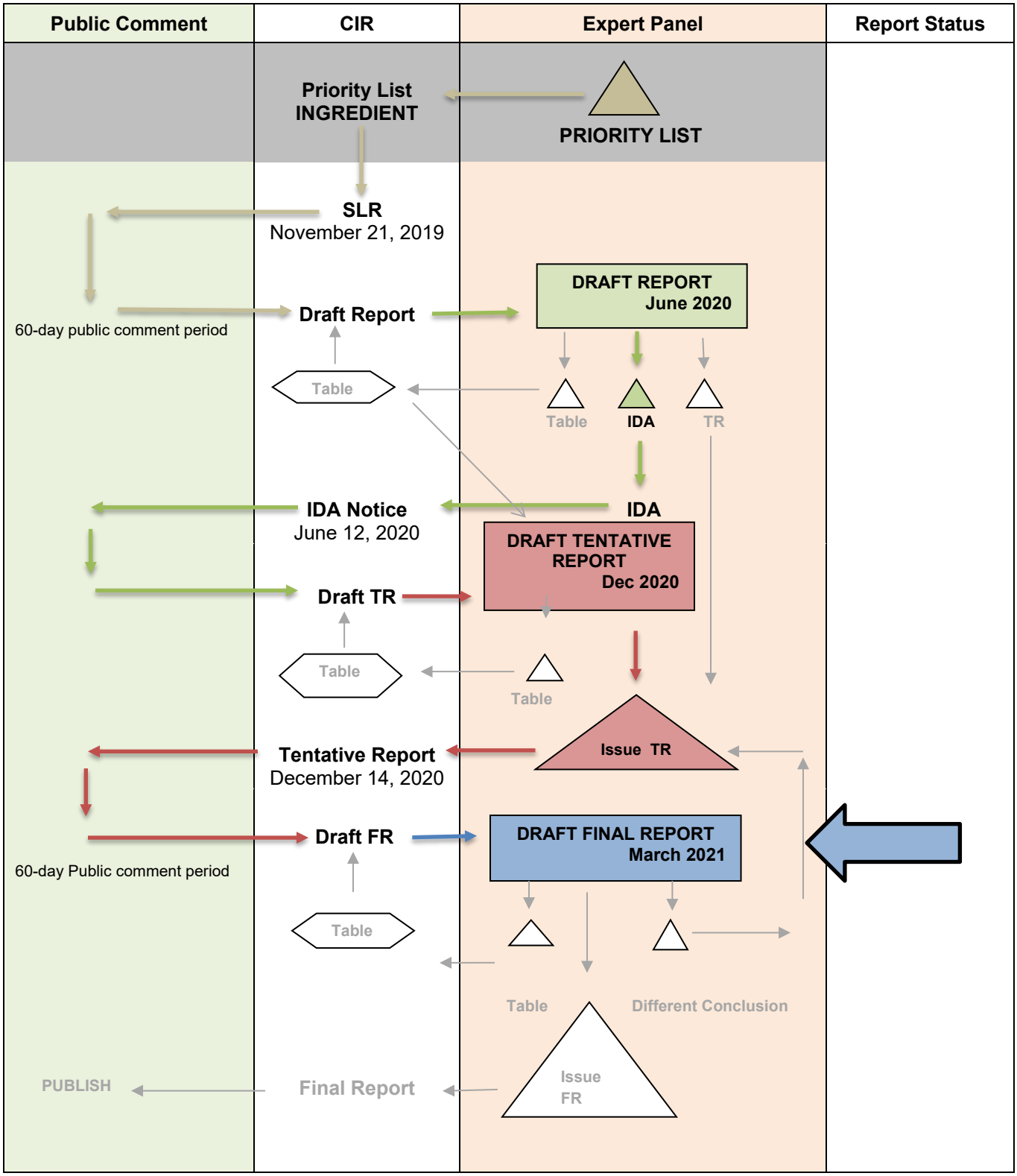
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY *Carica papaya* (Papaya)-derived ingredients

MEETING March 2021



Papaya-Derived Ingredients History

November 2019
-SLR posted

December 2019
-comments received from Council on SLR
-manufacturing and impurities data on Carica Papaya (Papaya) Fruit Extract received from Council
-summary information on Carica Papaya (Papaya) Fruit Extract

January 2020
-2020 FDA VCRP data received

June 2020
-Expert Panel reviews Draft Report
-Expert Panel issues and Insufficient Data Announcement
    -requests irritation and sensitization data on Carica Papaya (Papaya) Fruit Extract at current maximum use concentration of 0.25%
    -requests impurities, genotoxicity, and irritation/sensitization data on Carica Papaya (Papaya) Leaf Extract
-Data received from Council:
    -An HRIPT on a lotion containing 0.04% Carica Papaya (Papaya) Fruit Extract
    -An HRIPT on a lipstick containing 0.02% Carica Papaya (Papaya) Fruit Extract

July 2020
-Data received from Council:
    -A 5-d cumulative irritation patch test on a bar soap containing 0.003% Carica Papaya (Papaya) Fruit Extract
    -A 5-d cumulative irritation patch test on a talcum powder containing 0.003% Carica Papaya (Papaya) Fruit Extract
    -An HRIPT on a product containing 0.02% Carica Papaya (Papaya) Fruit Extract
    -Corrected concentration of use data (hair conditioners are now reported to be used at up to 0.0006% (no previous concentration of use reported) and depilatories are used at up to 0.01% (previously reported to be used at up to 0.05%)

September 2020
-Data received from Council:
    -An HRIPT on an SPF 50 lotion containing 0.0075% Carica Papaya (Papaya) Fruit Extract
    -A photosensitization assay on an SPF 50 lotion containing 0.0075% Carica Papaya (Papaya) Fruit Extract
    -A phototoxicity assay on an SPF 50 lotion containing 0.0075% Carica Papaya (Papaya) Fruit Extract
    -An HRIPT on a lotion/body butter containing 0.0586% Carica Papaya (Papaya) Fruit Extract

December 2020
-Expert Panel reviews Draft Tentative Report
-Expert Panel issues an insufficient data conclusion for the 5 *Carica papaya*-derived ingredients

-data needs to come to conclusion of safety for fruit ingredients
    -photoxicity/photosensitization data or clarification on existing photosensitization/phototoxicity assay in report
-data needs to come to conclusion of safety for leaf ingredients:
    -genotoxicity data
    -irritation and sensitization at max use concentration
    -phototoxicity/photosensitization data

January 2021
-Comments received from Council on Tentative Report
-Updated 2021 FDA VCRP data received

March 2021
-Expert Panel reviews Draft Final Report

Papaya-derived ingredients Data Profile – March 2021 – Writer, Priya Cherian																															
				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P	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
Carica Papaya (Papaya) Fruit	X										X			X																
Carica Papaya (Papaya) Fruit Extract	X	X	X					X			X			X							X			X	X					
Carica Papaya (Papaya) Fruit Juice	X																													
Carica Papaya (Papaya) Fruit Water		X																												
Carica Papaya (Papaya) Leaf Extract	X	X						X			X			X																

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

[Carica Papaya (Papaya)- Derived Ingredient]

Ingredient	CAS #	InfoB	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Carica Papaya (Papaya) Fruit Extract	84012-30-6 (Generic)	✓	✓	✓	NR	✓	NR	NR	✓	NR	NR	NR	NR	NR	NR	NR	NR	NR	✓
Carica Papaya (Papaya) Fruit	NR	✓	✓	NR	NR	✓	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	✓
Carica Papaya (Papaya) Fruit Juice	NR	✓	✓	NR	NR	✓	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	✓
Carica Papaya (Papaya) Fruit Water	NR	✓	NR	NR	NR	✓	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Carica Papaya (Papaya) Leaf Extract	NR	✓	✓	NR	NR	✓	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	✓

Botanical and/or Fragrance Websites (if applicable)

Ingredient	CAS #	Dr. Duke's	Taxonomy	GRIN	Sigma-Aldrich	IFRA	RIFM
Carica Papaya (Papaya)	84012-30-6 (Generic)	NR	✓	✓	NR	NR	NR

Searched on May 31, 2019

Search terms

Carica Papaya (Papaya) Fruit
Carica Papaya (Papaya) Fruit Extract
Carica Papaya (Papaya) Fruit Juice
Carica Papaya (Papaya) Fruit Water
Carica Papaya (Papaya) Leaf Extract
Carica Papaya; compositional breakdown; Absorption, Acute, Allergy, Cancer, Carcinogen, Developmental toxicity, Genotoxicity, Irritation, Metabolism, Mutagenic, Penetration, Repeated dose, Reproduction, Reproductive toxicity, Sensitization, Skin, Subchronic, Teratogenic, Toxic, Toxicity, Toxicokinetic, Toxicology.
Pawpaw extracts toxicity
Carica Papaya (Papaya); GRAS
Papaya Extract

Updated key term search
Carica Papaya (Papaya): Cytotoxicity, dermal effects, (irritation, sensitization) ,dermal toxicity, effects on the skin, endocrine effects, endocrine toxicity, epidemiological study, genotoxicity, health effects, liver toxicity, immunotoxicity, in vitro test, irritation, mucous membrane, multicenter study, neurotoxicity, ocular effects, "ocular exposure, oral effects, oral toxicity, photosensitivity, phototoxicity, repeated dose, reproductive toxicity, retrospective study, sensitization, short-term toxicity, short term toxicity, skin penetration, subacute effects, subacute toxicity, subchronic effects, subchronic toxicity, in vitro toxicity, toxicity

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Toxnet (https://toxnet.nlm.nih.gov/); (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)

appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org
- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- EAFUS: http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- OTC ingredient list: https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

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
- American Herbal Products Association Botanical Safety Handbook (database) - http://www.ahpa.org/Resources/BotanicalSafetyHandbook.aspx
- European Medicines Agency Herbal Medicines - http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/herbal_search.jsp
- National Agricultural Library NAL Catalog (AGRICOLA) https://agricola.nal.usda.gov/
- The Seasoning and Spice Association List of Culinary Herbs and Spices
- http://www.seasoningandspice.org.uk/ssa/background_culinary-herbs-spices.aspx

Fragrance Websites, if applicable

- IFRA (International Fragrance Association) – http://www.ifraorg.org/
- Research Institute for Fragrance Materials (RIFM)

JUNE 2020 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – June 8, 2020

DR. BELSITO: Okay. So we're having papaya here for dessert from lunch; is that it?

DR. LIEBLER: Yep.

DR. BELSITO: Okay. This is the first time that we're looking at these, and we're looking at six ingredients to review. So let's see what we came up with. Okay. Where is it? All right.

First of all, council put in some comments here on some points, which I thought were all fine in terms of manufacturing and maximum concentrations and just a few edits. So I guess one of the things is -- the first thing is should we -- and this is page -- under composition. Should we define latex, simply because at least some people may think we're talking about latex from Hevea brasiliensis, which has caused significant amount of allergic contact urticaria death in the 1980's?

Now, papaya can cross react with latex. It's not as high -- the papaya latex is not as high as with bananas or kiwi or avocado, which are the strongest ones, and we can put that in the discussion. But I think it would be helpful just to point out that latex is a milky sap. And it doesn't really refer to latex as we think of it as a rubber product per se.

And then I guess the other thing that concerned me in the compositions was the -- it says toxins unique to the fruit are benzyl isothiocyanates. There is no level, but is anyone concerned about that? This is PDF page 11.

DR. LIEBLER: The problem with this is there's no denominator on these amount of, you know, 109 micrograms -- oh, I see. No, I'm sorry -- 109 micrograms per gram. Let's see.

DR. SNYDER: It's pretty low.

DR. LIEBLER: Yeah. Very low. I'm going to do a quick ppm calculation, but it's going to be really low.

DR. BELSITO: So discussion point or --

DR. LIEBLER: Yeah**.** It may not even really need to be that. I'd convert these to ppm, Priya. So it's micrograms per -- let's see -- 1000 milligrams, 1000/1000. So it's probably about 109 ppm BITC.

DR. BELSITO: Okay.

DR. LIEBLER: Check my math, but I think that's about right. And it's even lower when fully ripe. That's interesting. And so these here are from the ripe fruit? It says composition. I see method of manufacture. Because if it's from the ripe fruit, then it's -- these are even lower, like 10 ppm.

DR. BELSITO: It doesn't say.

DR. LIEBLER: Yeah. It doesn't, does it? I'm looking at it again. Okay. Anyway, I don't think this is sufficiently a concern that it needs to be in our discussion.

DR. BELSITO: Okay.

DR. LIEBLER: But I think if it's noted in ppm, it's easier for people to recognize that the concentrations are very low.

DR. BELSITO: Okay. And so obviously the usual boilerplate in the discussion for a botanical. And also the concentration of use for these are very low, too.

DR. SNYDER: Yeah**.** 0.02 percent for leave-on.

DR. BELSITO: Yeah.

DR. LIEBLER: So we had no mutagenicity, but for the fruit ingredients we feel that the GRAS status covers us for that?

DR. BELSITO: Yeah.

DR. LIEBLER: But the leaf isn't GRAS, right? But there's use of leaf extract in traditional medicines?

DR. BELSITO: Yeah. What do you make of the reproductive toxicity, Paul? With the sperm --

DR. SNYDER: Those are all very, very high levels, Don. Greater than 200 milligrams per kilogram or 500 milligrams per kilograms. So I wasn't concerned.

DR. BELSITO: Okay.

DR. SNYDER: There was a study that was negative at 15 percent. And the highest leave-on is 0.02 percent for us.

DR. BELSITO: Okay. And what we have in terms of studies at least, we have a few oral studies, one 42 days, another 28-day gavage study.

DR. SNYDER: (Inaudible).

DR. BELSITO: Pardon?

DR. SNYDER: There is one product study, also.

DR. BELSITO: Yeah. And then there's a two-year study. So I think that mitigates the mutagenicity, no?

DR. SNYDER: Yeah. I was -- it didn't raise any alarms to me with low concentration of use and everything's very high, so…

DR. BELSITO: One thing we don't have is we don't have any dermal sensitization or irritation.

DR. LIEBLER: Right.

DR. SNYDER: We do have evidence of allergic reaction on page 15.

DR. BELSITO: Yeah. A couple reports. And then we do have the issue where there can be cross-reactivity with latex. But, I mean, we dealt with that in the avocado report, I think. I wanted to look that up, and I forgot to do that. And then we basically have one report of delay-type hypersensitivity and some IgE mediated hypersensitivity.

And if you think about it, I mean, given the fact that this is a food, if it were a significant allergen, you'd expect some reports of cheilitis and hand dermatitis from people handling it. And there aren't really. I mean, there's one report. This would be very unusual for us to go ahead with a report and say "safe as used" when we had absolutely good skin sensitization data.

DR. SNYDER: Yeah. Well, it's the first review, so we could ask for it.

DR. LIEBLER: Yeah. And I think we're insufficient for that.

DR. BELSITO: Okay. I'm just curious how we handle papaya or papaya avocado. We mentioned that. Because we reviewed that, right? Or was it just the oil?

DR. LIEBLER: Avocado?

DR. BELSITO: Okay. Why isn't it coming up?

DR. HELDRETH: Yes, for avocado we've only looked at avocado oil and some of its esters.

DR. BELSITO: Okay.

DR. HELDRETH: And its hydrolyzed protein.

DR. BELSITO: And kiwi?

DR. HELDRETH: Let me look. I'm not seeing under that name but let me just make sure the ingredient name isn't different.

DR. BELSITO: I'm sure it is.

DR. HELDRETH: Right**.** Yeah. So in the dictionary kiwi is listed as Actinidia chinensis. I don't think we (inaudible) yet.

DR. BELSITO: And what about banana? Did we do any -- I don't remember banana being done.

DR. HELDRETH: Let me look.

DR. BELSITO: So this may be the first time that we deal with something that has a potential to cause issues in people who are already sensitized to latex.

DR. HELDRETH: On banana the (inaudible) name for that is Musa paradisiaca banana fruit and, no, we have not done that.

DR. BELSITO: Yeah. So to me, that was the biggest issue -- lack of sensitization and irritation. And then you see that hypersensitivity reactions, which the papaya is not a common food allergen. But it can cross react with Hevea brasiliensis latex. And some people who are latex allergic could have issues.

Is this used in lip products? I don't remember. Incidental ingestion at 0.02 percent -- the fruit extract. I mean, that would be pretty low. I don't know. What do you think? How do we -- we've dealt with other cosmetic ingredients that are foods and cause IgE-mediated allergy.

DR. SNYDER: The mucus membrane category has the highest, 0.25 percent.

DR. BELSITO: Yeah.

DR. LIEBLER: I think it certainly has to be handled in the discussion. Are you thinking in terms of looking for other data?

DR. BELSITO: No, I don't think we need extra data. It's clear. If you look at the list of fruits and nuts and vegetables that can cross react with Hevea brasiliensis, with the proteins, you know, papaya is one of them. But it's not high on the list. It's like banana, kiwi, and avocado are the big ones. I don't think we're going to have any issue with safety. It would need to be in the discussion, but I'm just curious as how we discuss proteins like -- cosmetic ingredients like, you know, wheat and others that can also cause immediate hypersensitivity.

We've never said label, right, but it would be on the label or warning? So I suppose just bring it into the discussion that it could be an issue for individuals who have immediate hypersensitivity to latex and put a reference in there regarding that reactivity. So I can get you a reference, Priya, on people where the latex and papaya cross reacting with bio Hevea brasiliensis. Just put it in some place.

DR. SNYDER: What about the potential to sensitize?

DR. BELSITO: I think it's low, but we've never gone ahead and approved anything that didn't have sensitization/irritation. This is the first time we're looking at it, so we can ask for that data.

DR. SNYDER: Yeah. I think we should.

DR. BELSITO: So I would say it's insufficient for sensitization/ irritation at concentration of use.

DR. SNYDER: I agree.

DR. BELSITO: Anything else?

DR. LIEBLER: I just want to raise one other point. We talked about the DART effects on the sperm earlier. This is on PDF 13. Priya added a sentence about this because this is about an extract of papaya seeds. And there are no seed components apparently in any of the ingredients. And all the food derived stuff you have the seeds filtered out, apparently. And so I don't disagree with including it.

I think the sentence that Priya has there -- "although papaya seed extract is not among the ingredients reviewed --" I think that's fine. I just want to make sure we have agreed that that's okay to include in the report. I mean, you can make the argument maybe there's a little seed in some of these due to just contamination in processing, but, strictly speaking, it's not one of the ingredients we're talking about. Anybody got a problem with the seed data being in the report?

DR. BELSITO: Well, if it adds confusion, and then we have to explain that we're not concerned about the effects because of the dose and it's not an ingredient, then I probably wouldn't include it.

DR. LIEBLER: Okay.

DR. BELSITO: Is there any DART at all?

DR. LIEBLER: There is a fruit blend, the paragraph right above it, on early-stage pregnancy in Sprague-Dawleys. I don't know. And then we have -- let's see. That's it. So that's the one study we have.

DR. BELSITO: But that also had sperm, motility, viability, serum testosterone concentrations.

DR. SNYDER: Table 7 has all of the developmental repo data. It's easy to look at in Table 7.

DR. LIEBLER: So there's plenty.

DR. SNYDER: Oh, yeah.

MS. CHERIAN: I had it in there because fruit is not the ingredient -- just fruit. And so I didn't know if seeds were in there or not. I don't have any manufacturing data saying that they prevent the seeds. So, that was why, but…

DR. BELSITO: That's true. If they just chop up the whole fruit, there could be seeds in there.

DR. LIEBLER: Yeah. Okay. I think maybe then for that reason we would leave it in.

DR. BELSITO: Okay. And then just talk about it in the discussion that the doses were much higher and irrelevant given the use of this -- what is it -- 0.2 percent?

DR. SNYDER: 0.02 percent.

DR. BELSITO: 0.02, right. Insufficient for sensitization/irritation at concentration of use. That's all we need.

DR. LIEBLER: Yup. Okay.

DR. BELSITO: For any particular one? Or --

DR. SNYDER: Fruit extract.

DR. BELSITO: Pardon?

DR. SNYDER: Fruit extract. That's the one that's used the most.

DR. BELSITO: For the extract.

MS. CHERIAN: So just the fruit extract?

DR. BELSITO: Yeah.

MS. CHERIAN: Do you want leaf extract as well?

DR. BELSITO: It looks like the leaf extract is very similar to the fruit extract. Looking at page 11 in the PDF.

DR. LIEBLER: Just in terms of the (inaudible) identified, (Inaudible) are unclear. But it doesn't have anything surprising or necessarily a concern relative to the fruit extract.

DR. BELSITO: I'm fine with just sensitization and irritation with the food extract. Dan, Paul, Curt?

DR. KLAASEN: Yes.

DR. SNYDER: That's fine.

DR. BELSITO: Any other comments on this?

DR. LIEBLER: No.

DR. BELSITO: Okay. So then I guess we go from papaya to palm.

DR. HELDRETH: That's right.

Marks Team – June 8, 2020

DR. MARKS: And I moved my speaker away, so I think we're having less reverberations. I'm not sure what was causing it. So I'm not sure who was busier on the single day. This is another memo from Priya on February 21st of this year.

It's the draft report on five papaya-derived ingredients. It's the first time we've reviewed these ingredients. And, of course, one of the questions whenever you have these botanicals are whether they're GRAS or not.

So a couple of my notes -- one of them -- there's been issues with IgE-mediated hypersensitivity via the pollen in inhalation and fruit consumption. Is that relevant to cosmetic use? We get the heavy metals in pesticides resource document. We have Alex's comments, but I didn't think they would probably change the conclusion.

I would thought we would probably end up with an insufficient data announcement because I wanted to see irritation and sensitization data for the fruit extract, even though (inaudible) at very high concentration, and also on the leaf extract where we have only a couple uses but there's no reported concentration of use. So Lisa, Ron, Tom, first thing I always -- and, Lisa, you're part of this grouping/clustering, so I always ask when we get new ingredients -- and now I'll go right to you first -- did you feel the ingredients were okay in this group of five ingredients? And then I'll have Tom and Ron chip in on that and then any comments, any needs. So are the ingredients okay?

DR. PETERSON: Yeah. I thought to include the five together made sense. It struck me that the leaf extract's very different from the fruit products. I thought there was insufficient information -- needing the impurities on the leaf extracts.

DR. MARKS: So impurities on the leaf extract. Okay.

DR. PETERSON: And I agree with your insufficiency with the dermal sensitivity.

DR. MARKS: Tom?

DR. SLAGA: Genotox.

DR. MARKS: Ron, other needs?

DR. BERGFELD: Did he say genotox?

DR. MARKS: No, I didn't say that. I leave that up to -- that's why I left that up to Ron.

DR. BERGFELD: Ron and Tom?

DR. MARKS: I mean Tom. Ron and Tom and, of course, Lisa is a cancer biologist.

DR. SLAGA: I agree, but we need the dermal irritation/sensitization. But we also need genotox.

DR. MARKS: And what did you say about the genotox, Tom? I can't hear your speaker.

DR. PETERSON: We need it.

DR. MARKS: We need it. Okay.

DR. SHANK: On which ones?

MS. FIUME: Is the genotox for specific ingredients or for any in the group so that Priya could add it to her IDA?

DR. SLAGA: You just need bacterial and mammalian.

DR. MARKS: I'm sorry, Tom. I didn't hear that. We didn't get that on here. I'll kind of jump in. I included all the fruit. If I got everything on the fruit extract, I would apply to read across to the fruit itself, to the fruit juice, and the fruit water because I think the composition in the extract would be representative of everything in the fruit -- those four fruit ingredients. And then the leaf extract, of course, the leaf (inaudible) and so that's much different. So if we got the genotox, say, in the fruit extract, I think that could be read across there. Do we need genotox in the leaf extract, too, Ron or Tom?

DR. PETERSON: It seemed like the leaf extract was the most -- was the more active of the two in part, at least with the data that's in the report. So I would vote for the leaf extract as well.

DR. MARKS: Tom?

DR. SLAGA: Yes?

DR. MARKS: Okay. And you're okay as far as the fruit extract. We don't need genotox on that?

DR. SHANK: It's a food.

DR. SLAGA: Not, on the extract of it because (inaudible).

DR. PETERSON: I'm not worried about it.

DR. MARKS: Okay. Is it GRAS? I assume it is.

DR. SHANK: No, it's a food.

DR. MARKS: What?

DR. SHANK: GRAS applies to additives. The fruit extract is a food.

DR. MARKS: Oh, okay.

DR. SHANK: So I don't think you need genotox on that.

DR. MARKS: So just the genotox on the leaf extract since we don't use that as food presumably.

DR. SHANK: Right.

DR. MARKS: Okay.

DR. PETERSON: Yes.

DR. MARKS: Any other needs?

DR. SHANK: Do you want sensitization data on anything?

DR. MARKS: Yeah. I mentioned that. I'm sorry, Ron. I probably wasn't clear. Yeah. I wanted irritation and sensitization data for the fruit extract. That has the most uses, 349, and it's leave-on concentration max is 0.02 percent, so irritation and sensitization for the fruit extract at use concentration and add also for the leaf extract. The problem there is it's only got two uses, so I'm not sure we'll get the data. And then we don't know what the concentration is. Is that right, Priya? I didn't see the concentration mentioned.

MS. CHERIAN: Let me double check.

DR. SHANK: It isn't mentioned.

MS. CHERIAN: No, it's not mentioned.

DR. MARKS: Yeah. Yeah. So but I'd ask for it -- ask for irritation and sensitization on the leaf extract because I don't feel we can read across from the leaf to the fruit.

DR. PETERSON: No, I don't --

DR. SHANK: So what concentration -- for the sensitization, what concentration should be done?

DR. MARKS: 0.02 percent in leaf extract.

DR. SHANK: Yeah. That 0.02 percent is for fruit extract. We don't know what the concentration of leaf extract is.

DR. MARKS: That's correct. And I would be surprised, ultimately, we're going to have an insufficient conclusion for the leaf because we'll see whether we get the impurities and the genotox on the leaf and the sensitization on the leaf. But that's what we need. Any other comments, needs?

Otherwise tomorrow, I'm going to move that we issue an insufficient data announcement, and the needs were what I mentioned: irritation/sensitization for the fruit extract; and the leaf extract, impurities; and genotox on the leaf extract. Sound good, Tom, Ron, Lisa?

DR. SHANK: Yes.

DR. MARKS: Lisa?

DR. PETERSON: Yep.

DR. MARKS: Good. Okay. Let's see. Next is Caprylhydroxamic Acid.

Full Panel – June 9, 2020

DR. MARKS: Okay, this is the first review of five ingredients in the papaya-derived foods. And, when we looked at these five ingredients, we felt that we needed irritation and sensitization data for the Fruit Extract. It has 349 uses at 0.02 percent maximum leave-on, so we'd like to confirm that that's safe from an irritation and sensitization. And then we felt we needed the Leaf Extract, it only have two uses, no concentration. We also wanted impurities and genotox on the Leaf Extract. So, for those needs we move that an insufficient data announcement be made.

There is an issue of IgE-mediated hypersensitivity, via the pollen inhalation and fruit consumption with papaya. We discussed whether this was relevant to the cosmetic use and whether or not it is exposure with cosmetic use, and no reports whether this would be an issue; that could be handled in the discussion. But, again, the motion is insufficient data announcement.

DR. BERGFELD: Is there a second or a comment?

DR. BELSITO: I mean, we did not have the insufficiencies as much on the Leaf Extract; it was very, very low. But, we thought it was insufficient for sensitization and irritation on the Fruit Extract. So, I mean, I'm fine with adding other insufficiencies.

DR. BERGFELD: Okay.

DR. BELSITO: Dan, do you agree?

DR. LIEBLER: Yeah, I agree. No objection to that.

DR. MARKS: And, Don, impurities, these will get listed and obviously this is the first bite on the papaya, no pun intended. Impurities and genotox on the Leaf Extract, we wanted to see also.

DR. BELSITO: That's fine, we're going insufficient so if people want to look at that, the more data we get the better, right?

DR. MARKS: Yep.

DR. SHANK: Right.

DR. BERGFELD: Any other comment?

DR. MARKS: Yeah, Don?

DR. SHANK: Was Don second?

DR. BELSITO: Yes, it was a second.

DR. BERGFELD: I gathered it was a second. Any other comment the team has?

DR. MARKS: Yeah, Don, how did your team handle the IgE issue?

DR. BELSITO: Actually, I have to get the information. So, I mean, a couple of things; one, I think, in the report we really need to define that latex is not necessarily latex rubber. It's just a milky sap. And, papaya is one of the fruits that do cross react with Hevea brasiliensis, not quite as strongly as banana and avocado and kiwi, but it's there, so. But, we agreed that it could be handled in the discussion, just as with a lot of the other botanicals we're dealing with where people have IgE-mediated food allergy to them.

DR. BERGFELD: Okay?

DR. MARKS: Good, thanks, Don. I just wanted to be sure we were on the same page.

DR. BERGFELD: I think that the handling of IgE is rather new for us and that we need to keep putting that into the discussion, that's my opinion, in all the various ingredients that we handle, this reactant.

DR. BELSITO: Then, as we move into the botanicals, it might not be a bad idea to construct some type of, you know, boilerplate issue when you have a substance that can cause IgE-mediated allergy either by inhalation or by consumption or potentially both.

DR. BERGFELD: Okay. I think that, Bart, can we assign you and Monice to figuring that out?

DR. HELDRETH: Yes, absolutely.

DR. BERGFELD: At least as a draft?

DR. HELDRETH: Yes, and our in-house toxicologist, Jinqiu Zhu, certainly could be involved in that. He's well versed in those subjects.

DR. BERGFELD: Okay. Any other discussion before I call the question? All those in favor -- pardon me?

DR. HELDRETH: I'm sorry. I just wanted to make sure, for Priya's sake, do we have a full listing of the data needs for the IDA? Could you possibly repeat that, the full set of data needs?

DR. BERGFELD: Jim?

DR. MARKS: Yes, sure. So, our team and Don's concurred we have a few more data needs at this point, basically, irritation and sensitization for the Fruit Extract. We also want to see it for the Leaf Extract, if available, and then impurities and genotox on the Leaf Extract.

DR. BERGFELD: Anything to add, Don?

DR. BELSITO: No.

DR. BERGFELD: Okay. Bart, we clear now?

DR. HELDRETH: Thank you.

DR. BERGFELD: Okay. Any other discussion or questions, comment? All right, call the question, all those in favor please indicate by raising your hand. Thank you. Opposed, be verbal. Thank you. Unanimous, then, as an IDA will go out. Now, Dr. Belsito, you have the next big discussion, MI, which is haunting us.

DECEMBER 2020 PANEL MEETING – SECOND REVIEW/DRAFT TENTATIVE REPORT

Belsito Team – December 7, 2020

DR. BELSITO: Okay. So we're moving to papaya. Save this. Okay. So at the June meeting we issued an IDA and requested irritation and sensitization data for the fruit extract at the maximum concentration of use that was 0.25 percent in a rinse off. And we requested impurities, genotox, irritation and sensitization on the leaf extract. We've gotten unpublished data, including a whole bunch of HRIPTs, some photosensitization, phototoxicity. We got a corrected concentration of use data for the fruit extract. So what do we think?

DR. SNYDER: Safe as used for the fruit extract, insufficient for the leaf extract.

DR. BELSITO: Well, insufficient for what reason, Paul?

DR. SNYDER: Well, we have two uses, no concentration of use. We have no sensitization data, no genotox data. We do have a little bit of impurities.

DR. BELSITO: Okay. So for the leaf, I said have essentially negative 90-day oral, negative 90 -- no sensitization and irritation, no reported use. Yeah. I had the same thing. All three components okay except the leaf. And we just don't have much data on that, do we?

DR. SNYDER: Right.

DR. BELSITO: We have a 90-day oral and we have a negative male fertility, but no sensitization, irritation, no reported uses.

DR. SNYDER: We have two reported uses, no concentration of use.

DR. BELSITO: Right.

DR. SNYDER: Yeah.

DR. BELSITO: Curt, Dan?

DR. LIEBLER: I'm right with you on that. I agree.

DR. BELSITO: Okay. So everything is safe as used except for the leaf. And what we need is sensitization and irritation at concentration of use?

DR. LIEBLER: Yep.

MS. FIUME: Have we requested those data in the past?

DR. SNYDER: Yes. On the IDA we said the irritation, sensitization on the fruit extract and impurities, the genotox, and irritation, sensitization of leaf extract I thought.

DR. BELSITO: Yes.

MS FIUME: Oh, I'm sorry. I'm sorry, I did not see that. I apologize.

MS. CHERIAN: Is genotox data still insufficient for the leaf extract?

DR. BELSITO: Yes. Well, I don't know. I mean yeah, I guess, because we just have a 90-day oral on the leaf, right? Is that sufficient to clear genotox impurities?

DR. LIEBLER: Different endpoint.

DR. BELSITO: Okay.

DR. LIEBLER: It's different from genotox. And the impurities --

DR. BELSITO: Okay. So we need impurities, genotox, sensitization and irritation at concentration of use.

DR. LIEBLER: Yeah. It's really composition and impurities, but yes. Oh, wait a second. We now have -- oh yeah. I flagged this. PDF 18, the last item before Use, *Carica papaya* leaf extract.

DR. BELSITO: Um hmm.

DR. LIEBLER: It describes (audio skip) in its extract and its composition.

DR. SNYDER: That's why I took off the impurities and just left genotox.

DR. LIEBLER: Yeah. So that wasn't highlighted in yellow. Did we overlook last time or, Priya, was that just added?

MS. CHERIAN: That was not just added.

DR. LIEBLER: Okay. I guess we overlooked it last time. But yeah, Paul's right. We just need genotox.

DR. BELSITO: And sensitization and irritation at concentration of use.

DR. LIEBLER: Yes.

DR. BELSITO: Okay. Anything else discussion-wise, what do we want to put in? Obviously, anything that Priya didn't include here that we want in. The only thing I would say in the discussion, Priya, was in the third paragraph you said, "The Panel recognized the apprehension regarding potential IGE-mediated hypersensitivity." I don't think we need the words "apprehension regarding."

MS. CHERIAN: Okay.

DR. BELSITO: "The Panel recognized the potential of IGE-mediated hypersensitivity." I think "apprehension" makes it seem too -- too much --

DR. KLAASSEN: Dramatic.

DR. BELSITO: You're right, exactly. Thank you, Curt.

MS. CHERIAN: Okay. Thank you.

DR. BELSITO: Okay. Anything else? Okay. Wow, we're moving right along here.

DR. LIEBLER: Priya, is your dog allowed on the bed?

MS. CHERIAN: I didn't even know she was in the shot. Yes. She's allowed on the bed.

DR. LIEBLER: Just looking out for you, just in case.

DR. BELSITO: These Zoom meetings are a riot, aren't they? Okay. Save file, save, thank you. Okay.

Cohen Team – December 7, 2020

DR. COHEN: So Carica Papaya, a Papaya-derived ingredient. This is Priya's. This is a draft tentative report. In June of this year, we issued an IDA for the ingredient group and wanted irritation and sensitization data on the fruit extract at the reported max use concentration of 0.25 percent. We also requested impurities, genotox, irritation, and sensitization data on the leaf extract.

There are five derived ingredients. And just to recall the max use is 0.25 percent in a rinse off, at 0.02 on a leave on. We received a lot of HRIPT information with up to the 0.0586 percent of the fruit extract. I did not see leaf extract or the requested impurities, genotox, irritation/sensitization data on the leaf extract. Hypersensitivity reactions were delayed and immediate, were well laid out in this report. Comments from the group?

DR. SLAGA : Yes. I agree with you -- sufficient for the fruit, but not for the leaf ingredient.

DR. COHEN: Okay.

DR. SHANK: Right, the fruit, the fruit extract, the fruit juice, fruit water safe as used, insufficient for the leaf extract. Leaf extract, the leaf is not a food, so we need impurities, genotox, and irritation/sensitization data on the leaf extract.

DR. PETERSON: I don't have anything more to add.

DR. SLAGA : I agree with that.

DR. BERGFELD: No.

DR. COHEN: I had one or two questions for the group. In the phototox and photosensitivity study, the study used 0.0075 percent fruit extract, but was it in an SPF 50 lotion? So what I don't know is if the finished products have UVA blockers, like Benzophenone-3 or -4 Avobenzone or physical blockers, are we able to draw conclusions on UVA light exposure? I mean, it just seems like an interesting co-ingredient in this particular test.

DR. SHANK: That's a good point.

DR. BERGFELD: It sounds like it would block that response.

DR. COHEN: Well, yeah, I mean, if we knew that it was only a UVB blocker, maybe that's one issue. But these days, there's so many broad-spectrum blockers out there that have either physical agents or UVA blockers, I don't know how you can draw conclusion on that specifically. So how do -- do we need or want phototox in the absence of a -- in the prep- -- the absence of UV blockers in the formulation?

DR. BERGFELD: As a dermatologist, I'm going to say yes.

DR. COHEN: Yeah. I came across one article that used the leaf extract with its chlorophyll to be used experimentally as a photosensitizer for another type of project, so we still don't have much on leaf. But perhaps we might want phototox on leaf?

DR. BERGFELD: Yeah.

DR. SLAGA : That would be fine.

DR. COHEN: Okay. So again, administratively, this report moves forward as sufficient for the fruit, the extract, fruit juice, fruit water, but insufficient for the leaf extract materials.

DR. BERGFELD: But you haven't covered the photosensitivity tox test with the UVA blocker in it.

DR. COHEN: For the fruit part, yeah.

DR. BERGFELD: Yeah. Right.

DR. COHEN: Yes. So it's insufficient across the whole board?

DR. BERGFELD: Yes.

DR. COHEN: Okay.

DR. HELDRETH: Yes, that's what I'm seeing.

DR. COHEN: Yeah. Okay. Thank you.

DR. HELDRETH: Yes.

DR. SHANK: The needs are different.

DR. HELDRETH: That's correct.

DR. SHANK: The fruit extract and juice, and all the fruit stuff, is okay except for the phototox.

DR. BERGFELD: Right.

DR. COHEN: Got it.

DR. SHANK: And the leaf extract has a lot of deficiencies.

DR. COHEN: Okay. So it's a total ID- -- it's an IDA.

DR. SHANK: Yes.

DR. HELDRETH: But, actually, it would be an insufficient data conclusion since we're at the TR stage.

DR. COHEN: Ah, okay.

DR. BERGFELD: Could we ask for a better definition of that study on the fruit extract to see what was in the UVA blocker?

DR. HELDRETH: Yes.

DR. BERGFELD: The SPF 50?

DR. COHEN: Yes.

DR. BERGFELD: Could they define that?

DR. HELDRETH: Yeah, typically, in a situation like this, we've seen the panel say, either provide a clarification on these two phototox studies, whether the SPF is going to block the reaction, or provide us with a completely distinct study to alleviate the concern.

DR. BERGFELD: Okay. David, is that okay with you?

DR. COHEN: Yeah, that's actually perfect. Thank you.

MS. CHERIAN: So, just to make sure what the insufficient are for the leaf extract, it would be impurities, genotox, irritation/sensitization, and phototoxicity, correct?

DR. BERGFELD: Right.

DR. COHEN: Could you repeat? It was a little broken up.

MS. CHERIAN: Oh, I'm sorry. I said that leaf extract insufficiencies would be impurities, genotox, irritation and sensitization, and phototoxicity data.

DR. COHEN: Yeah, that's what I have. Yes.

MS. CHERIAN: Okay. Thank you.

DR. COHEN: Any other comments? Okay. Next on the list is sugarcane.

DR. PETERSON: Could we take a fiver? Would it be possible to take a five-minute break?

DR. COHEN: Sure. So let's see. It's 10:17. You want to come back at 10:25?

DR. PETERSON: Sure.

DR. BERGFELD: Good.

DR. PETERSON: That's perfect. Thank you.

DR. HELDRETH: That works.

DR. COHEN: Good. See you there.

DR. BERGFELD: Thank you, Lisa.

Full Panel – December 8, 2020

DR. BELSITO: Yes, so this is Papaya, and at the 2020 June meeting we issued an IDA for this ingredient asking for irritation and sensitization data on the Fruit Extract at maximum concentration of use, which is .25 percent in a rinse-off. We also asked for impurities, genotox, irritation and sensitization data on the Leaf Extract, which we didn't get.

So, we felt that we could go ahead with the idea that all of the fruit components were safe as used. However, the leaf we still needed genotoxicity and sensitization at maximum concentration of use.

DR. BERGFELD: Dr. Cohen, is there a second or a comment?

DR. COHEN: Second, and a comment. Don, we agreed with that. We might suggest a phototox on the leaf. There was an article I found using papaya leaf chlorophyll as an experimental photosensitizer, not related to human sensitization. The only proviso was for the fruit, I thought the phototox and photosensitivity study might have been difficult to interpret. They used a 0.0075 percent food extract that was in a SPF 50 lotion.

So the concern was that if there were UVA blockers, like benzophenone-3, -4, Avobenzone or physical blockers, it might mitigate any UVA exposure to the skin, and it may make it very hard to interpret the results for that.

So, we could either look at the ingredients of the lotion used and if there were no UVA blockers, perhaps, just pass it. Or if there were UVA blockers, ask for phototox.

DR. BERGFELD: Comment, Don?

DR. BELSITO: No, I missed that. I'm looking now. Yeah, it's an SPF-50 sunscreen lotion. I mean, so, you know, we going out for an IDA so we certainly can ask for photo irritation and photosensitization without -- or clarification as to exactly what was involved. I'm suspecting with a SPF of 50, it probably have some UVA blockers in it.

DR. BERGFELD: Absolutely.

DR. COHEN: Yeah, I couldn't tell, didn't want to make any conclusions other than just not being able to conclude anything from it.

DR. BELSITO: Right, good point, David. Thank you.

DR. BERGFELD: So this is a tentative report. And, Bart, I need clarification on what we move to. Can we do an IDA on a tentative report, or we do insufficient report?

DR. HELDRETH: Alternatively, you could also go with an insufficient data conclusion to keep the report moving forward.

DR. BELSITO: Yeah. So we have to readjust our -- the conclusion that I made because all the fruit components are not okay.

DR. BERGFELD: I'm sorry, I didn't hear you Don. Don, would you start over?

DR. BELSITO: I said I need to slightly readjust my conclusion here because based upon the phototox and photosensitization studies that we have, the fruit components are not okay.

DR. BERGFELD: Yeah.

DR. BELSITO: So, data needed for the fruit components would be absorption -- or, you know, photo absorption, or further clarification on the studies on that sunscreen lotion, specifically what sunscreens were included. And then also, insufficient for the leaf where we need genotoxicity and sensitization at concentration of use.

DR. BERGFELD: Okay. And this has been seconded by David.

DR. COHEN: Okay.

DR. BERGFELD: So this is the new list of needs -- an altered list of the needs. And, you're going out as an insufficient data announcement, or insufficient data conclusion?

DR. BELSITO: This was an IDA. So this will be an insufficient data announcement. Correct, Bart?

DR. HELDRETH: Since this is a draft tentative report, and you haven't issued a conclusion yet, you could issue an insufficient data conclusion and put out a tentative report for public comments.

DR. BELSITO: Okay.

DR. HELDRETH: It'll basically have the same effect, but it'll keep the process moving forward.

DR. BELSITO: Well, let's keep it moving.

DR. BERGFELD: So, we're going to adjust it via insufficient data conclusion. David, is that okay with you?

DR. COHEN: Yes.

DR. BERGFELD: Okay. Any other comments to be made regarding the discussion, regarding the conclusion? Anyone oppose?

MS. CHERIAN: I have a question.

DR. BERGFELD: Who's that?

MS. CHERIAN: I'm sorry, I got a quick question.

DR. BERGFELD: Okay, Priya. Yep.

MS. CHERIAN: So, we have an insufficient data conclusion for the Fruit Extract for phototoxicity and photosensitization data, or if we can clarify what was in the sunscreen. And we're insufficient for the Leaf Extract for genotox, sensitization, irritation and phototox. Correct? Okay, thank you.

DR. SHANK: That's right.

DR. BERGFELD: Okay. All right. I'm going to call the motion. All those in favor of an insufficient data conclusion, please -- excuse me, oppose -- please indicate by stating your name. Hearing none it's unanimous. We're moving on then to the next ingredient, which is the Amino Acid Diacetates, Dr. Cohen.

Safety Assessment of *Carica papaya* (Papaya) - Derived Ingredients as Used in Cosmetics

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The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. Previous Panel member involved in this assessment: James G. Marks, Jr., M.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Alice Akinsulie, former Scientific Analyst/Writer, and Priya Cherian, Scientific Analyst/Writer, CIR.

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ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of five *Carica papaya* (papaya)-derived ingredients as used in cosmetic formulations. These ingredients are mostly reported to function in cosmetics as skin conditioning agents. Industry should continue to use good manufacturing practices to limit impurities that could be present in these botanical ingredients. The Panel considered all the information, and concluded that the available data are insufficient to make a determination that the five *Carica papaya* (papaya)-derived ingredients are safe under the intended conditions of use in cosmetic formulations.

INTRODUCTION

This is a safety assessment of the following 5 *Carica papaya*-derived ingredients as used in cosmetic formulations:

Carica Papaya (Papaya) Fruit
Carica Papaya (Papaya) Fruit Extract
Carica Papaya (Papaya) Fruit Juice
Carica Papaya (Papaya) Fruit Water
Carica Papaya (Papaya) Leaf Extract

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), most of the *Carica papaya*-derived ingredients included in this safety assessment are reported to function as skin conditioning agents in cosmetic products (Table 1).[1] The exception is Carica Papaya (Papaya) Fruit, for which no function is reported.

The Expert Panel for Cosmetic Ingredient Safety (Panel) has previously reviewed the safety of a *Carica papaya*-derived ingredient. In 2017, a safety assessment of plant-derived oils was published, with the conclusion that 244 plant-derived fatty acid oils, including Carica Papaya (Papaya) Seed Oil, are safe in present practices of use and concentration described in the safety assessment.[2]

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

Botanicals, such as the *Carica papaya*-derived ingredients, may contain hundreds of constituents, some of which may have the potential to cause toxic effects. The latex of the papaya plant and its green (unripe) fruits contains the proteolytic enzyme papain.[3] Although papain is not among the ingredients reviewed in this report, information regarding this enzyme has been included when appropriate, as it may be useful. However, in this assessment, the Panel is reviewing the potential toxicity of each of the botanical ingredients as a whole, complex substance; potential toxicity from exposures to mixtures of different chemical compounds may not replicate the biological activity of the individual components.

In many of the published studies, it is not known how the substance being tested in each case compares to the cosmetic ingredient. Therefore, if it is not known whether the chemicals being discussed are cosmetic ingredients, the test substances will be identified via common nomenclature (e.g., simply as "papaya extract" or "*Carica papaya* extract"), using lowercase and/or appropriate italicization to identify genus and species. If it is known that the test substance is a cosmetic ingredient, the International Nomenclature Committee (INCI) terminology (e.g., Carica Papaya (Papaya) Leaf Extract) will be used.

CHEMISTRY

Definition and Plant Identification

The definitions of the *Carica papaya*-derived ingredients included in this safety assessment are provided in Table 1. Two of the ingredients, Carica Papaya (Papaya) Fruit Extract and Carica Papaya (Papaya) Leaf Extract, have the generic CAS No. 84012-30-6.[1] A CAS No. is not specified for the other ingredients.

The papaya plant is a member of the Caricaceae family that originated in central America.[4] The plant contains long, succulent leaves and 5-petalled flowers that are fleshy, waxy, and slightly fragrant. These plants often grow to a height of 3 - 6 m. Generally, the fruit is elongated and club-shaped; it grows 15 - 50 cm long, and 10 - 20 cm thick, weighing up to 9 kg. When the fruit is green and hard (unripe), it is rich in white latex (a thixotropic fluid with a milky appearance that contains about 85% water).[5] The skin of unripe fruit is smooth and green.[6] When ripe, the skin turns yellow or orange. The flesh of ripe fruit is yellow, orange, or red in color. Numerous small black seeds (about 5 mm long) are attached to the wall by soft, white, fibrous tissue. *Carica papaya* is native to Mexico, Belize, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Panama. In the United States (US), the trees are cultivated in Florida.

Chemical Properties

According to a supplier, a mixture of Carica Papaya (Papaya) Fruit Extract, glycerin, and water is a water-soluble liquid that is clear in color.[7] In addition, according to one supplier, there were no spectral absorbance peaks in the ultraviolet A (UVA) or ultraviolet B (UVB) for a sample containing 0.006% of Carica Papaya (Papaya) Fruit Extract.[8] Not enough information was provided to determine the absorbance wavelength of a peak in the ultraviolet C (UVC). A mixture of Carica Papaya (Papaya) Leaf Extract, glycerin, and water is also a liquid, is completely soluble in water, and is a light to medium amber in color.[9] Other available chemical properties of these two ingredients are described in Table 2.

Methods of Manufacturing

Carica Papaya (Papaya) Fruit Extract

According to a supplier, the fresh or dried papaya fruit is extracted with a specified eluent under appropriate temperature conditions to yield a concentrate.[10] The concentrate containing the phytochemical constituents is then blended with the desired diluent and preservation system to produce the final ingredient. Typical eluents include water, butylene glycol, *Carthamus tinctorius* (safflower) seed oil, glycerin, and propylene glycol. The ingredient is evaluated for physiochemical properties according to specification requirements for the batch to be released, and the concentrate is evaluated for contaminants. According to a different supplier, ripe papaya fruit is extracted with water at a temperature of 100 °C.[11] The supplier stated that because the material is heated to this temperature, the enzymes are denatured, and therefore no enzymatic activity is present.

Carica Papaya (Papaya) Leaf Extract

An ethanolic extract of the *Carica papaya* leaf was prepared using harvested leaves that were air dried and reduced to powdered form using mortar and pestle.[12] The surface of the leaves were sterilized via a 0.1% solution of mercuric chloride. The powdered sample (400 g) was extracted by cold maceration using 2 l of ethanol. The macerated mixture was filtered and evaporated in a temperature-regulated water bath (maintained at 50° C) to yield 27.2 g of a dark green semi-solid extract. In a different study, a crude extract of *Carica papaya* leaf was prepared by grinding sterilized leaves (200 g) with an electric blender.[13] The extract was squeezed through sterile gauze pieces, and 16 ml of the crude extract was obtained followed by centrifugation at 4000 rpm for 30 minutes. The supernatant was then filtered through filter paper.

Carica Papaya (Papaya) Fruit Water

According to the *Dictionary* definition, Carica Papaya (Papaya) Fruit Water is a product of distillation.[1]

Composition and Impurities

Carica Papaya Fruit

The analysis of phytochemical constituents of the raw and ripe fruit of *Carica papaya* showed the presence of carbohydrates, tannins, saponins, proteins, amino acids, alkaloids, phenolic compounds, and phytosterols.[14] A study was performed in order to evaluate the chemical composition of the unripe pulp of *Carica papaya*.[15] Phytochemical screening showed the presence of saponins and cardenolides, while chemical analyses revealed the presence of sodium, calcium, iron, phosphorous, zinc, copper, magnesium, and manganese, in considerable quantities. Pulp contained starch (43.28%), sugars (15.15%), crude protein (13.63%), crude fat (1.29%), moisture (10.65%), and fiber (1.88%). A different study was performed to compare the nutritive value of *Carica papaya* at different ripening stages.[16] Results indicated that unripe papaya has the most carbohydrates, vitamins, and proteins, as compared to ripe and very ripe papaya. Unripe papaya also contained the highest amounts of saponins, alkaloids, tannins, flavonoids, and phenols.

Carica papaya fruit contains various piperidine alkaloids, such as carpaine, pseudocarpain, dehydrocarpaine I and II, and phenolics, such as protocatechuic acid, *p*-coumaric acid, caffeic acid, 5,7-dimethoxycoumarin, chlorogenic acid, and kaempferol.[17] A single papaya fruit contains approximately 25 g of latex.[18] Papain, an enzyme that may induce immunoglobin E (IgE)-mediated allergic reactions through oral, respiratory, or dermal routes of exposure, is found in the fruit,[6] and proteases such as papain, chymopapain A and B, and endopeptidase papain III and IV are found in the latex and other parts of the shrub.[17] Cysteine peptidases in papaya fruit include glycyl endopeptidase and caricain. Organic acids present in ripe papaya include citric acid, L-malic acid, quinic acid, succinic acid, tartaric acid, oxalic acid, and fumaric acid.

The major components of papaya dry matter are carbohydrates. The total dietary fiber content of ripe papaya fruit varies from 11.9 to 21.5 g/100 g.[6] The crude protein content ranges from 3.74 to 8.26 g/100 g, and the total lipid content varies between 0.92 and 2.2 g/100 g dry matter. The total fatty acid content in ripe papaya is reported to be low.[6] Palmitic acid and linoleic acid are the two major fatty acids in papaya.

The major natural toxins found in unripe *Carica papaya* fruit are benzylglucosinolate, benzyl isothiocyanate (BITC), and alkaloids.[6] These toxicants may cause irritation of the mucus epithelial membrane. Soaking in water and heat treatment removes these toxic compounds in papaya and other plants. BITC content decreases from 109 ppm when papaya fruit is green, to 10 ppm when papaya fruit is fully ripe.

Carica Papaya Fruit Extract

In one study, an aqueous extract of *Carica papaya* fruit contained 408.54 g/kg total phenolic content, and an ethanol extract contained 296.85 g/kg phenolic content.[19] According to another study, extracts of unripe *Carica papaya* fruit contained terpenoids, alkaloids, flavonoids, carbohydrates, glycosides, saponins, and steroids.[20]

Heavy metals testing was performed on the concentrate of a Carica Papaya (Papaya) Fruit Extract in a safflower oil base.[10] No antimony, arsenic, cadmium, chromium, iron, lead, mercury, or nickel was detected. In addition, no residual pesticides were detected in this Carica Papaya (Papaya) Fruit Extract. Testing was conducted to determine the presence of 26 fragrance allergens defined by the 7th amendment to the EU Cosmetic Directive in a concentrate of Carica Papaya (Papaya) Fruit Extract in an alcohol base. None of the 26 allergens tested were present in concentrations > 1 ppm (Table 3).

Carica Papaya Fruit Juice

The major constituents of a *Carica papaya* fruit juice were reported as lipids, and the carboxylic acids, n-butyric, n-hexanoic, n-octanoic, myristic, palmitic, stearic, linoleic, linolenic, vaccenic, and oleic acids.[21]

Carica Papaya Leaf Extract

A methanolic extract of *Carica papaya* leaf extract was found to contain polyphenols, tannins, flavonoids, saponins, terpenoids, glycosides, alkaloids, and high amounts of glycosides.[22] Carpaine is a major alkaloid found in various parts of papaya, but is primarily found in leaves.[23] In a study, 29 samples of *Carica papaya* leaves were used to examine relative carpaine concentration. The assay involved pressurized solid-liquid extraction and quantification with the aid of ultrahigh-performance liquid chromatography-tandem mass spectroscopy (UHPLC-MS/MS). Carpaine concentration in dry leaves was found to range from 0.02 to 0.31%. Papaya leaves also contain toxicants, such as BITC.[6]

USE

Cosmetic

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

According to 2021 VCRP survey data, Carica Papaya (Papaya) Fruit Extract has the highest reported frequency of use for the *Carica papaya*-derived ingredients; it is reported to be used in 172 cosmetic products (104 leave-on products, 66 rinse-off products, and 2 diluted for bath use; Table 4).[24] The results of a concentration of use survey conducted by the Council in 2018 (and corrected in 2020) indicate that Carica Papaya (Papaya) Fruit Extract is being used at maximum use concentrations up to 0.25% in rinse-off products and maximum use concentrations up to 0.02% in leave-on products.[25,26] Concentration of use data were not reported for any of the other ingredients reviewed in this report. Also, according to VCRP and Council survey data, Carica Papaya (Papaya) Fruit Water is not reported to be used in cosmetic products.

Carica papaya-derived ingredients may be used in products that can be incidentally ingested or come into contact with mucous membranes; for example, Carica Papaya Fruit Extract is reported to be used in lipstick at up to 0.02%.[25] Carica Papaya Fruit Extract is also reported to be used in formulations applied near the eye; it is reported to be used in eye lotions (concentration of use data were not available).[24]

Additionally, Carica Papaya (Papaya) Fruit Extract is reported to be used in spray products that could possibly be inhaled; for example, it is used in pump spray suntan products at up to 0.01%. 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.[27-30] 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.[27,29] Carica Papaya (Papaya) Fruit Extract is reportedly used in deodorant sprays (aerosol) at maximum concentrations up to 0.0008%. There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[29] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. Carica Papaya (Papaya) Fruit Extract is also reported be used in powders (dusting and talcum powders) at up to 0.0003%. 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.[31-33]

The *Carica papaya*-derived ingredients are not restricted from use in any way under the rules governing cosmetic products in the European Union.[34]

Non-Cosmetic

Carica papaya fruit is commonly known for its food use and nutritional value throughout the world.[35] Ripe papaya fruit are typically eaten raw, but are also used in jam, jelly, marmalade, puree, wine, nectar, juice, mixed beverages, ice cream, baby food, and pie.[36] According to 21CFR184.1585, papain derived from *Carica papaya* fruit is generally recognized as safe (GRAS) for food use with no limitations other than current good manufacturing practice. According to the Organisation for Economic Co-operation and Development (OECD), several constituents/parameters are suggested to be analyzed when papaya processing by-products are fed to buffalo, fish, and poultry.[6] These include moisture, crude protein, fat, ash, carbohydrate by differences, total dietary fiber, total sugars, total ascorbic acid, beta-carotene, beta-cryptoxanthin, and BITC.

Several plant parts of *Carica papaya* have been researched for use as alternative or therapeutic treatments; these uses are reported herein for informational purposes only. Because of purported antioxidant and anti-inflammatory properties, *Carica papaya* leaf extracts have been used as treatment for dengue fever, and to boost thrombopoiesis and erythropoiesis.[37] Other reported effects of leaf extracts include: antifungal, anti-inflammatory, and antioxidant properties.[20,38] The extracts have also been researched for the management of burn injuries.[39] The milky juice of *Carica papaya* fruit, when extracted and dried, is used as chewing gum, toothpaste, and meat tenderizer.[20] The juice has also been used to treat digestive problems, intestinal worms, warts, sinusitis, and cutaneous tubercles. In western Uganda, the papaya fruit is used as traditional medicine to induce labor during childbirth.[40] In ayurvedic medicine, the *Carica papaya* fruit is used for treatment of digestive ailments, as well as ringworm and psoriasis.[35] The fruit is also reported to be used as an abortifacient, laxative, diuretic, anti-inflammatory and antibacterial agent.

TOXICOKINETIC STUDIES

No relevant toxicokinetic studies on *Carica papaya*-derived ingredients were found in the published literature. In general, toxicokinetics data are not expected to be found on botanical ingredients because each botanical ingredient is a complex mixture of constituents.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

The acute oral toxicity studies summarized below are presented in Table 5.

An oral LD_{50} of 2520 mg/kg was determined in acute toxicity study involving Wistar rats given up to 3200 mg/kg of an aqueous unripe *Carica papaya* fruit extract.[41] No mortality was observed in male Wistar rats given up to 1500 mg/kg of a methanolic *Carica papaya* leaf extract via gavage.[42] An oral LD_{50} of greater than 2000 mg/kg bw was determined in a study involving rats given up to 2000 mg/kg bw of an aqueous *Carica papaya* leaf extract.[43] No mortalities were observed when a methanolic *Carica papaya* leaf extract was given to Wistar mice in doses of up to 3200 mg/kg.[44]

Short-Term and Chronic Toxicity Studies

The short-term and chronic oral studies summarized below are described in Table 6**.**

No signs of toxicity were observed when Wistar albino rats were given a *Carica papaya* fruit extract (up to 250 mg/kg/d), orally, for 42 d.[41] Wistar rats given a methanolic *Carica papaya* leaf extract (400 mg/kg bw/d) via gavage for 28 d displayed a statistically significant decrease in aspartate aminotransferase, statistically significant increase in blood urea nitrogen levels, and moderate hyperemia in the kidney and heart muscles.[42] No extract-related effects were noted when green *Carica papaya* leaf extract (up to 2000 mg/kg/d) was given to Sprague-Dawley rats for 28 d via gavage.[17] Similarly, no adverse effects were reported when Wistar mice were given a methanolic *Carica papaya* leaf extract (up to 3200 mg/kg/d) for 60 d.[44] A study was performed in order to evaluate the toxicity of irradiated and non-irradiated *Carica papaya* fruit given to Swiss white mice for 2 yr.[45] All papaya fruit-treated groups received a diet consisting of 15% *Carica papaya* fruit (irradiated or non-irradiated). No treatment-related clinical, hematological, pathological, or behavioral abnormalities were noted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

The oral DART studies summarized below are described in Table 7.

The effect of a ripe *Carica papaya* fruit blend (500 ml papaya/l water) on different stages of pregnancy was studied in Sprague-Dawley rats by administering the test substance on days 1 - 5, days 6 - 11, days 12 - 17, and days 1 - 20 of gestation.[46] No signs of fetal or maternal toxicity were observed in any of the treatment groups. A three generation study was performed in order to evaluate the potential reproductive toxicity of irradiated and non-irradiated *Carica papaya* fruit given to Swiss white mice (F_0 and F_2 parents: 45 sex/group; F_1 parents: 75 sex/group).[47] A control group received no papaya in the diet. No statistically significant differences in hematology, pathology, mortality, survival, body weight, or number of pups delivered were observed in parental or offspring animals when compared to control animals. An aqueous *Carica papaya* leaf extract (60 or 120 mg/kg) was given to pregnant Wistar rats via gavage on days 12 - 18 of gestation.[48] Abnormalities in morphometry of fetuses was noted in rats

treated with 60 mg/kg of the extract, while 100% resorption was noted in rats treated with 120 mg/kg of the extract. The effect of an aqueous extract of *Carica papaya* leaf on male fertility was evaluated in male Wistar rats.[49] Treated rats were given 500 mg/kg bw extract orally for 21 d. Statistically significant reductions in mean values of sperm count, motility, viability, and serum testosterone concentration was noted in treated rats compared to control rats. In a different study, male rats were given 100, 200, or 400 mg/kg bw of a methanolic *Carica papaya* fruit extract via gavage for 28 d.[42] The mid- and high doses induced a significant decrease in rat sperm count.

Although papaya seed extract is not among the ingredients reviewed in this report, information regarding this botanical material has been included below, as it may be informative.

The effects an aqueous extract of *Carica papaya* seeds on ovulation and estrous cycle were evaluated in female Sprague-Dawley rats.[50] Rats (10 rats/group) were given 50, 100, or 800 mg/kg bw/d of the extract via gavage in two independent experiments. The aqueous extract of *Carica papaya* seeds at all doses disrupted the normal sequence of the estrous cycle of the rats, but produced no effect on ovulation and the number of ova shed. Administration of an aqueous extract of *Carica papaya* seed (50 mg/kg bw/d) to male albino mice (6/group) for 10 to 30 d via gavage caused a significant decrease in sperm count and sperm motility when compared to the control animals that were given water only.[51] The potential reproductive effects of an aqueous alkaloid extract of *Carica papaya* seeds was studied in male Wistar rats (5 rats/group).[52] Each rat was dosed orally (route of administration not stated) with the extract daily, for 3 d, with doses of either 10, 50, or 150 mg/kg/d, and the male rats were then mated with untreated fertile female rats. No pregnancies were reported in female rats mated with males treated with 50 or 150 mg/kg/d of the extract. Another set of male rats (5/group) were treated with the same doses of the papaya seed extract and used for semen analysis and testes histopathology. Results showed that oral administration of *Carica papaya* seed extract prevented fertilization, reduced sperm cell counts, promoted sperm cell degeneration, and induced testicular cell lesions, in a dose-dependent manner. In a different study, the contraceptive potential of an aqueous *Carica papaya* seed extract was evaluated.[53] Male New Zealand White rabbits (6 animals/group) were given the test substance via gavage in doses of 20, 50, 75, or 100 mg/kg bw/d for 150 d. No treatment-related adverse effects were observed; fertility, semen quality, and hematological parameters were similar among treated and control groups.

GENOTOXICITY STUDIES

Genotoxicity studies on *Carica papaya*-derived ingredients were not found in the published literature, and unpublished data were not submitted.

CARCINOGENICITY STUDIES

Carcinogenicity studies on *Carica papaya*-derived ingredients were not found in the published literature, and unpublished data were not submitted.

OTHER RELEVANT STUDIES

Anti-Tumor Activity

Carica Papaya (Papaya) Leaf Extract

The effects of a *Carica papaya* leaf extract (0.625 to 20 mg/ml) was studied on tumor cell lines and human peripheral blood mononuclear cells (PBMC).[54] The extract significantly inhibited the proliferative responses of immortalized solid tumor cell lines derived from cervical carcinoma (HeLa), breast adenocarcinoma (MCF-7), hepatocellular carcinoma (HepG2), lung adenocarcinoma (PCI4), pancreatic epithelial carcinoma (Panc-1), and mesothelioma (H2452), in a dose-dependent manner. In PBMC, a decreased production of interleukins (IL-2 and IL-4) and an increased production of Th1 type cytokines, such as IL-12p40, IL-12p70, interferon (IFN-γ), and tumor necrosis factor (TNF-α) were noted. The expression of 23 immunomodulatory genes was also enhanced by the addition of this extract.

Allergenicity of a Papaya Protein

The IgE-mediated sensitization potential of recombinant Cari p 1 (rCari p 1; Cari p 1 is a 56 kDa IgE-reactive protein found in papaya fruit and pollen) was evaluated in female BALB/c mice (6/group).[55] Two groups of mice were subcutaneously injected with purified r Cari p 1 (10 µg antigen/animal) emulsified in an adjuvant. Seven d after injection, one group of mice was given papaya fruit extract via the oral route, while the other group was challenged with papaya pollen extract via the intranasal route. The amount of test substance given was not specified. Positive and negative control groups were administered ovalbumin and phosphate-buffered saline (PBS) alone, respectively. Mice were sacrificed 24 h after administration, and lung and gut tissues were evaluated. Allergy-induced inflammatory changes in the lung and duodenum tissue were recorded under a light microscope. Allergen-induced eosinophilic inflammations and mucus secretions were observed in the lung and duodenum tissues of mice after nasal and oral challenge, respectively. Inflammatory changes in gut and respiratory mucosa were similar among mice treated with rCari p 1 and mice treated with ovalbumin (positive control), suggesting allergenicity.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Details of the human dermal irritation and sensitization studies summarized below are provided in Table 8.

A 5-d skin irritation study was performed on 29 subjects to evaluate the irritation potential of a bar soap containing 0.0003% Carica Papaya (Papaya) Fruit Extract.[56] The test article was applied as a 1% aqueous solution (final test concentration of 0.000003% Carica Papaya (Papaya) Fruit Extract, each day, under a semi-occlusive patch, for a total of 4 applications. A 1% aqueous solution of sodium lauryl sulfate was used as the positive control. The test substance was considered to be non-irritating. A different 5-d irritation study was performed according to the same procedure as above, using a powder containing 0.0003% Carica Papaya (Papaya) Fruit Extract.[57] The test substance was applied neat, under a semi-occlusive patch, to 27 subjects. The test substance was considered to be non-irritating.

No irritation or sensitization occurred in several human repeated insult patch tests (HRIPTs). The test articles were a sun protection factor (SPF) lotion containing 0.0075% Carica Papaya (Papaya) Fruit Extract (tested neat; 119 subjects; occlusive conditions), a lipstick containing 0.02% Carica Papaya (Papaya) Fruit Extract (tested neat; 104 subjects; semi-occlusive conditions), a product containing 0.02% Carica Papaya (Papaya) Fruit Extract (tested at a 10% dilution (final test concentration of 0.002% Carica Papaya (Papaya) Fruit Extract; 105 subjects; occlusive conditions), a lotion containing 0.04% Carica Papaya (Papaya) Fruit Extract (tested neat; 49 subjects; occlusive conditions), and a lotion/body butter formulation containing 0.0586% Carica Papaya (Papaya) Fruit Extract (tested neat; 107 subjects; occlusive conditions).[58-62]

Phototoxicity/Photosensitization

Carica Papaya (Papaya) Fruit Extract

A phototoxicity assay was conducted in 23 subjects with an SPF 50 sunscreen lotion containing 0.0075% Carica Papaya (Papaya) Fruit Extract.[63] The test substance was applied neat, under an occlusive patch (2 cm x 2 cm), on duplicate sites on the lower back, one irradiated and one non-irradiated. After a 24-h exposure, one site was irradiated with long-wave ultraviolet light (UVA; 320 – 410 nm), plus full spectrum solar-simulated radiation. Reactions were graded immediately after light exposure, as well as 24 and 48 h later. The test substance did not possess a detectable phototoxic potential in human skin.

A photosensitization assay was completed on 30 subjects with an SPF 50 sunscreen lotion containing 0.0075% Carica Papaya (Papaya) Fruit Extract.[64] For 3 wk, six 24-h induction patches were applied containing the undiluted test substance (occlusive conditions; 2 cm x 2 cm patch). Applications were performed in duplicate; one site was subsequently irradiated with UVA light (320 – 410 nm). After 10 d, a challenge patch was applied at virgin sites with and without irradiation. The test substance did not possess a detectable photocontact-sensitizing potential in human skin.

OCULAR IRRITATION STUDIES

No ocular irritation studies on *Carica papaya*-derived ingredients were found in the published literature, and unpublished data were not submitted

CLINICAL STUDIES

Case Report

A 55-yr-old woman without a history of atopic disease of drug allergy developed a maculopapular symmetric exanthematous rash approximately 2 d after taking throat lozenges containing papaya juice.[65] The patient discontinued the intake of the lozenges and was treated with a systemic antihistaminic and a topical menthol-containing preparation. The rash cleared within 2 wk of this treatment. Four wk after symptoms resolved, the patient was patch tested. Patch tests were performed with the European standard series, the powdered lozenges, and their single components (sorbitol (2%), chlorhydrate (2%), papaya extract (2%), aroma (92%), saccharine sodium (2%), bacitracin (5%) and magnesium stearate (pure)). In addition, papain (in dilutions of 0.1 and 1% in water), was also tested. No substance of the European standard series or lozenge powder was positive in patch-testing except for the 2% papaya extract. Five control subjects did not show any reaction to the papaya extract. In addition, the 1% solution of papain in water showed a weak reaction which was interpreted as irritant.

Papaya Protein Allergen in Pollen-Sensitized Patient Sera

Papaya has been reported to elicit IgE-mediated hypersensitivity via pollen inhalation and fruit consumption.[55] A degranulation assay was used to evaluate the ability of rCari p 1 induce the release of histamine from the IgE-sensitized effector cells using the sera of pollen-sensitized patients suffering with respiratory allergy. Patients were diagnosed with an elevated level of specific IgE-antibody against fruit and pollen extract of papaya via an enzyme-linked immunosorbent assay. Control sera from a healthy patient and a patient with either dust mite or mustard allergy was also collected. A passive sensitization technique was used in which the granulocytes from a healthy donor were stripped off the bound IgE using 50 mM lactate buffer (pH 3.5). The cells were passively sensitized with either four different patient sera (at 1:10 v/v dilutions) containing high titers of anti-Cari p 1 IgE-antibody or control sera for 120 min at 37°C. The IgE-sensitized cells were then challenged with purified rCari p 1 at a serially increasing concentration ranging from 1.0 to 10,000.0 ng/ml. These IgE-sensitized effector cells displayed a dose-

dependent release of histamine upon stimulation with rCari p 1. The maximum percentage of degranulation was seen at a concentration of 1000 ng/ml, in which histamine release took place within a range from 30 - 72% among the four patients tested. Further increasing the allergen concentration (10,000 ng/ml) caused a sharp decrease in histamine release. No release was observed with control sera.

Papaya Sensitization in Respiratory Allergic Patients

Patients in Calcutta, India with respiratory allergies (allergic rhinitis and asthma) were evaluated for allergy to several common food allergens (including papaya fruit) using a questionnaire and skin prick test.[66] To perform the skin prick test, a drop of the food extract (20 µl) in (PBS was placed on the forearm, and the skin was pricked with a needle. Histamine diphosphate and PBS were used as positive and negative controls, respectively. Of the 236 patients tested for papaya hypersensitivity, 62 patients showed a positive response. The majority of these positive reactions were from patients in the age group of 16 - 40.

Papaya Pollen Hypersensitivity

The ability of papaya flower pollen to induce respiratory IgE-mediated allergy was evaluated in 6 patients with clinical histories of allergy (seasonal rhinoconjunctivitis or bronchial asthma) in relation to papaya tree exposure.[67] A skin prick test was performed with papaya pollen extract, commercial papaya fruit extract, and papain extract. Ten pollen-allergic patients allergic to *Artemisia* and 10 patients allergic to dust mites were used as control groups in both in vitro and in vivo studies. Prior to testing, 3 of the 6 patients reported previous ingestion of papaya fruit with no reactions, and the remaining 3 patients did not regularly consume the fruit. None remembered any adverse reaction to papaya fruit ingestion. Skin prick test responses to the pollen extract were positive in all 6 patients, to papaya fruit in 2 patients, and to papain in 2 patients. Levels of total and specific IgE to papaya fruit, papain, and pollen were also measured. Levels of specific IgE to papaya pollen, fruit, and papain were positive in all 6 patients and negative in controls. Radioallergosorbent test (RAST) inhibitions were performed in a pool of sera from the papaya pollen-allergic patients. Sera was incubated with 100 µl of 10-fold dilutions (1 mg/ml to 100 ng/ml) in PBS containing 0.03% human albumin, of papaya pollen and fruit extracts, and a papain commercial extract. The degree of inhibition was measured in percentage, the 0 level being defined as the uptake of the solid phase when the allergen was replaced with PBS. *Artemisia vulgaris* and *Dermatophagoides pteronyssinus* commercial extracts were used as negative inhibition controls. A progressive RAST-inhibition was obtained, reaching 100% inhibition with the papaya pollen extract at the maximum concentration, 72% inhibition with the papaya fruit extract, and 99% inhibition with papain extract. A 50% inhibition was observed with the *Artemisia* extract, and inhibition was not higher than 20% when incubating with the *Dermatophagoides pteronyssinus* extract.

Cross-Reaction Between Latex and Papaya Fruit

Serum samples from 136 patients with immediate-type hypersensitivity against latex proteins were analyzed for IgE antibodies against a panel of different fruit extracts, including a papaya fruit extract.[68] Among the 136 samples tested for papaya fruit extract, IgE antibodies were detected in 69 samples (50.7%). In addition, 18/44 samples tested contained IgE antibodies against papain. Values of allergen-specific IgE were > 0.35 kU/l in 36 samples. Cross-reacting IgE antibodies recognizing latex and fruit allergens were demonstrated by RAST-inhibition tests. Preincubation of 5 sera samples with latex extracts caused a 99.7% mean specific inhibition of papaya fruit-specific IgE. Inhibition of latex-specific IgE after preincubation of serum samples (n = 6) with papaya fruit extract (up to 10 µl) was weaker (mean inhibition of 24.2%).

The potential role of chitinases and complex glycans as cross-reactive determinants linked to latex-food allergy was evaluated.[69] Extracts from several different plant foods, including papaya fruit, and from latex were obtained. These extracts were immunodetected with anticomplex glycans and antichitinase sera raised in rabbits, as well as with sera from patients with latex-fruit allergy (n = 8), and sera from patients allergic to latex without food allergy (n = 5). Pooled sera from 5 atopic subjects allergic to mites, but not to latex or foods, was used as a negative control. Many reactive bands, mainly in the 30 - 100 kDa molecular size range, were detected in most extracts. Putative chitinases appeared in papaya (30 - 35 kDa) and latex (35 - 45 kDa). To compare the patterns obtained with anticomplex glycan and antichitinase sera with those revealing specific IgE-binding proteins, replica membranes were immunodetected with a pool of sera from patients with latex-fruit allergy. Reactive proteins were located in papaya (30 - 35 kDa) and latex (6 - 10, 20, and 35 - 45 kDa). All of these specific IgE-binding components, except for the 6 to 10 kDa and 20 kDa latex bands were also recognized by specific polyclonal antibodies to chitinases. Papaya extract was also tested in sera from patients with latex allergy, but no fruit allergy. No reactive bands were observed, however in control serum, high molecular size bands were detected. These results suggest that mainly class I chitinases contained in these plant foods are the allergens involved in cross reactions with latex, and also indicate that the 16 to 20 kDa, 23 to 28 kDa, and 50 to 70 kDa bands shown by the antichitinase serum are not relevant IgE-binding components.

SUMMARY

The safety of 5 *Carica papaya*-derived ingredients as used in cosmetics is reviewed in this safety assessment. All ingredients reviewed in this report are derived from the papaya plant. According to the *Dictionary*, the majority of these ingredients are reported to function as skin-conditioning agents in cosmetic products. The *Carica papaya* plant contains various phytochemicals, such as phenolic acids, flavonoids, isoflavonoids, saponins, phytosterols, and alkaloids. These phytochemicals vary based on specific parts of the plant.

According to 2021 VCRP survey data, the ingredient with the most reported uses is Carica Papaya (Papaya) Fruit Extract, which is reported to be used in 172 cosmetic products (104 leave-on products, 66 rinse-off products, and 2 diluted for bath use). The results of a concentration of use survey conducted by the Council in 2018 (and corrected in 2020) indicate that Carica Papaya (Papaya) Fruit Extract is being used at maximum use concentrations up to 0.25% in rinse-off products and maximum use concentrations up to 0.02% in leave-on products. Carica Papaya (Papaya) Fruit Extract is reported to be used in spray products that could possibly be inhaled; for example, it is used in pump spray suntan products at up to 0.01%.

An oral LD_{50} of 2520 mg/kg was determined in acute toxicity study involving Wistar rats given up to 3200 kg/mg of an aqueous unripe *Carica papaya* extract. No toxicity was observed in male Wistar rats given up to 1500 mg/kg of a methanolic *Carica papaya* leaf extract via gavage. An oral LD_{50} of greater than 2000 mg/kg bw *Carica papaya* leaf extract (highest dose tested) was determined in a study involving rats. No mortalities were observed when a methanolic *Carica papaya* leaf extract was given to mice at doses of up to 3200 mg/kg.

No signs of toxicity were observed when Wistar albino rats were given a *Carica papaya* fruit extract (up to 250 mg/kg/d), orally, for 42 d. Wistar rats given a methanolic *Carica papaya* leaf extract (400 mg/kg bw/d) via gavage for 28 d displayed a statistically significant decrease in aspartate aminotransferase, statistically significant increase in blood urea nitrogen levels, and moderate hyperemia in the kidney and heart muscles. No extract-related effects were noted when a green *Carica papaya* leaf extract (up to 2000 mg/kg/d) was given to Sprague-Dawley rats for 28 d via gavage. Similarly, no adverse effects were reported when Wistar mice were given a methanolic *Carica papaya* leaf extract (up to 3200 mg/kg/d) for 60 d. A study was performed in order to evaluate the toxicity of irradiated and non-irradiated papaya fruit given to Swiss white mice in the diet for 2 yr. All papaya-treated groups received a diet consisting of 15% *Carica papaya* fruit (irradiated or non-irradiated). No treatment-related clinical, hematological, pathological, or behavioral abnormalities were noted.

The effect of a ripe papaya fruit blend (500 ml papaya/l water) on different stages of pregnancy was studied in Sprague-Dawley rats by administering the test substance on days 1 - 5, days 6 - 11, days 12 - 17, and days 1 - 20 of gestation. No signs of fetal or maternal toxicity were observed in any of the treatment groups. No signs of reproductive toxicity were observed in a 3-generation study involving Swiss mice given a diet consisting of 15% *Carica papaya* fruit (irradiated or non-irradiated). An aqueous *Carica papaya* leaf extract (60 or 120 mg/kg) was given to pregnant Wistar rats via gavage on days 12 - 18 of gestation. Abnormalities in morphometry of fetuses was noted in rats treated with 60 mg/kg of the extract, while 100% resorption was noted in rats treated with 120 mg/kg of the extract. The effect of an aqueous extract of *Carica papaya* leaf on male fertility was evaluated in male Wistar rats. Treated rats were given 500 mg/kg bw extract orally for 21 d. Statistically significant reductions in mean values of sperm count, motility, viability, and serum testosterone concentration was noted in treated rats compared to control rats. In a different study, male rats were given 100, 200, or 400 mg/kg bw of a methanolic *Carica papaya* extract via gavage for 28 d. The mid- and high doses induced a significant decrease in rat sperm count. Sperm motility reduction was noted when an aqueous *Carica papaya* seed extract (50 mg/kg bw/d was given to male albino mice for 10 to 30 d. The potential reproductive effects of an aqueous alkaloid extract of *Carica papaya* seeds (10, 50, and 150 mg/kg/d) was studied in male Wistar rats. Results showed that oral administration of *Carica papaya* seed extract prevented fertilization, reduced sperm cell counts, promoted sperm cell degeneration, and induced testicular cell lesions, in a dose-dependent manner. An aqueous *Carica papaya* seed extract was given orally to female Sprague-Dawley rats in doses of 50, 100, or 800 mg/kg bw/d. At all doses, a disruption of the normal sequences of the estrous cycle was observed. No treatment-related adverse effects were noted when aqueous *Carica papaya* seed extract was given to male New Zealand white rabbits, orally at doses of up to 100 mg/kg bw/d, for 150 d. Fertility, semen quality, and hematological parameters were similar among treated and control groups.

A *Carica papaya* leaf extract significantly inhibited the proliferative responses of HeLa, MCF-7, HepG2, PCI4, Panc-1, and H2452. For each cell type, inhibition was dose-dependent.

No skin irritation was noted in a 5-d skin irritation study evaluating a bar soap containing 0.0003% Carica Papaya (Papaya) Fruit Extract (final test concentration was 0.000003% Carica Papaya (Papaya) Extract in water). Similarly, no irritation was noted in a 5-d skin irritation assay involving a powder containing 0.0003% Carica Papaya (Papaya) Fruit Extract (test substance applied neat). No irritation or sensitization occurred in several HRIPTs evaluating an SPF lotion containing 0.0075% Carica Papaya (Papaya) Fruit Extract (tested neat), a lipstick containing 0.02% Carica Papaya (Papaya) Fruit Extract (tested neat), a product containing 0.02% Carica Papaya (Papaya) Fruit Extract (tested at a 10% dilution (final test concentration of 0.002% Carica Papaya (Papaya) Fruit Extract), a lotion containing 0.04% Carica Papaya (Papaya) Fruit Extract (tested neat), and a lotion/body butter formulation containing 0.0586% Carica Papaya (Papaya) Fruit Extract (tested neat).

A phototoxicity and photosensitization study was performed with a SPF 50 sunscreen lotion containing 0.0075% Carica Papaya (Papaya) Fruit Extract. The test substance was applied neat in both assays. No skin reactions were noted.

A 55-yr-old woman without a history of atopic disease or drug allergy developed a rash 2 d after taking throat lozenges containing papaya juice (2%). Patch tests were performed with the European standard series, components of the powdered lozenge, and papain. A positive response was observed with papaya juice, and a weak positive response was observed with 1% papain.

The IgE mediated sensitization potential of a papaya protein, rCari p 1, was evaluated in female BALB/c mice (6/group). Animals were injected with purified r Cari p 1. Seven d after injection, one group of mice was given a *Carica papaya* fruit extract orally, and a different group was given *Carica papaya* pollen extract via an intranasal route. Inflammatory changes in gut and respiratory mucosa were similar among mice treated with rCari p 1, and mice treated with ovalbumin (positive control), suggesting allergenicity. A degranulation assay was performed on the same papaya protein, using sera of pollen-sensitized patients. The maximum percentage of degranulation was seen at a concentration of 1000 ng/ml, in which histamine release took place within a range from 30 - 72% among the four patients tested. Further increasing the allergen concentration (10,000 ng/ml) caused a sharp decrease in histamine release.

Patients in Calcutta, India with reported allergic rhinitis and asthma were evaluated for food allergy via a questionnaire and skin prick test. Of the 236 patients evaluated for papaya allergy, 62 displayed a positive response. Six patients with clinical histories of seasonal rhinoconjunctivitis or bronchial asthma in relation to papaya tree exposure were studied. Skin prick test responses to the pollen extract were positive in all 6 patients, to papaya fruit in 2 patients, and to papain in 2 patients. Levels of specific IgE to papaya pollen, fruit, and papain were positive in all 6 patients and negative in controls. On RAST inhibition studies using papaya pollen extract in solid phase, a significant cross-reactivity was found among papaya pollen, papaya fruit, and papain.

Serum samples from 136 patients with immediate-type hypersensitivity against latex proteins were analyzed for IgE antibodies against papaya fruit extract and papain. IgE antibodies were detected in 69/136 samples for papaya fruit extract, and in 18/44 samples tested for papain. In a different study, the potential role of chitinases and complex glycans as cross-reactive determinants linked to latex-food allergy was evaluated. Sera from patients allergic to both latex and fruit, and sera from patients allergic to latex only was used. Putative chitinases appeared in papaya (30 - 35 kDa) and latex (35 - 45 kDa). In latex-fruit allergic patient sera, reactive proteins were located in both papaya (30 - 35 kDa) and latex (6 - 10, 20, and 30 - 45 kDa). No reactive bands were observed in sera of patients with latex allergy only, however, high molecular size bands were observed in the control group.

DISCUSSION

This report assesses the safety of cosmetic ingredients derived from the plant *Carica papaya*. Several of these ingredients have been ingested as food and food products for many years. As systemic exposure resulting from food consumption would be much higher than that resulting from use in cosmetics (these ingredients are reported to be used at 0.25% or less), concerns regarding systemic toxicity on the *Carica papaya* fruit ingredients have been mitigated. The Panel noted DART effects seen at high concentrations in *Carica papaya* leaf and seed studies; however, the concern for these effects was mitigated as the doses used in these studies resulted in far greater systemic exposures than would be possible from cosmetic use.

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

The Panel recognized the potential IgE-mediated hypersensitivity reactions following pollen inhalation and fruit consumption. However, concern for this was mitigated due to a lack of case reports involving, and, in clinical practice, a lack of patients exhibiting, allergic reactions (hand dermatitis and cheilitis) following handling and ingestion of papaya. The Panel also discussed the potential cross-reacting IgE antibodies in latex and papaya, and suggested that those individuals that are latex-allergic take caution when using papaya-derived products.

The Panel discussed the issue of incidental inhalation exposure from powders and spray products. The Council survey results indicate that Carica Papaya (Papaya) Fruit Extract is being used in spray products, such as suntan pump spray products (at concentrations up to 0.01%) and in dusting and talcum powders (at up to 0.0003%). Inhalation studies were not available; however, 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.

At its December 2020 meeting, the Panel concluded the data are insufficient to determine safety of all 5 *Carica papaya* (papaya)-derived ingredients. The additional data needed to determine safety for Carica Papaya (Papaya) Fruit, Carica Papaya (Papaya) Fruit Extract, Carica Papaya (Papaya) Fruit Juice, and Carica Papaya (Papaya) Fruit Water as used in cosmetics are phototoxicity/photosensitization data. These data have been requested due to the fact that the existing studies in the report regarding phototoxicity/photosensitization on Carica Papaya (Papaya) Fruit Extract include an SPF 50 sunscreen lotion as part of the test formulation, and it is unknown whether the ingredients in this sunscreen formulation would inhibit the potential phototoxicity/photosensitization of Carica Papaya (Papaya) Fruit Extract. In lieu of phototoxicity data on the *Carica papaya*

(papaya)-derived fruit ingredients, the Panel would also accept a clarification on the specific ingredients of the SPF 50 lotion in the existing phototoxicity/photosensitization assays.

In addition, the following data are needed to determine safety for Carica Papaya (Papaya) Leaf Extract:

- genotoxicity data
- irritation and sensitization data at maximum concentration of use
- phototoxicity/photosensitization data.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the available data are insufficient to make a determination that the following *Carica papaya*-derived ingredients are safe under the intended conditions of use in cosmetic formulations:

Carica Papaya (Papaya) Fruit
Carica Papaya (Papaya) Fruit Extract
Carica Papaya (Papaya) Fruit Juice
Carica Papaya (Papaya) Fruit Water*
Carica Papaya (Papaya) Leaf Extract

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

TABLES

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

Ingredient/CAS No.	Definition	Function
Carica Papaya (Papaya) Fruit	Carica Papaya (Papaya) Fruit is the fruit of the papaya, *Carica papaya*	Not Reported
Carica Papaya (Papaya) Fruit Extract 84012-30-6 (generic)	Carica Papaya (Papaya) Fruit Extract is the extract of the fruit of the papaya, *Carica papaya.*	Skin-Conditioning Agent – Misc.
Carica Papaya (Papaya) Fruit Juice	Carica Papaya (Papaya) Fruit Juice is the liquid expressed from the fruit of the papaya, *Carica papaya*.	Skin-Conditioning Agent – Misc.
Carica Papaya (Papaya) Fruit Water	Carica Papaya (Papaya) Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of *Carica papaya*.	Skin-Conditioning Agent – Misc.
Carica Papaya (Papaya) Leaf Extract 84012-30-6 (generic)	Carica Papaya (Papaya) Leaf Extract is the extract of the leaves of the papaya, *Carica papaya*.	Skin-Conditioning Agent – Misc.

Table 2 Chemical properties

Property	Value	Reference
Carica Papaya (Papaya) Fruit Extract (in glycerin and water)		
Physical Form	Liquid	11
Color	Yellowish-brown to brown	11
Odor	Characteristic	7
pH	3.0 – 5.0	11
Density (g/ml @ 25 ºC)	1.05 - 1.15	7
Boiling Point (ºC)	290	7
Water Solubility	Complete	7
Carica Papaya (Papaya) Leaf Extract (in glycerin and water)		
Physical Form	Liquid	9
Color	Light to medium amber	9
Odor	Characteristic	9
Density (g/ml @ 25 ºC)	1.05 - 1.15	9
Boiling Point (ºC)	290	9
Water Solubility	Complete	9

Table 3. Potential fragrance allergen evaluation of a Carica Papaya (Papaya) Fruit Extract[10]

Allergen	Threshold (ppm)
alpha-isomethyl inone	< 1
amyl cinnamal	< 1
amylcinnamyl alcohol	< 1
anise alcohol	< 1
benzyl alcohol	< 1
benzyl benzoate	< 1
benzyl cinnamate	< 1
benzyl salicylate	< 1
butylphenyl methylpropianol	< 1
cinnamal	< 1
cinnamyl alcohol	< 1
citral	< 1
citronellol	< 1
coumarin	< 1
eugenol	< 1
evernia furfuracea extract	Not detected
evernia prunastri extract	Not detected
farnesol	< 1
geraniol	< 1
hexyl cinnamal	< 1
hydroxycitronellal	< 1
hydroxyisohexyl 3-cyclohexene carboxaldehyde	< 1
isoeugenol	< 1
limonene	< 1
linalool	< 1
methyl 2-octynoate	< 1

Table 4. Frequency (2021)[24] and concentration (2018;[25] 2020[26]) of use according to duration and type of exposure for *Carica papaya* (papaya)-derived ingredients

	# of Uses	*Max Conc of Use (%)*[25]	*# of Uses*	*Max Conc of Use (%)*[26]	*# of Uses*	*Max Conc of Use (%)*[25]
	Carica Papaya (Papaya) Fruit		**Carica Papaya (Papaya) Fruit Extract**		**Carica Papaya (Papaya) Fruit Juice**	
Totals*	**11**	**NR**	**172**	**0.000002 – 0.25**	**5**	**NR**
Duration of Use						
Leave-On	*1*	*NR*	*104*	*0.000002 – 0.02*	2	*NR*
Rinse-Off	*6*	*NR*	*66*	*0.0006 – 0.25*	3	*NR*
Diluted for (Bath) Use	*1*	*NR*	*2*	*NR*	NR	*NR*
Exposure Type						
Eye Area	NR	NR	8	NR	NR	NR
Incidental Ingestion	NR	NR	1	0.000002 – 0.02	NR	NR
Incidental Inhalation-Spray	1[a]	NR	35[a]; 43[b]	0.00023 - 0.01; 0.00025 – 0.01[a]; 0.02[b]	1[a]; 1[b]	NR
Incidental Inhalation-Powder	NR	NR	43[b]	0.0003; 0.000085 – 0.02[b]; 0.02[c]	1[b]	NR
Dermal Contact	7	NR	150	0.000085 – 0.25	5	NR
Deodorant (underarm)	NR	NR	*NR*	0.005; spray: 0.0008	NR	NR
Hair - Non-Coloring	NR	NR	20	0.00023 – 0.0006	NR	NR
Hair-Coloring	4	NR	NR	0.008	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	2	NR	16	0.000002 – 0.25	2	NR
Baby Products	NR	NR	NR	NR	NR	NR

	# of Uses	*Max Conc of Use (%)*[25]
	Carica Papaya (Papaya) Leaf Extract	
Totals*	**1**	**NR**
Duration of Use		
Leave-On	*1*	*NR*
Rinse Off	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*
Exposure Type		
Eye Area	1	NR
Incidental Ingestion	NR	NR
Incidental Inhalation-Spray	1[b]	NR
Incidental Inhalation-Powder	1[b]	NR
Dermal Contact	1	NR
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	NR	NR
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	NR	NR
Baby Products	NR	NR

NR = Not reported.

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

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

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

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

Table 5. Acute oral toxicity studies

Ingredient	Animals	Dose	Procedure	LD_{50} /Results	Reference
Carica papaya fruit extract (aqueous; unripe fruit)	Wistar albino rats; 5/group (number of animals/sex not specified)	400, 800, 1600, and 3200 mg	Animals were administered test article orally and observed for 24 h. Method of oral administration not stated. Control group received 1.0 ml of saline	LD_{50} = 2520 mg/kg; no significant changes in liver, renal, and hematological parameters compared to control groups	[41]
Carica papaya leaf extract (methanolic)	male Wistar rats; 6/group	0, 100, 500, 1000, and 1500 mg/kg	Animals were administered test article via gavage and observed for 48 h after treatment. Control animals were given water only.	No mortalities. Slight behavioral changes such as depression, reduced motor activity, and ataxia were observed in animals. A slight increase in urine output was noted.	[42]
Carica papaya leaf extract (aqueous)	Sprague-Dawley rats; 5 females/group	0 or 2000 mg/kg bw extract; given in a 2 ml volume via gavage	Control group received water. Animals were observed for 30 min after treatment, followed by observation hourly for 8 h and once daily for the next 13 d.	No evidence of gross lesions in any organ and all organs were free of gross pathological changes. The LD_{50} was greater than 2000 mg/kg bw.	[43]
Carica papaya leaf extract (methanolic)	Wistar white mice (5/group) (number of animals/sex not stated)	200, 400, 800, 1600, and 3200 mg/kg via gavage	Animals were administered test article via gavage and observed for 24 h. A control group consisting of 5 animals was not treated with extract.	There were no test article-related deaths during the study however, changes in behavior, such as scratching, weakness, crooked tail, reduced movement, were observed.	[44]

Table 6. Short-term and chronic oral toxicity studies

Ingredient/Dose/Concentration/Vehicle	Animals	Method	Results	Reference
Short-term studies				
Carica papaya fruit extract (aqueous; unripe fruit) 50, 100, 150, 200, and 250 mg/kg bw	Wistar albino rats; 5/group (number of animals/sex not stated)	42-d study; method of oral administration not specified	No clinical signs observed during the treatment and observation period. There were no significant decreases in body weight, or hematological/clinical abnormalities.	[41]
Carica papaya leaf extract (methanolic) 0, 100, 200, and 400 mg/kg bw/d	male Wistar rats; 8/group	28-d study; animals treated via gavage; control group given water only	The extract at 200 and 400 mg/kg significantly ($p < 0.05$) decreased aspartate aminotransferase values compared to the control. No significant difference between total bilirubin, ALP, ALT, gamma glutamyl transferase, and triglycerides in treated vs. control rats. No significant changes in total protein and albumin values between extract-treated and normal rats. Histopathological studies showed mild kidney and cardiac hyperemia, and slight hepatic degeneration at the high-dose level.	[42]
green *Carica papaya* leaf extract (aqueous) 10, 140, and 2000 mg/kg/d	Sprague-Dawley rats; 10 /sex/group	28-d oral study in accordance with OECD TG 407; administered via gavage; control group left untreated	No mortality or extract-related effects were noted at necropsy. Slightly lower body weights of the male rats treated with the highest dose (2000 mg/kg) were noted at wk 3 ($p = 0.049$). The MCV in the male rats treated with 140 mg/kg was slightly lower ($p = 0.039$) than the controls, but statistically significant. Liver biochemistry revealed a significantly higher ALT level in the male rats treated with 10, 140 mg/kg ($p = 0.03$ and $p = 0.02$, respectively), whereas the ALP level was significantly higher only in rats treated 140 mg/kg ($p = 0.04$). Also, triglycerides were significantly higher in male rats in the 140 and 2000 mg/kg dose group ($p = 0.005$ and $p = 0.018$, respectively) compared to the control group.	[17]
Carica papaya leaf extract (methanolic) 200, 400, 800, 1600, and 3200 mg/kg/d	Wistar strain mice; 30 males/group	60-d oral study; gavage	No signs of toxicity were observed after evaluation of animals and blood chemistry parameters, however a statistically significant increase in SGOT levels were apparent compared to controls.	[44]
Chronic Studies				
Irradiated and non-irradiated papaya fruit (diet composed of 15% papaya)	Swiss white mice; 75/sex/group	2-year study; T-I and T-II mice fed 15% of either 75 kiloradians (Krads) (T-1) or 200 Krads (T-II) irradiated papaya fruit; positive control given non-irradiated papaya; negative control group received stock feed. Following three, six, 12, and 18 mo of feeding, two mice of each sex from each group were sacrificed and subjected to complete gross pathologic examinations. All animals remaining at 24 mo were killed and examined.	No significant changes in final body weights were noted in any groups from the tenth wk through the twentieth mo. After the twentieth mo, body weight losses were observed in all groups as a result of general debilitation due to old age. Irradiated papayas had no effect on food intake in mice. When compared to the control groups, there were no treatment-related changes in hematological and clinical chemistry, or gross pathology.	[45]

Abbreviations: ALP = alkaline phosphatase; ALT = alanine transaminase; LDH = lactic acid dehydrogenase; MCV = mean cell volume; SGOT = serum glutamic-oxaloacetic transaminase

Table 7. Oral developmental and reproduction toxicity (DART) studies

Test Article	Species/ Strain	Test population	Dose/Concentration (vehicle)	Procedure	Results	Reference
Carica papaya fruit blend (ripe)	Sprague-Dawley rats	5 females/group	500 ml papaya/l water given freely	The test substance was administered through a water bottle to groups of pregnant rats during different phases of pregnancy (pre-fetal-implantation (days 1 - 5), post fetal-implantation (days 6 - 11 and 12 - 17), and throughout gestation (days 1 - 20)). The control group received water only. On day 16 of gestation, Caesarean sections were performed on rats that received papaya blend before fetal implantation. During Caesarean sections, the number of implantations were recorded for each rat. On day 20 of gestation, Caesarean sections were performed on the rats that received treatment on post fetal-implantation and throughout gestation. Variables recorded include: number of fetal deaths and viable fetuses, fetus weight, and fetus malformations.	There were no significant differences in the number of implantation sites and viable fetuses in the rats given ripe papaya relative to the control group. No signs of fetal or maternal toxicity was observed in any group. Fetal weight in the treated groups versus control groups did not reveal any significant differences. No external abnormalities were observed in any group. In rats given ripe papaya before fetal implantation, no statistically significant differences were noted in the number of implantation sites relative to the control.	[46]
Irradiated and non-irradiated papaya fruit	Swiss white mice	F_0 and F_2 parents: 45/sex/group F_1 parents: 75/sex/group	T-I and T-II mice fed 15% of either 75 Krads (T-1) or 200 Krads (T-II) irradiated papaya fruit; positive control given non-irradiated papaya; negative control group diet without papaya	Male and female mice that were fed either the test substance via feed or control feed for 10 wk were selected and bred twice to obtain 2 litters; the second litter was used to select parental animals for the next generation. Matings were continued following this protocol for 3 generations. At the time of weaning the second litters (F1b and F2b), weanlings were isolated and maintained on the prescribed diet for 1 wk. The study terminated following the weaning of the F3b weanlings.	There were no statistically significant differences in parental animals vs. control animals for the following parameters: body weight gain, mortality and reactions, hematologic and clinical blood chemistry, pathologic studies, and reproductive performance. Similarly, there were no statistically significant differences in offspring animals for the following parameters: numbers delivered and viable, survival, body weight at weaning, hematologic and blood chemistry, pathologic studies, and reactions.	[47]
Carica papaya leaf extract (aqueous)	Wistar rats	6 females/group	0, 60 mg/kg, or 120 mg/kg/d	A control group was given tap water, while test groups were treated with the extract via gavage from days 12 through 18 of gestation. On day 20 of gestation, animals were killed	There was a significant ($p < 0.001$) reduction in the body weights, crown-rump lengths, and head lengths of the fetuses in the 60 mg/kg dose group compared with the control; a slight reduction in the tail lengths was noted in the group treated with 60 mg/kg ($p < 0.05$) compared with the control. The number of viable fetuses was less in the group treated with 60 mg/kg, which had an average of 5 fetuses per pregnant rat (30 viable fetuses in all), compared with the control which had 6 fetuses per pregnant rat (33 fetuses in all). The size of the fetuses of the group treated with 60 mg/kg appeared smaller, and in some cases showed slight deformities. There were no fetuses found in the group treated with 120 mg/kg (100% resorption); empty amniotic sacs were observed. The decreased morphometry and resorption in this study indicated adverse effects of some of the constituents of the extract on the developing fetuses. However, there were no reported teratogenic effects. Maternal effects were not noted, but fecal matter was soft in continence compared with the control.	[48]

Table 7. Oral developmental and reproduction toxicity (DART) studies

Test Article	Species/ Strain	Test population	Dose/Concentration (vehicle)	Procedure	Results	Reference
Carica papaya leaf extract (aqueous)	Wistar rats	9 males/group	500 mg/kg bw/d	The test group was administered a single daily dose of the extract, orally, for 21 d while the control was administered with 0.9% physiological saline. Method of oral administration was not specified.	Histopathological examination of the rat testis showed visible lesion and degeneration of the seminiferous tubule epithelium in all the animals in the test group when compared to the control group. A significant reduction ($p < 0.05$) of sperm count, motility, viability: death-live ratio and serum testosterone concentration were observed.	[49]
Carica papaya leaf extract (methanolic extract)	Wistar rats	8 males/group	100, 200, and 400 mg/kg bw/d	Test animals were dosed for 28 d via gavage and control animals received 10 ml/kg of distilled water. Reproductive organ weights, sperm count, spermatozoa defects, were measured and a serum biochemical analysis was performed.	A significant ($p < 0.01$) decrease in sperm count was noted in the 200 and 400 mg/kg group compared to the control. Several sperm defects were also observed in the 100 and 200 mg/kg groups, including a tailless head, headless tail, rudimentary tail, bent tail, curved tail, and a curved midpiece to bent midpiece, when compared to the controls., and severe necrosis of the germinal epithelium in testes of the 400 mg/kg dose group.	[42]
Carica papaya seed extract (aqueous extract)	albino Swiss mouse	6 males/group	50 mg/kg bw/d; 0.1 ml controls were given distilled water only	Mice were dosed via gavage for either 10, 20, or 30 d. Animals were sacrificed post-treatment for evaluation.	A significant decline ($P < 0.001$) of sperm count was noted in mice after 10 to 30 d of treatment then compared to control group of mice. The sperm motility and seminal pH also declined significantly ($P < 0.001$) during 10 to 30 d treatment in treated group of mice compared to control. Sperm mortality ($P < 0.001$) and abnormality of spermatozoa increased significantly ($P < 0.001$) in treated group than the control group of mice.	[51]
Carica papaya seed extract (powdered seeds first extracted with petroleum ether for fat removal, petroleum ether residues were re-extracted in ethanol)	Rat (Wistar)	5 males/group	10, 50, or 150 mg/kg/d; controls given corn oil	Treatments were given orally for 3 d; however, method of oral administration was not stated. After treatment, male rats were mated with fertile, untreated female rats (in a ratio of 1:1) and evaluated.	Untreated female Wistar rats mated with male rats that were dosed with 50 or 150 mg/kg/d papaya seed extract showed no pregnancies, whereas female rats mated with male rats treated with corn oil delivered an average of 9 pups after a 21-d gestation period. One female rat mated with male rats treated with 10 mg/kg/d papaya daily for 3 d delivered only 4 pups.	[52]
Carica papaya seed extract (powdered seeds first extracted with petroleum ether for fat removal, petroleum ether residues were re-extracted in ethanol)	Rat (Wistar)	5 males/group	10, 50, or 150 mg/kg/d; controls given corn oil	Animals were dosed for 3 d and used for semen analysis and testes histopathology. Method of oral administration was not stated. Twenty-four h after the last treatment, animals were sacrificed and examined.	Sperm cell count was decreased in all rats treated with the papaya seed extract, in a dose-dependent manner. Control animals showed normal sperm cell counts. Rats treated with the extract displayed pathological effects ranging from mild atrophy of seminiferous tubules to severe Leydig and Sertoli cell metaplasia to degeneration of spermatozoa.	[52]
Carica papaya seed extract (aqueous extract)	Sprague-Dawley rats	10 females/group	GI and GII: 50, 100 and 800 mg/kg bw/d	Rats dosed via gavage in two independent experiments (GI and GII). One group received water only and served as the control. Rats in GI received the oral doses for 3 consecutive cycles while the rats in GII were administered the different doses of the extract at 9 AM on the day of proestrus, and sacrificed the following day	In experiment GI, *Carica papaya* seed extract produced an irregular cycle pattern in 66.7% of the rats treated with 50 mg/kg bw, 83.3% of the rats treated with 100 mg/kg bw, and 100% of the rats treated with 800 mg/kg bw. 94% of the control animals in GI showed a regular cycle pattern and none of the treated rats showed a continuous diestrus pattern. In all the treated groups, the period of estrus in the cycle of the rats was lower when compared to the control group. The rats were also inclined to be proestrus, but failed to move to the estrus phase. The test article had no effect on ovulation in all rats treated at all doses when compared to the control.	[50]

Table 7. Oral developmental and reproduction toxicity (DART) studies

Test Article	Species/ Strain	Test population	Dose/Concentration (vehicle)	Procedure	Results	Reference
Carica papaya seed extract (aqueous extract)	New Zealand White rabbits	6 males/group	0, 20, 50, 75, or 100 mg/kg bw/d	Rabbits were dosed via gavage for 150 d. The control group received water only. A blood analysis, fertility test, and semen analysis were performed.	No treatment-induced body weight changes were apparent. No appreciable changes in semen volume, sperm concentration, motility, and viability were observed when compared with controls and pre-treatment values. No appreciable alterations were observed in total red blood cell count, white blood cell counts, hemoglobin, and hematocrit levels when compared to controls and pre-treatment values. The fertility test resulted in normal pregnancy rates in both control and treated animals.	[53]

Table 8. Human dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
IRRITATION					
Bar soap containing 0.0003% Carica Papaya (Papaya) Fruit Extract	1% aqueous solution; 0.2 ml	29	The test substance was placed on the skin of 29 subjects, under a semi-occlusive patch (2 cm x 2 cm). Applications occurred over a 5-d period, with 4 evaluations. Patches were applied for 24 h, removed, and the site was evaluated, each day, for 4 d. A 1% aqueous solution of sodium lauryl sulfate was used as a positive control. The dermatologist observed reactions on study day 5.	Non-irritating	[56]
Powder containing 0.0003% Carica Papaya (Papaya) Fruit Extract	100%; 0.2 ml	27	5-d irritation study; same procedure as above; 0.2% aqueous solution of sodium lauryl sulfate used as positive control; semi-occlusive conditions	Non-irritating	[57]
SENSITIZATION					
SPF 50 lotion containing 0.0075% Carica Papaya (Papaya) Fruit Extract	100%; 0.2 ml	119	HRIPT; The test substance was applied neat, under an occlusive patch (2 cm x 2 cm), on the back of each subject. After a 24-h exposure period, the patches were removed. A series of 9 test patches were applied followed by a 2-wk non-treatment period. Challenge patches were applied to previously unexposed sites and allowed to remain in skin contact for 24 h. Challenge sites were scored at 24 and 72 h post-patching.	Non-irritating; Non-sensitizing	[59]
Lipstick containing 0.02% Carica Papaya (Papaya) Fruit Extract	100%; dose not reported	104	HRIPT; same procedure as above; semi-occlusive conditions	Non-irritating; Non-sensitizing	[60]
Product containing 0.02% Carica Papaya (Papaya) Fruit Extract	10% aqueous solution;	105	HRIPT; same procedure as above; occlusive patch	Non-irritating; Non-sensitizing	[62]
Lotion containing 0.04% Carica Papaya (Papaya) Fruit Extract	100%; 0.02 ml	49	HRIPT; same procedure as above; occlusive patch	Non-irritating; Non-sensitizing	[61]
Lotion/body butter containing 0.0586% Carica Papaya (Papaya) Fruit Extract	100%; 0.2 ml	107	HRIPT; same procedure as above; occlusive patch	Non-irritating; Non-sensitizing	[58]

HRIPT = human repeated insult patch test

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2021 FDA VCRP data – Papaya-derived ingredients

Carica Papaya (Papaya Fruit)

Bath Oils, Tablets, and Salts	1
Hair Shampoos (coloring)	4
Bath Soaps and Detergents	1
Cleansing	2
Moisturizing	1
Paste Masks (mud packs)	2

Total = 11

Carica Papaya (Papaya) Fruit Extract

Other Bath Preparations	2
Eye Lotion	4
Other Eye Makeup Preparations	4
Hair Conditioner	7
Shampoos (non-coloring)	8
Tonics, Dressings, and Other Hair Grooming Aids	2
Other Hair Preparations	3
Lipstick	1
Other Makeup Preparations	2
Bath Soaps and Detergents	12
Douches	1
Cleansing	27
Depilatories	2
Face and Neck (exc shave)	34
Body and Hand (exc shave)	9
Moisturizing	24
Night	2
Paste Masks (mud packs)	9
Skin Fresheners	6
Other Skin Care Preps	12
Indoor Tanning Preparations	1

Total = 172

Carica Papaya (Papaya) Fruit Juice

Bath Soaps and Detergents	2
Face and Neck (exc shave)	1
Moisturizing	1
Paste Masks (mud packs)	1

Total = 5

Carica Papaya (Papaya) Leaf Extract

Face and Neck (exc shave)	1

No reported uses for **Carica Papaya (Papaya) Fruit Water**

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: February 10, 2021

SUBJECT: Carica Papaya (Papaya) Fruit Extract

Pôle Enjeux Techniques et Environnementaux. 2014. Profil UV Carica Papaya (Papaya) Fruit Extract (1% dilution of a material containing 0.6% Carica Papaya (Papaya) Fruit Extract was tested).

[redacted]

Pôle Enjeux Techniques et Environnementaux

DEPARTEMENT ANALYSE

[redacted] 10/01/2014

RÉF | *REF* [redacted]

DE | *FROM*

[redacted]

À | *TO*

[redacted]

PROFIL UV

Nom INCI USA : CARICA PAPAYA (PAPAYA) FRUIT EXTRACT

Code MP	*N° de lot*	*Conservation*
[redacted]	[redacted]	Température ambiante

19/11/2013 [redacted]

OBJET / *OBJECT*

Détermination du spectre UV de la MP [redacted] à 1% entre 280 et 400nm.

RESULTATS / *RESULTS*

ANALYSE / ANALYSIS

Echantillon	Test	Valeurs
[redacted]	Profil UV-Visible	Profil joint ci-dessous

TECHNIQUES / TECHNIQUES

Méthode	Analyse	Technicien	Données brutes	Date d'analyse
CID-035-00	Profil UV-Visible	[redacted]		09/01/2014

[redacted]

Pôle Enjeux Techniques et Environnementaux

DEPARTEMENT ANALYSE

DEPARTEMENT ANALYSE

The material tested contains 0.6% Carica Papaya (Papaya) Fruit Extract

[redacted]

Nom INCI USA : CARICA PAPAYA (PAPAYA) FRUIT EXTRACT

Solution à 1%

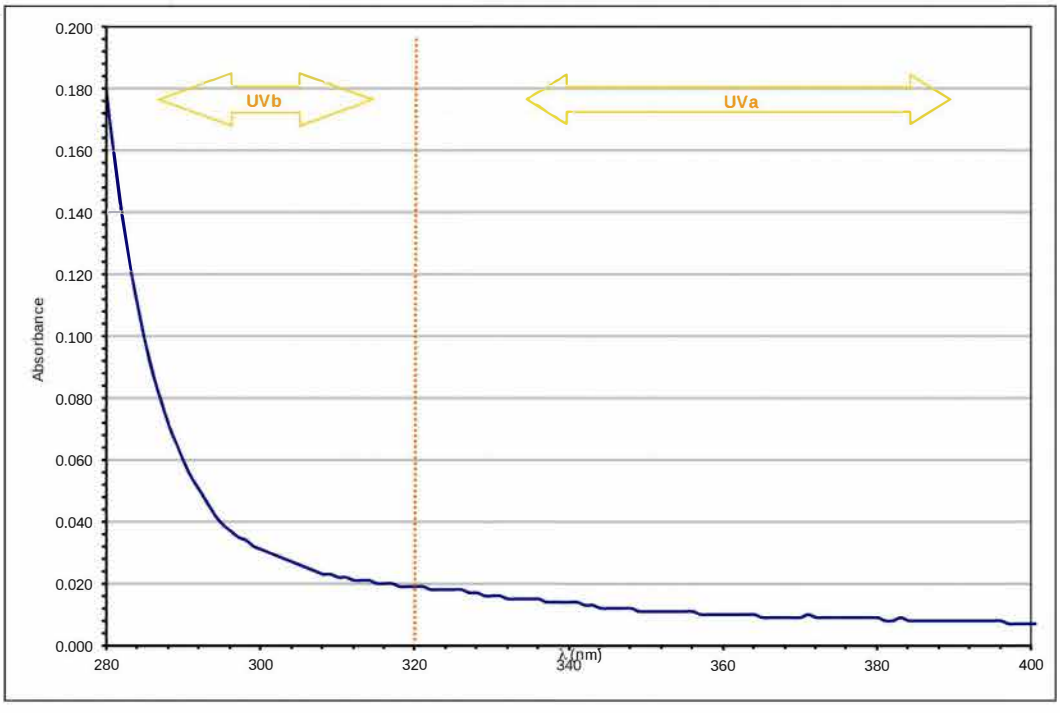
Produit à étudier : [redacted]	*Date des essais :*	*09/01/2014*	*Solvant de dilution :*	*ETOH 96*
Lot n° :	*Prise d'essai (mg) :*	*252.3*	*Remarques :*	*Agitation magnétique*
	Volume de dilution (ml) :	*25*		*A l'abri de la lumière*

Zone 280 à 400 nm

Calculs avec UVa (320-400nm) et UVb (280-320)

*Surface E1%*nm UVa : 1*

*Surface E1%*nm UVb : 1*



Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: January 11, 2021

SUBJECT: Tentative Report: Safety Assessment of *Carica papaya* (Papaya)-Derived Ingredients as Used in Cosmetics (release date: December 16, 2020)

The Personal Care Products Council respectfully submits the following comments on the tentative report, Safety Assessment of *Carica papaya* (Papaya)-Derived Ingredients as Used in Cosmetics.

Abstract; Conclusion – The word "intended" should be used to describe the use of cosmetic products rather than the use of the papaya-derived ingredients.

Non-Cosmetic – In the description of the GRAS status of papain, the statement "specific or unspecified food use" is not clear. The CFR citation (21CFR184.1585) states: "the ingredient is used in food with no limitation other than current good manufacturing practice." The ingredient must meet the specifications listed in the *Food Chemical Codex*.

Discussion – It would be helpful if the Discussion stated that DART effects were reported in studies of leaf extracts and seed extracts. DART effects were not reported in studies of the fruit.

The 0.0003% product was reported in the product category "Powders (dusting and talcum powder)" under FDA's category fragrance preparation. It is misleading to call this product a "body powder".

Table 6 – As some studies provide dose rather than concentration, Dose should be added to the heading of the first column

The dietary concentration of papaya fruit (reference 44) should be stated in the first column.

Table 7 – In the Results column for the first study from reference 51, please clearly state that the material tested was a seed extract (it currently just states "papaya").

Although the Species/Strain column (reference 52) says "rabbits", the Procedure column says "rats". Based on the reference title "rabbits" is correct.