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

Status:	Draft Tentative Report for Panel Review
Release Date:	November 13, 2020
Panel Meeting Date:	December 7 - 8, 2020

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; 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 and Liaisons

From: Priya Cherian, Scientific Analyst/Writer, CIR

Date: November 13, 2020

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

Enclosed is the Draft Tentative Report of the Safety Assessment of *Carica papaya* (Papaya)-Derived Ingredients as Used in Cosmetics (*papaya122020rep*). 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 June 2020 meeting, the Expert Panel for Cosmetic Ingredient Safety (Panel) issued an Insufficient Data Announcement for this ingredient group, and requested irritation and sensitization data on Carica Papaya (Papaya) Fruit Extract at the reported maximum use concentration of 0.25%. In addition, the Panel requested impurities, genotoxicity, and irritation/sensitization data on Carica Papaya (Papaya) Leaf Extract. Since the June Panel meeting, unpublished data have been received and incorporated (highlighted in yellow in the report document). These data include:

- An HRIPT on a lotion containing 0.04% Carica Papaya (Papaya) Fruit Extract (*papaya122020data1*)
- An HRIPT on a lipstick containing 0.02% Carica Papaya (Papaya) Fruit Extract (*papaya122020data1*)
- A 5-d cumulative irritation patch test on a bar soap containing 0.003% Carica Papaya (Papaya) Fruit Extract (*papaya122020data2*)
- A 5-d cumulative irritation patch test on a powder containing 0.003% Carica Papaya (Papaya) Fruit Extract (*papaya122020data2*)
- An HRIPT on a product containing 0.02% Carica Papaya (Papaya) Fruit Extract (*papaya122020data3*)
- An HRIPT on an SPF 50 lotion containing 0.0075% Carica Papaya (Papaya) Fruit Extract (*papaya122020data4*)
- A photosensitization assay on an SPF 50 lotion containing 0.0075% Carica Papaya (Papaya) Fruit Extract (*papaya122020data4*)
- A phototoxicity assay on an SPF 50 lotion containing 0.0075% Carica Papaya (Papaya) Fruit Extract (*papaya122020data4*)
- An HRIPT on a lotion/body butter containing 0.0586% Carica Papaya (Papaya) Fruit Extract (*papaya122020data4*)
- Corrected concentration of use data for Carica Papaya (Papaya) Fruit Extract (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%); *papaya122020data5*)

Also included in this package for your review are the report history (*papaya1220200hist*), flow chart (*papaya122020flow*), literature search strategy (*papaya122020strat*), updated data profile (*papaya122020prof*), and 2020 VCRP data (*papaya122020FDA*). Additionally, comments on the Draft Report were received and addressed (*papaya122020pcpc*).

The Panel should carefully consider and discuss the data (or lack thereof), and the draft Abstract and draft Discussion presented in this report. A Tentative Report with a safe, safe with qualifications, unsafe, insufficient data, or split conclusion should then be issued.

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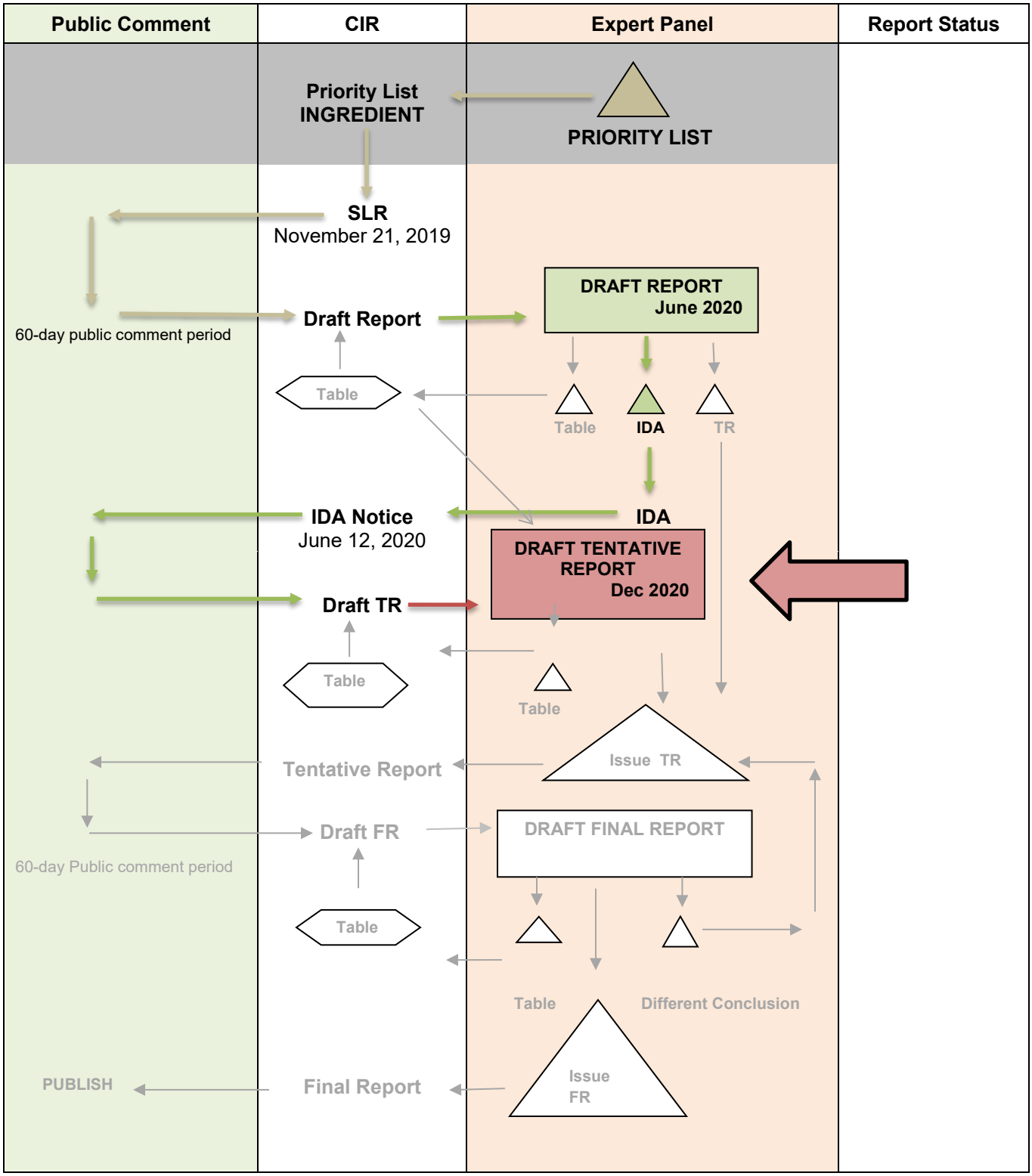
SAFETY ASSESSMENT FLOW CHART

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

MEETING December 2020



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

Papaya-derived ingredients Data Profile – December 2020 – 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.

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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.

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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DRAFT ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of five *Carica papaya* (Papaya)-derived ingredients as used in cosmetic formulations. Industry should continue to use good manufacturing practices to limit impurities that could be present in botanical ingredients. These ingredients are mostly reported to function as skin conditioning agents. The Panel considered the available data and concluded that… [to be determined].

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 mixture; the Panel is not reviewing the potential toxicity of the individual constituents.

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] 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.[8] 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.[9] 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.[10] 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.[11] 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.[12] 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.[13] A study was performed in order to evaluate the chemical composition of the unripe pulp of *Carica papaya*.[14] 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.[15] 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.[16] A single papaya fruit contains approximately 25 g of latex.[17] 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.[16] 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 destroys 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.[18] According to another study, extracts of unripe *Carica papaya* fruit contained terpenoids, alkaloids, flavonoids, carbohydrates, glycosides, saponins, and steroids.[19]

Heavy metals testing was performed on the concentrate of a Carica Papaya (Papaya) Fruit Extract in a safflower oil base.[9] 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.[20]

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.[21] Carpaine is a major alkaloid found in various parts of papaya, but is primarily found in leaves.[22] 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 toxins, 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 2020 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 349 cosmetic products (187 leave-on products, 161 rinse-off products, and 1 diluted for bath use; Table 4).[23] 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.[24,25] 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%.[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.[26-29] 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.[26,28] 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.[28] 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 in the VCRP to be used in powder formulations, such as face powders (concentration not reported) and 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.[30-32]

The *Carica papaya*-derived ingredients are not restricted from use in any way under the rules governing cosmetic products in the European Union.[33]

Non-Cosmetic

Carica papaya fruit is commonly known for its food use and nutritional value throughout the world.[34] 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.[35] According to 21CFR184.1585, papain derived from *Carica papaya* fruit is generally recognized as safe (GRAS) for specified or unspecified food use. 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.[36] Other reported effects of leaf extracts include: antifungal, anti-inflammatory, and antioxidant properties.[19,37] The extracts have also been researched for the management of burn injuries.[38] The milky juice of *Carica papaya* fruit, when extracted and dried, is used as chewing gum, toothpaste, and meat tenderizer.[19] 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.[39] In ayurvedic medicine, the *Carica papaya* fruit is used for treatment of digestive ailments, as well as ringworm and psoriasis.[34] 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 kg/mg of an aqueous unripe *Carica papaya* fruit extract.[40] No mortality was observed in male Wistar rats given up to 1500 mg/kg of a methanolic *Carica papaya* leaf extract via gavage.[41] 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.[42] No mortalities were observed when a methanolic *Carica papaya* leaf extract was given to Wistar mice in doses of up to 3200 mg/kg.[43]

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.[40] 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.[41] 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.[16] 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.[43] 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.[44] 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.[45] 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).[46] 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.[47] 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.[48] 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.[41] 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.[49] 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.[50] The potential reproductive effects of an aqueous alkaloid extract of *Carica papaya* seeds was studied in male Wistar rats (5 rats/group).[51] 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.[52] 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).[53] 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).[54] 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 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.

Irritation

Carica Papaya (Papaya) Fruit Extract

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.[55] 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.[56] The test substance was applied neat, under a semi-occlusive patch, to 27 subjects. The test substance was considered to be non-irritating.

Sensitization

Carica Papaya (Papaya) Fruit Extract

No sensitization or irritation occurred in several HRIPTs evaluating 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).[57-61]

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.[62] 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.[63] 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.[64] 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.[54] 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.[65] To perform the skin prick test, a drop of the food extract (20 µl) in phosphate-buffered saline (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.[66] 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.[67] 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.[68] 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 2020 VCRP survey data, the ingredient with the most reported uses is Carica Papaya (Papaya) Fruit Extract, which is reported to be used in 349 cosmetic products (187 leave-on products, 161 rinse-off products, and 1 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 green a *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 sensitization or irritation 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.

DRAFT DISCUSSION

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

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; 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 and heavy metals 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 apprehension regarding 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 suntan pump spray products at concentrations up to 0.01%. Also, Carica Papaya (Papaya) Fruit Extract is reported to be used in powder formulations such as face powders (concentration not reported) and body powders (at up to 0.0003%). 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.

CONCLUSION

To be determined.

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	10
Color	Yellowish-brown to brown	10
Odor	Characteristic	7
pH	3.0 – 5.0	10
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	8
Color	Light to medium amber	8
Odor	Characteristic	8
Density (g/ml @ 25 ºC)	1.05 - 1.15	8
Boiling Point (ºC)	290	8
Water Solubility	Complete	8

Table 3. Potential fragrance allergen evaluation of a Carica Papaya (Papaya) Fruit Extract[9]

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 (2020)[23] and concentration (2018;[24] 2020[25]) of use according to duration and type of exposure for *Carica papaya* (papaya)-derived ingredients

	# of Uses	*Max Conc of Use (%)*[24]	*# of Uses*	*Max Conc of Use (%)*[25]	*# of Uses*	*Max Conc of Use (%)*[24]
	Carica Papaya (Papaya) Fruit		**Carica Papaya (Papaya) Fruit Extract**		**Carica Papaya (Papaya) Fruit Juice**	
Totals*	**11**	**NR**	**349**	**0.000002 – 0.25**	**5**	**NR**
Duration of Use						
Leave-On	*1*	*NR*	*187*	*0.000002 – 0.02*	2	*NR*
Rinse-Off	*10*	*NR*	*161*	*0.0006 – 0.25*	3	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*1*	*NR*	NR	*NR*
Exposure Type						
Eye Area	NR	NR	14	NR	NR	NR
Incidental Ingestion	NR	NR	7	0.000002 – 0.02	NR	NR
Incidental Inhalation-Spray	1[a]	NR	67[a]; 68[b]	0.00023 - 0.01; 0.00025 – 0.01[a]; 0.02[b]	1[a]; 1[b]	NR
Incidental Inhalation-Powder	NR	NR	3; 68[b]	0.0003; 0.000085 – 0.02[b]; 0.02[c]	1[b]	NR
Dermal Contact	7	NR	302	0.000085 – 0.25	5	NR
Deodorant (underarm)	NR	NR	1[a]	0.005; 0.0008[d]	NR	NR
Hair - Non-Coloring	NR	NR	39	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	70	0.000002 – 0.25	2	NR
Baby Products	NR	NR	NR	NR	NR	NR

	# of Uses	*Max Conc of Use (%)*[24]
	Carica Papaya (Papaya) Leaf Extract	
Totals*	**2**	**NR**
Duration of Use		
Leave-On	*2*	*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	2	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

[d] Product is used as a spray

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	[40]
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.	[41]
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 minutes 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.	[42]
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.	[43]

Table 6. Short-term and chronic oral toxicity studies

Ingredient/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.	[40]
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, alkaline aminotransferase, 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.	[41]
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.	[16]
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.	[43]
Chronic Studies				
Irradiated and non-irradiated papaya fruit	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.	[44]

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.	[45]
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.	[46]
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.	[47]

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.	[48]
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.	[41]
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.	[50]
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 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.	[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	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.	[51]
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.	[49]

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	Rats 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.	[52]

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	[55]
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	[56]
			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	[58]
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	[59]
Product containing 0.02% Carica Papaya (Papaya) Fruit Extract	10% aqueous solution;	105	HRIPT; same procedure as above; occlusive patch	Non-irritating; Non-sensitizing	[61]
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	[60]
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	[57]

HRIPT = human repeated insult patch test

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59. Clinical Research Laboratories Inc. 2014. Repeated insult patch test (lipstick containing 0.02% Carica Papaya (Papaya) Fruit Extract). Unpublished data submitted by Personal Care Products Council on June 15, 2020.

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2020 FDA VCRP Data – Papaya-derived ingredients

1. **Carica Papaya (Papaya) Fruit – 11 total uses**

Hair Shampoos (coloring)	4
Bath Soaps and Detergents	2
Cleansing	1
Paste Masks (mud packs)	3
Skin Fresheners	1

2. **Carica Papaya (Papaya) Fruit Extract – 349 total uses**

Bubble Baths	1
Eye Lotion	7
Eye Makeup Remover	2
Other Eye Makeup Preparations	5
Hair Conditioner	14
Rinses (non-coloring)	2
Shampoos (non-coloring)	14
Tonics, Dressings, and Other Hair Grooming Aids	4
Wave Sets	1
Other Hair Preparations	4
Face Powders	3
Foundations	1
Lipstick	5
Other Makeup Preparations	3
Dentifrices	1
Mouthwashes and Breath Fresheners	1
Bath Soaps and Detergents	45
Deodorants (underarm)	1
Douches	1
Other Personal Cleanliness Products	16
Shaving Cream	2
Cleansing	41
Depilatories	4
Face and Neck (exc shave)	51
Body and Hand (exc shave)	17
Moisturizing	50
Night	4
Paste Masks (mud packs)	17
Skin Fresheners	6
Other Skin Care Preps	24
Indoor Tanning Preparations	2

3. Carica Papaya (Papaya) Fruit Juice – 5 total uses

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

4. Carica Papaya (Papaya) Leaf Extract – 2 total uses

Other Eye Makeup Preparations	1
Face and Neck (exc shave)	1

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: June 15, 2020

SUBJECT: Carica Papaya (Papaya) Fruit Extract

RCTS Inc. 2010. Human repeated insult patch test (lotion containing 0.04% Carica Papaya (Papaya) Fruit Extract).

Clinical Research Laboratories Inc. 2014. Repeated insult patch test (lipstick containing 0.02% Carica Papaya (Papaya) Fruit Extract).

Reliance Clinical Testing Services, Inc.
3207 Esters Road
Irving, TX 75062
Phone 972-871-7578 Fax 469-524-0714
Website: www.rctslabs.com

RCTS, INC. *"Your Assurance of Quality in Clinical Testing"*

Lotion contained 0.04% Carica Papaya (Papaya) Fruit Extract

FINAL REPORT
RCTS' STUDY NO. 2787
TRA PROJECT NO.: 99001-27
HUMAN REPEATED INSULT PATCH TEST (HRIPT)

Sponsor:	[redacted]		
Sponsor's Representative:	[redacted]		
Sponsor's Test Article Code:	TRA 10-140	**RCTS' Test Article Code:**	2787.6273
Testing Facility:	RCTS, Inc. 3207 Esters Road Irving, TX 75062		
Study Objective:	To determine the irritation and contact sensitization potential of a test article under occlusive patch test conditions after repeated applications to the skin of at least fifty (50) human subjects.		
Method:	Modified Draize HRIPT Procedure Induction: Patches applied on the back, generally 3 times each week for 3 weeks. Patches worn for approximately 24-hours. Rest phase: 10-14 days. Challenge: One 24-hour patch on a virgin site. Skin Grading: Induction evaluation occurred approximately 24- to 48-hours after patch removal. Challenge evaluation occurred approximately 24- and 72-hours after patch application (additional readings were made, if warranted).		
Number of Subjects:	Forty-nine (49) subjects satisfactorily completed the test procedure.		
Panel Description:	Male and female subjects aged 19-70 years successfully completed the test procedure.		
Conclusions:	☒ Non-sensitizing ☐ Sensitizing ☐ Additional data needed	☒ Non-irritating ☐ Irritation acceptable (normal) for product type ☐ Irritation higher than normal for product type	
Study Start Date:	11/8/2010	**Study End Date:**	12/16/2010
Document Status:	Final	**Date:**	01/07/2011

I, the undersigned, certify that this document accurately describes the conduct and results of this investigation and that the study was conducted in the spirit of GCP and ICH E6 guidelines.

Barry T. Reece, M.S., M.B.A.
Principal Investigator
Managing Partner, RCTS, Inc.

1/7/11
Date of Final Report

Raymond L. Garcia, M.D.
Medical Investigator
Board Certified Dermatologist

Melissa Wunderlich, B.A.
Study Coordinator
Clinical Research Coordinator

QUALITY ASSURANCE AND CONTROL

This study was conducted in accordance with the spirit of Good Clinical Practice regulations described in CFR 21, Part 50 (Protection of Human Subjects - Informed Consent), Part 56 (Institutional Review Boards) and the International Conference on Harmonization – Good Clinical Practice Guidelines, May 9, 1997, Federal Register.

For purposes of this clinical study:

☒	Informed Consent was obtained.
☐	Informed Consent was not obtained.
☒	An IRB review was neither requested nor required.
☐	An IRB was convened and approval to conduct the proposed clinical research was granted.

The Quality Assurance Department conducted in-study inspections (audits) on a random sampling of subjects during the study. Written status reports of the inspections and findings were submitted to Management.

Date of Inspection	Type of Inspection	Date Reported to Management
11/08/2010	Day 1 procedures including study organization and management, qualification of subjects, consenting process and patching procedures.	11/08/2010
11/22/2010 11/29/2010	Induction phase including patching procedures and scoring of the test sites.	11/24/2010 11/29/2010
12/13/2010	Challenge phase including patching procedures	12/13/2010
12/14/2010	24-Hour read of Challenge phase.	12/14/2010
12/16/2010	72-Hour read of Challenge phase.	12/16/2010
01/04/2011	Final Review of Data Tables	01/04/2011
01/05/2011	Review of Draft Report	01/05/2011
01/07/2011	Final Review of Final Report	01/07/2011

This study report has been reviewed by the Quality Control Group to ensure that it correctly describes the methods of testing and that the reported results accurately reflect the data obtained during the clinical study (RCTS' Study No. 2787; RCTS' Test Article Code 2787.6273).

This report is considered to be a true and accurate reflection of the methods of testing and source data obtained.

Kristen Caldwell, B.S.
Quality Control
01/07/2011
Date

Samatha Prema, M.S.
Manager, Quality Control
01/07/11
Date

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APPENDICES

Clinical Safety Evaluation
Human Repeated Insult Patch Test (HRIPT)

1. SUMMARY

A Modified Draize procedure[1] was conducted to determine the potential of **Test Article: TRA 10-140** to induce irritation and contact sensitization in a population of normal, healthy subjects.

Under the conditions of a Human Repeated Insult Patch Test Procedure (Modified Draize; occlusive patch conditions), **Test Article: TRA 10-140** produced generally transient, barely-perceptible (0.5-level) to mild (1-level) patch test responses (specific and non-specific) on fifteen (15/49 or 31% of the test population) test subjects during the Induction and/or Challenge phases of the study. The skin reactivity observed was considered neither evidence of clinically meaningful irritation nor allergic in nature.

2. OBJECTIVE

To determine the irritation and contact sensitization potential of a test article under occlusive patch test conditions after repeated applications to the skin of at least fifty (50) human subjects.

3. STUDY PERSONNEL

Principal Investigator: Barry T. Reece, M.S., M.B.A.
Medical Investigator: Raymond L. Garcia, M.D. (Board Certified Dermatologist)
Study Coordinator: Melissa Wunderlich, B.A.

4. SPONSOR

[redacted]

5. SPONSOR'S REPRESENTATIVE

[redacted]

6. TESTING FACILITY

The study was conducted at and by RCTS, Inc. at 3207 Esters Road, Irving, TX 75062.

7. EXPERIMENTAL DESIGN

7.1 INFORMED CONSENT

The investigator (or his designee) explained the nature of the study, its purpose and associated procedures, the expected duration and the potential benefits and risks of participation to each subject prior to his/her entry into the study. Each subject was provided with a copy of the informed consent form, had ample opportunity to ask questions and was informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision. No subject entered the study before his/her informed consent form was obtained.

7.2 SUBJECT SELECTION

Sixty-five (65) subjects, 37 females and 28 males, ranging in age from 19 to 70 years were empanelled in this study.

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[1] Draize, J.H., Woodard, G. and Calvery, H.D.: Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. Journal of Pharmacology and Experimental Therapeutics 83, 377-390, 1944.

7.2.1 INCLUSION CRITERIA

Subjects included in the study:

1. Were male and female volunteers between the ages of eighteen (18) and seventy (70), in general good health based upon a study screener (no physical required);
2. Were of any skin type or ethnicity, provided their degree of skin pigmentation did not significantly interfere with evaluations;
3. Were free of any systemic or dermatological disorder including a known history of allergies or other medical conditions which, in the opinion of the investigator, might have interfered with the conduct of the study, interpretation of results or increased the risk of adverse reactions;
4. Agreed to refrain from swimming, using hot tubs/saunas and any type of tanning;
5. Were able to read, understand and provide written informed consent;
6. Agreed to complete the course of the study and to comply with instructions; and
7. Agreed to arrive without lotions, creams or oils applied to their back.

7.2.2 EXCLUSION CRITERIA

Subjects excluded from the study:

1. Were women who were pregnant, nursing or planning to become pregnant during the course of the study;
2. Were individuals with any visible dermatological condition that might have interfered with evaluations;
3. Were individuals with abnormal skin pigmentation at the test sites that might have interfered with subsequent evaluations of dermal responsiveness;
4. Were individuals who were taking medications that might have interfered with the test results, including any regimen of steroidal/non-steroidal anti-inflammatory drugs or antihistamines;
5. Were individuals with a known history of allergies to cosmetics or personal care products;
6. Were individuals who were under treatment for asthma or diabetes; and/or
7. Were individuals who were enrolled in a study or had participated in a patch test study within 14 days prior to the start of this study.

7.2.3 SUBJECT DEMOGRAPHICS

Demographic information is summarized in Text Table 7-1.

Text Table 7-1 Demographics of Subjects

		Enrolled N=65	Completed N=49
Age of Test Subjects (years)	Mean	41.3	41.3
	SD	13.4	13.9
	Median	44.0	42.0
	Range	19-70	19-70
Gender of Test Subjects	Female	37 (56.9%)	31 (63.3%)
	Male	28 (43.1%)	18 (36.7%)
Ethnicity	African American	31 (47.7%)	23 (46.9%)
	Caucasian	24 (36.9%)	19 (38.8%)
	Hispanic	9 (13.8%)	6 (12.2%)
	Native American	1 (1.5%)	1 (2.0%)

Discontinued subjects' data are shown, up to the point of discontinuation, but are not used in the Results and Conclusions section of this final report.

7.3 TEST ARTICLE

The test article was provided by [redacted]. The test article was received on November 04, 2010 and identified as follows:

Text Table 7-2 Test Article Information

Sponsor's Test Article Code	RCTS' Test Article Code	Manufacturer	Description	Identity	Patch Conditions
TRA 10-140*	2787.6273	[redacted]	Pink Cream	Personal Care Product	Occlusive

*Tested neat (as received).

The testing facility confirmed receipt of the test article and used the test article only within the framework of this clinical study and in accordance with the study protocol. Responsibility of the identity, purity, strength, composition and stability of the test article remained with the sponsor. The test article was stored at room temperature in a secured location until use.

8. METHOD

The Human Repeated Insult Patch Test (HRIPT) was conducted as follows:

8.1 INDUCTION PHASE

The Induction phase was initiated on November 08, 2010.

8.1.1 Screening/Induction 1/Day 1

At the Screening/Day 1 visit, potential subjects received all necessary written and verbal information and signed an informed consent form prior to entering the study. Subjects who fulfilled all of the inclusion and none of the exclusion criteria outlined in the study protocol were allowed to participate in the study and received a unique subject number.

Prior to test article application the test site was evaluated to ensure no dermatological condition, or anything that would interfere with the evaluation of the test site, was present. The site was initially wiped with a cotton ball treated with 70% isopropyl alcohol after which approximately 0.2 mL, or enough to cover the entire patch, of the test article was placed onto a 2 cm x 2 cm occlusive patch (Parke-Davis Readi Bandages) and the patch applied to the back of each subject above the waist, between the left scapula and the spinal mid-line. The test article was tested neat (as received). The subjects were instructed to remove the patch 24-hours after application.

8.1.2 Inductions 2-9/Days 2-20

On Days 2-20, subjects arrived at the testing facility at which time they were queried as to any adverse events they may have experienced or any concomitant medications they may have taken since their last visit to the testing facility. The test site was then scored by a trained evaluator just prior to the next patch application using the following 6-point scale:

0 = No evidence of any effect
0.5 = Barely Perceptible (Minimal, faint, uniform or spotty erythema)
1 = Mild (Pink, uniform erythema covering most of the contact site)
2 = Moderate (Pink-red erythema uniform in the entire contact site)
3 = Marked (Bright-red erythema with/without petechiae or papules)
4 = Severe (Deep-red erythema with/without vesiculation or weeping)

All other observed dermal sequelae (i.e., edema, dryness, papular responses, hypo- or hyperpigmentation) were appropriately recorded and described as mild, moderate or severe.

Following evaluation, the test site was cleansed with a cotton ball wet with 70% isopropyl alcohol and a fresh patch of the test article was applied to the subject's back. The subjects were instructed to remove the patch 24-hours after application. Test article applications were generally made on Monday, Wednesday and Friday for three (3) consecutive weeks. Twenty-four (24) hour rest periods followed Tuesday and Thursday removals and 48-hour rest periods followed each Saturday removal. There was a 96 hour rest period after the test article removal during the Thanksgiving Holiday.

Procedurally, if a subject developed a 2-level (moderate) erythema reaction or greater during the Induction phase, or if the skin responses warranted a change in site, the patch was applied to a previously unpatched, adjacent site. If a 2-level reaction (or greater) occurred at the new site, no further applications were made; however, all subjects were subsequently patched with the test material at a naïve site during the Challenge phase of the study unless, in the opinion of the Principal Investigator, it was unwise to do so.

8.1.3 Day 22 (read only)

On Day 22 subjects returned to the testing facility and a trained evaluator examined the test site and recorded the degree of erythema and any other dermal sequelae present. At the conclusion of the Day 22 visit no further patches were applied and the subjects began a 10-14 day rest period following the final Induction application.

8.2 CHALLENGE PHASE

The Challenge phase was initiated on December 13, 2010. The final Challenge patch reading was made on December 16, 2010.

8.2.1 Day 1 of Challenge Phase

Approximately 10-14 days following the application of the last Induction patch, subjects returned to the testing facility for the Challenge phase of the study. The same test article evaluated in the Induction phase was applied in the Challenge phase under the same testing conditions. Application consisted of applying the test article to a patch and applying the patch to a naïve site located away from the original application site (opposite side of the back). During the challenge phase the test article remained in contact with the skin for a period of approximately 24 hours.

8.2.2 Days 2 and 4 of Challenge Phase (24 and 72 hours after patch application)

Subjects returned to the testing facility twenty-four (24) hours after Challenge patch application for supervised patch removal. The site was scored 24- and 72-hours after test article application (i.e., immediately after patch removal and again 48-hours after patch removal) using the same 6-point scale as used for the Induction phase. All subjects were instructed to report any delayed skin reactivity that might have occurred after the final Challenge patch reading. When warranted, selected test subjects returned to the testing facility for additional examinations and scoring to determine possible increases or decreases in Challenge patch reactivity.

9. PROTOCOL AMENDMENTS

There were no protocol amendments made to the original protocol.

10. ADVERSE EVENTS OR OTHER UNEXPECTED EVENTS

There was one (1) unexpected event reported during the course of the study:

- One (1) test subject (Subject No. 36) developed a headache during the rest period of the study (total amount of test article received prior to adverse event ≈ 1.3 mL). The subject took 1 dose of Advil® to treat the event and the headache subsided after 1 day. This adverse event is definitely unrelated to the test article.

11. PROTOCOL DEVIATIONS

The following protocol deviations were recorded during the course of the study.

- Only 49 subjects successfully completed the study.
- Subject Nos. 55 and 58 were allowed 2 missed visits as opposed to one as stated in the protocol. However, the missed visits were made up at the end of the Induction Phase.

In the opinion of the Principal Investigator, the above deviations did not affect the validity of the study data.

12. CHANGES IN THE CONDUCT OF THE STUDY

There were no changes in the conduct of the study.

13. RESULTS AND CONCLUSIONS

A summary table for the frequency of clinical observations for the Induction and Challenge phases is shown below:

Frequency Table

Clinical Score	Induction Exposure Number 1	2	3	4	5	6	7	8	9	Challenge Reading (hrs) 24	72	96	120	168	192
0	49	49	47	49	49	48	46	46	46	38	49	0	0	0	0
0.5	0	0	2	0	0	0	3	3	3	11	0	0	0	0	0
1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	49	49	49	49	49	49	49	49	49	49	49	0	0	0	0

Under the conditions of a Human Repeated Insult Patch Test Procedure (Modified Draize; occlusive patch conditions), **Test Article: TRA 10-140** produced generally transient, barely-perceptible (0.5-level) to mild (1-level) patch test responses (specific and non-specific) on fifteen (15/49 or 31% of the test population) test subjects during the Induction and/or Challenge phases of the study. One subject (Subject No. 33) displayed crusting with erythema during the Induction Phase of the study. The skin reactivity observed was considered neither evidence of clinically meaningful irritation nor allergic in nature.

Sponsor's Test Article Code:
TRA 10-140

Post-Text Table I
Distributed for Comment Only -- Do Not Cite or Quote

RCTS' Test Article Code:
2787.6273

RCTS Panel Number: 2787

HRIPT

Patch Type: Occlusive

No.	Subject's Initials	Age	Gender	Ethnicity	Induction Exposure Number 1	2	3	4	5	6	7	8	9	Challenge Reading (hrs) 24	72	96	120	168	192
1	PM	26.7	Female	African American	0	0	0	0	0	0	0	0	0	0	0				
2	DJ	22.4	Female	Hispanic	0	0	0.5	0	0s	0s	0	0	0	0.5	0				
3	MJ	49.7	Male	African American	0	0	0	0	0	0	0.5	0	0	0	0				
4	SH	48.4	Female	African American	0	0	0	0	0	0	0	0	0	0	0				
5	RA	30.9	Female	Hispanic	0	0	0	0	0	0	0	0	0	0	0				
6	BR	44.8	Female	Hispanic	0	0	0	0	0	0	0	0	0	0	0				
7	OH	22.5	Male	African American	0	0	0	0	0	0	0	0	0	0	0				
8	JT	46.0	Male	African American	Disc														
9	KS	49.8	Male	Caucasian	Disc														
10	EP	38.2	Male	Caucasian	0	0	0	0	0	0	0	0	0	0	0				
11	CB	46.5	Female	Caucasian	0	0	0	0	0	0	0	0	0	0.5	0				
12	DA	49.8	Male	African American	0	0	Disc												
13	DP	50.5	Female	African American	0	0.5ec	0	0	Disc										
14	TH	32.5	Female	African American	0	0	0	0	0	0	0	0	0	0	0				
15	CC	45.9	Female	African American	0	0	0	0	0	0	0	0	0	0	0				
16	RS	19.8	Male	Hispanic	Disc														
17	KJ	29.8	Female	African American	0	0	0	0	0	0	0	0	0	0	0				
18	JR	46.5	Male	Hispanic	0	0	0	0	0	0	Disc								
19	CG	48.0	Male	Caucasian	0	0	0	0	0	0	0	0	0	0	0				
20	MS	33.7	Female	African American	0	0	0	0	0	0	0	0	0	0	0				
21	GH	40.7	Male	Caucasian	0	0	0	0	0	0	0	0	0	0.5	0				
22	SA	46.2	Female	Caucasian	0	0	0	0	0	0	0	0	0	0.5p	0				
23	JB	34.0	Male	Native American	0	0	0	0	0	0	0	0	0	0	0				
24	BF	53.4	Male	Caucasian	0	0	0	Disc											
25	JJ	59.9	Female	African American	0	0	0	0	0	0	0	0	0	0	0				
26	DK	28.3	Male	African American	0	0	0	0	0	0	0	0	0	0	0				
27	LY	31.7	Male	African American	0	0	Disc												
28	JW	28.3	Female	African American	0	0	0	0.5	0	Disc									

Sponsor's Test Article Code:
TRA 10-140

RCTS' Test Article Code:
2787.6273

RCTS Panel Number: 2787
HRIPT

Patch Type: Occlusive

No.	Subject's Initials	Age	Gender	Ethnicity	Induction Exposure Number 1	2	3	4	5	6	7	8	9	Challenge Reading (hrs) 24	72	96	120	168	192
29	PA	23.2	Male	Caucasian	**Disc**														
30	JJ	29.1	Male	African American	**0**	**0**	**0**	**1d**	**1d**	**0.5**	**0.5**	**0**	**0**	**Disc**					
31	VB	55.9	Female	African American	**0**	**0**	**0**	**0**	**0**	**0**	**0.5**	**0.5**	**0**	**0**	**0**				
32	ST	36.4	Female	African American	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**				
33	ST	34.6	Female	Caucasian	**0**	**0**	**0**	**0**	**0**	**1kc**	**0**	**0**	**0.5**	**0.5**	**0**				
34	KP	24.1	Female	African American	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**				
35	HS	49.0	Female	Caucasian	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**				
36	DM	70.2	Male	Caucasian	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0.5**	**0**	**0**	**0**				
37	GS	27.3	Male	African American	**0**	**0**	**0**	**Disc**											
38	JJ	22.3	Male	African American	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**				
39	SZ	55.0	Female	Hispanic	**0**	**0**	**0**	**Disc**											
40	TW	50.8	Female	Caucasian	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**				
41	CU	49.5	Female	Caucasian	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**				
42	BM	56.7	Female	Caucasian	**Disc**														
43	SD	66.8	Female	Caucasian	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0.5**	**0**				
44	GM	70.4	Female	Caucasian	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0.5**	**0**				
45	AM	28.9	Female	African American	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**				
46	MK	66.5	Female	Caucasian	**0**	**0**	**0**	**0**	**0**	**0**	**0.5**	**0.5**	**0.5**	**0.5**	**0**				
47	RS	30.8	Female	Hispanic	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**				
48	CR	43.4	Male	Caucasian	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0.5**	**0.5**	**0**				
49	LG	45.3	Male	African American	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**				
50	RD	48.3	Male	Caucasian	**0**	**0**	**0.5**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**				
51	CG	30.9	Male	African American	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**				
52	IA	49.1	Female	Hispanic	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0.5**	**0**				
53	TM	67.6	Female	Caucasian	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**				
54	AE	26.9	Female	Caucasian	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**				
55	MT	57.0	Female	African American	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**				
56	FS	34.8	Male	African American	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**				

Sponsor's Test Article Code:
TRA 10-140

RCTS' Test Article Code:
2787.6273

RCTS Panel Number: 2787

HRIPT

Patch Type: Occlusive

No.	Subject's Initials	Age	Gender	Ethnicity	Induction Exposure Number 1	2	3	4	5	6	7	8	9	Challenge Reading (hrs) 24	72	96	120	168	192
57	SD	51.2	Female	African American	0	0	0	0	0	0	0	0	0	0	0				
58	JB	42.3	Male	Caucasian	0	0	0	0	0	0	0	0	0	0	0				
59	TR	37.2	Male	Caucasian	0	0	0	0	0	0	0	0	0	0.5	0				
60	GD	54.4	Male	African American	0	0	0	0	0	0	0	0	0	0	0				
61	SH	51.1	Female	Caucasian	0	0	Disc												
62	DB	19.4	Male	Hispanic	0	0	0	0	0	0	0	0	0	0	0				
63	BD	19.9	Female	African American	0	0	0	0	0	0	0	0	0	0	0				
64	MM	48.6	Female	African American	0	Disc													
65	VT	37.5	Female	African American	0	0	0	0	0	0	0	0	0	0	0				

Frequency Table

Clinical Score	Induction Exposure Number 1	2	3	4	5	6	7	8	9	Challenge Reading (hrs) 24	72	96	120	168	192
0	49	49	47	49	49	48	46	46	46	38	49	0	0	0	0
0.5	0	0	2	0	0	0	3	3	3	11	0	0	0	0	0
1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	49	49	49	49	49	49	49	49	49	49	49	0	0	0	0

Clinical Observation Scoring Scale

- ○ 0 = No Observable Effect
- ○ 0.5 = Slight, barely perceptible reaction (minimal, faint erythema, pink in color)
- ○ 1 = Mild (Erythema covering most of the contact site, pink in color)
- ○ 2 = Moderate (Pinkish-red erythema covering most of the contact site)
- ○ 3 = Marked (Bright red erythema. May or may not show signs of petechiae or papules)
- ○ 4 = Severe (Deep red erythema. May or may not show signs of vesiculation or weeping)

Disc = Discontinued
c= Change in Patch Site
d= Mild Dryness
e= Mild Edema
k= Crusting/Scabbing
p= Mild Papular Response
s= Mild staining

Test article tested neat as received

Clinical
Research
Laboratories, Inc.

Final Report

Repeated Insult Patch Test

Lipstick containing 0.02% Carica Papaya (Papaya) Fruit Extract

CLIENT: [redacted]

ATTENTION: [redacted]

TEST MATERIAL: [redacted]

CRL STUDY NUMBER: CRL100713-8

AUTHORIZED SIGNATURES:

Bruce E. Kanengiser, M.D.
President/Medical Director

Michael J. Muscatiello, Ph.D.
Executive Vice President/COO

Anita Lee Cham, M.D.
Dermatologist

REPORT DATE: February 20, 2014

371 Hoes Lane, Suite 100 • Piscataway, NJ 08854 • (732) 981-1616 • FAX (732) 981-0520

Clinical Research Laboratories, Inc.

Good Clinical Practice
Quality Assurance Audit Statement

Clinical Study Number: CRL100713-8

Start Date: December 20, 2013

Completion Date: February 7, 2014

The clinical study listed above was conducted in accordance with Clinical Research Laboratories, Inc. Standard Operating Procedures, which incorporate the principles of Good Clinical Practice defined by applicable guidelines and regulations established by U.S. Regulatory Agencies. The conduct of the study was monitored for compliance, and the associated records, including source documents or raw data, were reviewed for documentation practices and accuracy by a Project Manager/Study Director and/or a Quality Assurance Representative. Standard Quality Assurance audit procedures for this final report and study related documents were conducted.

Karen Hayley
Signature of QA Auditor

Feb. 20, 2014
Date

Clinical Research Laboratories, Inc.

FINAL REPORT

REPEATED INSULT PATCH TEST

PURPOSE

The purpose of this study was to determine the dermal irritation and sensitization potential of a test material.

INVESTIGATIVE SITE

Clinical Research Laboratories, Inc.
371 Hoes Lane, Suite 100
Piscataway, New Jersey 08854
732-981-1616

TEST MATERIAL

The following test material was provided by [redacted] and was received by Clinical Research Laboratories, Inc. on December 20, 2013:

Test Material	Test Condition	Patch Type
CHUBBY STICK – [redacted]	Test as received	Semi-occlusive*

The test material was coded with the following CRL identification number:

CRL100713-8

STUDY DATES

This study was initiated on December 20, 2013 and was completed on February 7, 2014.

* Semi-occlusive Strip (Strukmyer LLC, Mesquite,TX or equivalent)

Clinical Research Laboratories, Inc.

PANEL SELECTION

Each subject was assigned a permanent CRL identification number. All subjects signed an Informed Consent Form in compliance with 21 CFR Part 50: "Protection of Human Subjects" and a HIPAA Authorization Form in compliance with 45 CFR Parts 160 and 164. All subjects completed a Subject Profile/Medical History Form provided by Clinical Research Laboratories, Inc. prior to the study (Subject Demographics - Appendix I). Subjects who met the following Inclusion Criteria and none of the Exclusion Criteria were impaneled:

Inclusion Criteria

a. Male and female subjects between the ages of 18 and 70 years;

b. Subjects who do not exhibit any skin diseases which might be confused with a skin reaction from the test material;

c. Subjects who agree to avoid exposure of the test sites to the sun and to refrain from visits to tanning salons during the course of this study;

d. Subjects who agree to refrain from getting patches wet during the course of the study;

e. Subjects willing to sign an Informed Consent in conformance with 21CFR Part 50: "Protection of Human Subjects;"

f. Subjects who have completed a HIPAA Authorization Form in conformance with 45CFR Parts 160 and 164;

g. Subjects in generally good health who have a current Subject Profile/Medical History on file;

h. Subjects who are dependable and able to follow directions as outlined in the protocol.

Exclusion Criteria

a. Female subjects who are pregnant or nursing;

b. Subjects who report allergies to cosmetics, toiletries or personal care products;

c. Subjects who are currently using any systemic or topical corticosteroids, anti-inflammatory drugs, or antihistamines on a regular basis;

d. Subjects exhibiting any skin disorder, sunburn, scars, excessive tattoos, etc. in the test area.

Clinical Research Laboratories, Inc.

TEST METHOD

Prior to the application of the patch, the test area was wiped with 70% isopropyl alcohol and allowed to dry. The test material, which was prepared as described in the Test Material section of the report, was applied to the upper back (between the scapulae) and was allowed to remain in direct skin contact for a period of 24 hours.

Patches were applied to the same site on Monday, Wednesday, and Friday for a total of 9 applications during the Induction Period. This schedule may have been modified to allow for missed visits or holidays. If a subject was unable to report on an assigned test date, the test material was applied on 2 consecutive days during the Induction Phase and/or a makeup day was added at the end of the Induction Phase.

The sites were graded by a CRL technician for dermal irritation 24 hours after removal of the patches by the subjects on Tuesday and Thursday and 48 hours after removal of the patches on Saturday, unless the patching schedule was altered as described above.

The sites were graded according to the following scoring system:

Dermal Scoring Scale

0 No visible skin reaction
± Barely perceptible erythema
1+ Mild erythema
2+ Well defined erythema
3+ Severe erythema and edema
4+ Erythema and edema with vesiculation

If a "2+" reaction or greater occurred, the test material was applied to an adjacent virgin site. If a "2+" reaction or greater occurred on the new site, the subject was not patched again during the Induction Phase but was challenged on the appropriate day of the study. At the discretion of the Study Director, patch sites with scores less than a "2+" may have been changed.

Following approximately a 2-week rest period, the challenge patches were applied to previously untreated test sites on the back. After 24 hours, the patches were removed by a CRL technician and the test sites were evaluated for dermal reactions. The test sites were re-evaluated at 48 and 72 hours. Subjects exhibiting reactions during the Challenge Phase of the study may have been asked to return for a 96-hour reading.

Clinical Research Laboratories, Inc.

RESULTS

This study was initiated with 124 subjects. Twenty subjects discontinued study participation for reasons unrelated to the test material. A total of 104 subjects completed the study.

Individual dermal scores recorded during the Induction and Challenge Phases appear in Table I.

CONCLUSION

Based on the test population of 104 subjects and under the conditions of this study, the test material identified as CHUBBY STICK – [redacted] did not demonstrate a potential for eliciting dermal irritation or sensitization.

RETENTION

Test materials and all original forms of this study will be retained by Clinical Research Laboratories, Inc. as specified in CRL Standard Operating Procedures 30.6 and 30.6C, unless designated otherwise by the Sponsor.

Clinical Research Laboratories, Inc.

TABLE I

Summary of Dermal Scores

Test Material:	CHUBBY STICK – [redacted]

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	Discontinued											
8R	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	Discontinued											
18R	0	0	0	0	0	0	0	0	0	0	X	0*
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	X	0*
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0

R = Replacement
X = Subject Absent
*No reaction was observed at the 96 hour evaluation

Clinical Research Laboratories, Inc.

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	CHUBBY STICK – [redacted]

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	Discontinued										
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	Discontinued		
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	Discontinued										
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	Discontinued									
50	0	0	0	0	0	0	0	0	0	0	0	0

Clinical Research Laboratories, Inc.

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	CHUBBY STICK – [redacted]

Subject Number	**Induction Scores**									**Challenge Scores**		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**24 Hour**	**48 Hour**	**72 Hour**
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0	0	Discontinued		
59	0	0	0	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0	0	0	0	0	0
61	0	0	0	0	0	0	0	0	0	0	0	0
62	0	0	0	0	0	0	0	0	0	0	0	0
63	0	0	0	0	0	0	0	0	0	0	0	0
64	0	0	0	0	0	0	0	0	0	0	0	0
65	0	0	0	0	0	0	0	0	0	0	0	0
66	0	0	0	0	0	0	0	0	0	0	0	0
67	0	0	0	0	0	0	0	0	0	0	0	0
68	0	0	0	0	0	0	0	0	0	0	0	0
69	0	0	0	0	0	0	0	0	0	0	0	0
70	0	0	0	0	0	0	0	0	0	0	0	0
71	0	0	0	0	0	0	0	0	0	0	0	0
72	0	0	0	0	0	0	Discontinued					
73	0	0	0	0	0	0	0	0	0	0	0	0
74	0	0	0	0	0	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0	0	0	0	0	0

Clinical Research Laboratories, Inc.

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	CHUBBY STICK – [redacted]

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
76	0	0	0	0	0	0	0	0	0	0	0	0
77	Discontinued											
77R	Discontinued											
78	Discontinued											
78R	0	0	0	0	0	0	0	0	0	0	0	0
79	0	0	0	0	0	0	0	0	0	0	0	0
80	0	Discontinued										
80R	0	0	0	0	0	0	0	0	0	0	0	0
81	0	0	0	0	0	0	0	0	0	0	0	0
82	Discontinued											
82R	0	0	0	0	0	0	0	0	0	0	0	0
83	Discontinued											
83R	Discontinued											
84	0	0	0	0	0	0	0	0	0	0	0	0
85	0	0	0	0	0	0	0	0	0	0	0	0
86	0	0	0	0	0	0	0	0	0	0	0	0
87	0	Discontinued										
87R	0	0	0	0	0	0	0	0	0	0	0	0
88	0	0	0	0	0	0	0	0	0	0	0	0
89	0	0	0	0	0	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0	0	0	0	0	0
91	0	0	0	0	0	0	0	0	0	0	0	0
92	0	0	0	0	0	0	0	0	0	0	0	0
93	0	0	0	0	0	0	0	0	0	0	0	0
94	0	0	0	0	0	0	0	0	0	0	0	0
95	0	0	0	0	0	0	0	0	0	0	0	0
96	0	0	0	0	0	0	0	0	0	0	0	0

R = Replacement

Clinical Research Laboratories, Inc.

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	CHUBBY STICK – [redacted]

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
97	Discontinued											
97R	0	0	0	0	0	0	0	0	0	0	0	0
98	Discontinued											
98R	0	0	0	0	0	0	0	0	0	0	0	0
99	0	0	0	0	0	0	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0	0	0	0	0
101	0	0	0	0	0	0	0	0	0	0	0	0
102	0	0	0	0	0	0	0	0	0	0	0	0
103	0	0	0	0	0	0	0	0	0	0	0	0
104	0	0	0	0	0	0	0	0	0	0	0	0
105	0	0	0	0	0	0	0	0	0	0	0	0
106	0	0	0	0	0	0	0	0	X	0	0	0
107	0	0	0	0	0	0	0	0	0	0	0	0
108	0	0	0	0	0	0	0	0	0	0	0	0
109	0	0	0	0	0	0	0	0	0	0	0	0
110	0	0	0	0	0	0	0	0	0	0	0	0
111	Discontinued											
111R	0	0	0	0	0	0	0	0	0	0	0	0
112	Discontinued											
112R	0	0	0	0	0	0	0	0	0	0	0	0

R = Replacement
X = Subject Absent

Clinical Research Laboratories, Inc.

Appendix I

Subject Demographics

Subject Number	Subject Initials	CRL ID #	Age	Sex
1	DP	14491	37	F
2	EN	14911	60	F
3	RT	32357	31	F
4	AL	31718	53	F
5	RA	32349	53	F
6	SK	31929	65	F
7	DD	19959	52	F
8	SF	29522	24	F
8R	RB	32233	45	M
9	ED	14488	61	F
10	MP	32345	26	F
11	KD	32332	40	F
12	SH	29051	47	F
13	VM	28951	65	F
14	EJ	17508	64	F
15	BB	32333	39	F
16	AT	31693	58	F
17	MJ	31317	36	F
18	BR	32308	30	F
18R	CM	13579	62	F
19	AF	29526	44	F
20	DD	24732	51	F
21	MP	20531	47	F
22	DT	01334	56	F
23	RT	32331	56	M
24	JG	27625	62	F
25	MB	18220	67	F
26	MC	28585	37	F
27	MH	26838	61	F

Subject Number	Subject Initials	CRL ID #	Age	Sex
28	SS	28416	61	M
29	JC	32295	45	M
30	MV	32302	46	F
31	DS	19839	35	F
32	GC	28913	25	F
33	AM	22877	47	F
34	SS	11176	19	F
35	LS	32292	29	F
36	PO	32336	40	F
37	MM	30773	38	F
38	MP	14591	69	F
39	GT	32273	50	F
40	JC	32360	47	M
41	PS	25822	40	F
42	BS	25765	67	F
43	SS	25766	44	F
44	AR	24739	24	M
45	RN	29307	47	F
46	JM	13351	63	M
47	JS	31942	45	F
48	JD	01639	59	F
49	KD	31295	37	F
50	YG	32354	46	F
51	KM	29379	35	F
52	SP	32342	26	F
53	AJ	23193	51	F
54	BF	27894	55	F
55	AA	29940	19	F
56	EY	27235	57	M

Clinical Research Laboratories, Inc.

Appendix I
Subject Demographics
(Continued)

Subject Number	Subject Initials	CRL ID #	Age	Sex
57	JP	22148	38	F
58	JF	32122	49	F
59	ME	01693	58	F
60	CB	29973	35	M
61	GM	07979	19	F
62	RE	26689	41	M
63	DP	31035	49	F
64	KJ	32363	23	M
65	SW	32362	19	F
66	DM	15909	58	F
67	ML	28203	62	F
68	DT	28229	65	F
69	LB	28703	30	F
70	RT	32365	61	M
71	LV	32314	45	F
72	DT	23811	41	M
73	CB	20446	42	F
74	PM	04928	61	M
75	LD	20204	52	F
76	LM	24305	19	F
77	SK	32348	26	M
77R	LC	32390	34	F
78	TH	32340	33	F
78R	KF	01673	63	F
79	SM	28473	36	M
80	BA	32186	32	M
80R	PG	13069	63	F
81	AS	32356	27	F
82	FM	32367	22	M
82R	CR	32010	58	F
83	FV	30276	53	F
83R	RR	32237	19	M
84	MH	28950	32	F
85	BW	32344	21	M
86	MV	15003	65	F
87	SM	31542	44	F
87R	LH	15501	57	F
88	RC	28317	45	F
89	LJ	23672	57	F
90	SS	05426	51	F
91	AS	07888	23	F
92	IL	28446	20	F
93	ML	17765	43	F
94	LP	31921	39	F
95	GB	25248	52	F
96	CC	18896	33	F
97	LP	29485	22	M
97R	SB	32274	31	F
98	LJ	32350	25	M
98R	MR	32212	46	M
99	AK	15733	36	F
100	BP	21991	50	F
101	GD	12494	50	F
102	WG	11536	51	F
103	NS	32312	23	F
104	AM	31869	55	F
105	CC	29059	27	F
106	KH	30793	46	F
107	SH	30208	58	F
108	KE	31704	53	F
109	HP	31717	57	F
110	DO	32371	44	M
111	WJ	02706	56	F
111R	LF	32213	50	F
112	GG	07211	59	F
112R	TH	30703	48	F

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: July 1, 2020

SUBJECT: Carica Papaya (Papaya) Fruit Extract

TKL Research. 2015. 5-Day cumulative irritation patch test in subjects with normal skin: Bar soap (Product 138517 contains 0.0003% Carica Papaya (Papaya) Fruit Extract).

TKL Research. 2016. 5-Day cumulative irritation patch test in subjects with normal skin: Talcum powders (Product 140399 contains 0.0003% Carica Papaya (Papaya) Fruit Extract).

5-DAY CUMULATIVE IRRITATION PATCH TEST IN SUBJECTS WITH NORMAL SKIN

PROTOCOL NO. TKL-3500

BAR SOAP
Product 138517 contains 0.0003% Carica Papaya (Papaya) Fruit Extract
TKL STUDY NO. [redacted]

[redacted] **STUDY NO. DCR#** [redacted]

CONDUCTED FOR:

[redacted]

DATE OF FINAL REPORT:

August 21, 2015

TABLE OF CONTENTS

SIGNATURES

This study was conducted in compliance with the requirements of the protocol and TKL's Standard Operating Procedures, and in the spirit of GCP ICH Topic E6.[1] The report accurately reflects the raw data for this study.

_____ _____

Jonathan S. Dosik, MD Date
Dermatologist
Principal Investigator

_____ _____

Derek J. Grimes, CCRP Date
Vice President, Clinical Operations

_____ _____

Michelle Medina Date
Manager, Dermatologic Safety Testing

STATEMENT OF QUALITY CONTROL

The Quality Control Unit of the Dermatological Safety Department conducted a 100% review of all study-related documents. The protocol was reviewed prior to the start of the study, and the medical screening forms and informed consent documents were reviewed in-process of the study. The regulatory binder and study data were reviewed post-study to ensure accuracy. The study report was reviewed and accurately reflects the data for this study.

[1] ICH Topic E6 "Note for guidance on Good Clinical Practices (CPMP/ICH/135/95)" – ICH Harmonised Tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996.

TITLE OF STUDY

5-Day Cumulative Irritation Patch Test in Subjects with Normal Skin

SPONSOR

[redacted]

STUDY MATERIALS

Product Category: Bar Soap

Sample Number	PDM Number
138517	1*68004
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

DATE STUDY INITIATED

July 20, 2015

DATE STUDY COMPLETED

July 24, 2015

DATE OF FINAL REPORT

August 21, 2015

INVESTIGATIVE PERSONNEL

Jonathan S. Dosik, MD
Board-certified Dermatologist
Principal Investigator

Derek J. Grimes, CCRP
Vice President, Clinical Operations

Michelle Medina
Manager, Dermatologic Safety Testing

CLINICAL SITE

TKL RESEARCH, INC
One Promenade Boulevard, Suite 1101
Fair Lawn, NJ 07410

SUMMARY

Ten (10) study materials, Sample Nos. 138517, [redacted], [redacted] were evaluated as 1.0% w/v aqueous solutions using a semi-occlusive 5-day cumulative irritation patch study to determine their ability to cause irritation to subjects with normal skin. Sodium lauryl sulfate (SLS), 1.0% w/v aqueous solution, applied semi-occlusively served as a positive control. Twenty-nine (29) subjects completed the study. The Dermatologist observed reactions on Study Day 5.

This study determined the following irritation scores for all treated and completed subjects:

Irritation Scores for Products and Positive Control on All Subjects Treated and Completed

Sample No.	Irritation Scores (n=29 All Treated and Completed)		
	Total *	**Normalized ****	**Mean *****
SLS 1.0%	106.0	36.6	0.91 [b]
138517	2.0	0.7	0.02 [a]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

NOTE: Means with the same superscripts are not statistically different at $P<0.05$. The analyses of these data are performed using within subject analysis of variance (ANOVA). Product comparisons were made at the 5% level based on Fisher's least significant differences.

* The Total Irritation Score is the sum of all scores for reactions observed in all subjects at all evaluation times.

** The Normalized Score is the Total Irritation Score for each test product divided by the total number of readings for all subjects and multiplied, first by the number of evaluations, and then by 10 (to normalize to 10 subjects).

*** The Mean Irritation Score for each subject/product is the sum of all scores for the subject/product divided by the number of readings for the subject/product.

All of the tested products were statistically significantly less irritating than the positive control, 1.0% SLS. There were no other statistically significant differences between the products.

1.0 OBJECTIVE

The objective of the study was to determine the ability of the study materials to cause irritation to the skin of humans under controlled patch study conditions.

2.0 RATIONALE

Cumulative irritancy patch testing is a modified primary irritancy patch test that can detect weak irritants, which require multiple applications to cause a skin reaction. These reactions are due to direct damage to the epidermal cells and no immunologic (allergic) mechanism is involved. This procedure may detect so-called "fatiguing substances" which are mild irritants that cause more strongly positive reactions with successive multiple skin exposure.

3.0 STUDY DESIGN

3.1 STUDY POPULATION

A sufficient number of subjects with normal skin were enrolled to provide 25 completed subjects.

3.1.1 Inclusion Criteria

Individuals eligible for inclusion in the study were those who:

1. Were males or females 18 years of age or older (no more than 20% over age 65), in general good health;

2. Had normal skin;

3. Were free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events (AEs);

4. Were of any skin type or race providing the skin pigmentation allowed discernment of erythema;

5. Had completed a medical screening procedure; and

6. Had read, understood, and signed an informed consent (IC) agreement.

3.1.2 Exclusion Criteria

Individuals excluded from participation were those who:

1. Had any visible skin disease at the study site (back) which, in the opinion of the investigative personnel, would have interfered with the evaluation;

2. Were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results;

3. Were being treated for asthma (non-steroidal was permitted) or experiencing an asthmatic attack;

4. Had psoriasis and/or active atopic dermatitis/eczema;

5 Were females who were pregnant, planning to become pregnant during the study, or breastfeeding;

6. Had a known sensitivity to a cosmetic, skin care products, shampoos, shower gel/body washes, antiperspirants/deodorants, fragrances, soaps, detergents, fabric softeners, dish liquid, sunscreens, fibers, medications, insect repellents, antimicrobials or topical drugs as related to the material being evaluated;

7. Were or may have been immunologically compromised; and/or

8. Were insulin-dependent diabetics.

3.1.3 Informed Consent

A properly executed IC document was obtained from each subject prior to entering the study. The signed IC document is maintained in the study file. In addition, the subject was provided with a copy of the IC document. A sample is included as Appendix III.

3.2 DESCRIPTION OF STUDY

3.2.1 Outline of Study Procedures

The study extended over a 5-day period with 4 evaluations. On Day 1, the study material and the positive control were applied to the designated patch sites. Twenty-four hours later the patches were removed and the sites evaluated following removal of residue by lightly wiping the areas with a tissue. If the skin had not been disrupted, identical patches were applied to the same sites. This was repeated daily for a period of 3 days for a total of 4 applications. The Dermatologist was in attendance for one evaluation visit. The Dermatologist reviewed the raw data at the conclusion of the study.

3.2.2 Study Flow Chart

DAY	ACTIVITIES
1	Obtained IC, reviewed completed medical screening form, applied patches
2, 3, 4	Staff removed patches, graded, applied patches
5	Staff removed patches, graded

3.2.3 Method for Grading Responses

The symbols found in the data accompanying this report were used to express the response observed at the time of the examination. Each reaction obtained was assigned a numerical equivalent. See table below.

Symbol	Response	Numerical Equivalent
-	No visible reaction	0
- with p, pv, or combinations thereof	Papular (p) or papulovesicular (pv) response without erythema	0.5
?	Minimal or doubtful erythema (slightly different from surrounding normal skin)	1.0
? with p, pv, or combinations thereof	Minimal or doubtful erythema accompanied by papular or papulovesicular response	1.5
+	Definite erythema	2.0
+ with p pv, or combinations thereof	Definite erythema, accompanied by papular or papulovesicular response	2.5
++, +++	Definite erythema and definite edema (++) with vesicles (+++)	3.0
+D, ++D, +++D	Definite erythema with or without edema and severe damage to epidermis characterized by crusting, superficial erosions, or oozing (D)	3.0

The maximum obtainable individual score was 3.0. When a "++", "+++", "+D", "++D" or "+++D" reaction occurred at any point during the study, further patch application on that subject was terminated with respect to the product involved. An "NP" symbol and a score of 3.0 were assigned to all subsequent days.

A total irritation score for each product was calculated by summing each individual's scores on each of 4 evaluation days. The normalized score per product is the total score divided by the total number of readings for all subjects and multiplied by 4 (the number of days) and by 10 (to normalize to 10 subjects). Since these irritation scores were based on 4 applications of product, no attempt was made to classify these materials as to their irritation potential. A full 21-day cumulative irritation patch evaluation would have to be employed in order to precisely determine the irritation classification of each product.

3.2.4 Evaluation of Responses

All responses were graded by a trained dermatologic evaluator meeting TKL's strict certification requirements to standardize the assignment of response grades.

3.2.5 Statistical Analysis

For the purposes of statistical analysis, irritation scores were reduced to one summary score: the subject's mean irritation score. The analysis was conducted on 2 data sets: first, excluding all subjects who discontinued the study prematurely, and second, including those subjects. Subject's mean irritation scores were analyzed using the analysis of variance (ANOVA) including effects of subject and product. Product comparisons were made at the 5% level based on Fisher's least significant differences (Fisher, R A: *Statistical Methods and Scientific Inference, New York: Hafner Publishing Company, Inc 1956)* [John Wiley & Sons, 1980, 2nd ed]. Mean scores (and standard deviations) were presented in decreasing order of severity by product (See Appendix V).

4.0 STUDY MATERIAL

4.1 STORAGE, HANDLING, AND DOCUMENTATION OF STUDY MATERIAL

Receipt of the material used in this study was documented in a general logbook, which serves as a permanent record of the receipt, storage, and disposition of all study material received by TKL. On the basis of information provided by the Sponsor, the study material was considered reasonably safe for evaluation on human subjects. A sample of the study material was reserved and will be stored for a period of 6 months. All study material is kept in a locked product storage room accessible to clinical staff members only. At the conclusion of the clinical study, the remaining study material was returned to the Sponsor and the disposition documented in the logbook. Study solutions were discarded after use.

4.2 NATURE OF STUDY MATERIAL

Product Category: Bar Soap

Sample Number	PDM Number	Test Concentration	Patch Condition	Amount Applied
138517	1*68004	1.0% w/v aqueous solution	Semi-Occlusive	0.2 mL
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Special Instructions: All of the products were prepared fresh daily as 1.0% w/v aqueous solutions. Products were mixed well until dissolved, using stir bars on heated stir plate. Study material was applied to the patch pad no longer than 30 minutes prior to patch application. Replacement patches were made for those which began to dry out.

4.3 APPLICATION OF STUDY MATERIAL

The sponsor supplied all study materials except sodium lauryl sulfate. Study solutions were prepared fresh daily, as needed (see Sample Preparation, Appendix I of the protocol [Appendix IV of the report]). A 0.2 mL or g aliquot (or an amount sufficient to cover patch) of the study material/solution was applied to the patches. The patches were applied to the infrascapular area of the back, either to the right or left of the midline according to the randomization schedule (see Randomization, Appendix V of the protocol). Study samples and prepared solutions (if required) were stored at room temperature. SLS, 1.0% w/v aqueous solution, applied under semi-occlusive conditions served as a positive control.

4.4 PATCH DEFINITIONS

Material evaluated under occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patch is secured with hypoallergenic tape (Micropore), as needed.

Material evaluated under semi-occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad. The pad is affixed to the skin with hypoallergenic tape (Micropore).

5.0 INTERPRETATION

Cutaneous irritation accounts for the majority of cases of contact dermatitis. Reactions consist of local inflammatory responses characterized by erythema and/or edema, or an erosive reaction characterized by local tissue destruction or necrosis. These reactions are due to direct damage to the epidermal cells and require no prior sensitization. No immunologic (allergic) mechanism is involved.

To qualify as an “irritant”, a substance should evoke inflammation on initial exposure (primary irritation) or on repeated exposure to an identical site (cumulative irritation). An irritant substance will cause dermatitis if it is permitted to act in sufficient concentration for a sufficient length of time. Irritant reactions may develop in all subjects, although individual susceptibility varies greatly.

Cumulative irritancy patch testing can detect weak irritants that require multiple applications to produce skin irritation. During and after first contacts with weak irritants, no visible skin alterations are observed. After repeated contact, the skin gradually becomes erythematous; drying and cracking occur; and later, oozing, crusting, and erosion may develop. An eczematous reaction with papules, vesicles, and edema may also develop.

The procedure employed is a modification of that described by Dr. B. M. Lanman[1] at the Joint Conference on Cosmetic Sciences, April 21-23, 1968 in Washington, DC, and further modified by Phillips, et al[2] and Berger, et al.[3]

6.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) are designed to identify each subject by subject number and initials, and to record demographics, examination results, AEs, and end of study status. Originals or copies of all CRFs, correspondence, study reports, and all source data will be kept on hard-copy file for a

minimum of 5 years from completion of the study. Storage is maintained either at a TKL facility in a secured room accessible only to TKL employees, or at an offsite location that provides a secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. Documentation is available for the Sponsor's review on the premises of TKL.

7.0 RESULTS & DISCUSSION

Thirty (30) subjects between the ages of 20 and 75 were enrolled and 29 completed the study. One subject (No. 016) was lost to follow-up and yielded no-post-treatment data. Therefore, the "All Treated" data set and the "Completed" data set comprise 29 subjects (see Tables 1 and 2 in Appendix I and Data Listings 1 and 2 in Appendix II).
This study determined the following irritation scores for all treated and completed subjects:

Irritation Scores for Products and Positive Control on All Subjects Treated and Completed

Sample No.	Irritation Scores (n=29 All Treated and Completed)		
	Total *	Normalized **	Mean ***
SLS 1.0%	106.0	36.6	0.91 [b]
138517	2.0	0.7	0.02 [a]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

NOTE: Means with the same superscripts are not statistically different at $P<0.05$. The analyses of these data are performed using within subject analysis of variance (ANOVA). Product comparisons were made at the 5% level based on Fisher's least significant differences.

* The Total Irritation Score is the sum of all scores for reactions observed in all subjects at all evaluation times.

** The Normalized Score is the Total Irritation Score for each test product divided by the total number of readings for all subjects and multiplied, first by the number of evaluations, and then by 10 (to normalize to 10 subjects).

*** The Mean Irritation Score for each subject/product is the sum of all scores for the subject/product divided by the number of readings for the subject/product.

There were no AEs reported.

The Dermatologist was in attendance on Study Day 5.

A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3, Appendix II. A statistical analysis summary is presented in Appendix V.

8.0 CONCLUSION

All of the tested products were statistically significantly less irritating than the positive control, 1.0% SLS. There were no other statistically significant differences between the products.

9.0 REFERENCES

1 B.M. Lanman, E.B. Elvers and C.J. Howard. "The Role of Human Patch Testing in a Product Development Program" Joint Conference on Cosmetic Sciences, The Toilet Goods Association, Washington, D.C., April 21-23, 1968.

2 L. Philips, M. Steinberg, H.I. Maibach and W.A. Akers. "Comparison of Rabbit and Human Skin Response to Certain Irritants". Toxicol. Appl. Pharmacol. 21.369, 1972.

3 R.S. Berger and J.P. Bowman. "A Reappraisal of the 21-day Cumulative Irritation Test in Man" J. Toxicol. - Cut. & Ocular Toxical. 1 (2). 109-115, 1982.

[redacted]R

APPENDIX I

SUMMARY TABLES

Table 1: Summary of Subject Enrollment and Disposition

	N (%)
Subjects enrolled	30
Subjects completed all phases	29 (96.7)
Total subjects discontinued	1 (3.3)
Lost to follow-up	1 (3.3)

Note: All percentages are relative to total subjects enrolled.

See data listing 1 for further detail.

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PRODUCT = R

Table 2: Summary of Subject Demographics
All Enrolled Subjects

Age	
N (%) 18 to 44	10 (33.3)
N (%) 45 to 65	15 (50.0)
N (%) 66 and up	5 (16.7)
Mean (SD)	50.5 (16.0)
Median	51.0
Range	20.9 to 75.2
Gender	
N (%) Male	7 (23.3)
N (%) Female	23 (76.7)
Race	
Asian	1 (3.3)
Black	5 (16.7)
Caucasian	19 (63.3)
Hispanic	5 (16.7)

See data listing 2 for further detail.

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PRODUCT = R

TKL Study No.

Table 3: Summary of Dermatologic Response Grades
Number of Subjects by Product

Product = SAMPLE NO. 138517

	Reading No.			
Response	**1**	**2**	**3**	**4**
-	28	28	29	29
?	1	1	0	0
Total evaluable	29	29	29	29
Number discontinued	1	1	1	1

See Table 3.1 for Key to Symbols and Scores

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PRODUCT = R

TKL RESEARCH
TKL Study No.

Table 3: Summary of Dermatologic Response Grades
Number of Subjects by Product

Product = SLS 1.0% LOT# 000844251

	Reading No.			
Response	**1**	**2**	**3**	**4**
-	22	19	3	0
?	6	9	23	2
+	1	1	3	25
+D	0	0	0	2
Total evaluable	29	29	29	29
Number discontinued	1	1	1	1

See Table 3.1 for Key to Symbols and Scores

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PRODUCT = R

TKL Study No. [redacted]

Table 3.1: Key To Symbols and Scores

Symbol	Response
-	No visable reaction
- with p, pv, or combinations thereof	Papular (p) or papulovesicular (pv)
?	Minimal or doubtful erythema (slightly different from surrounding normal skin)
? with p, pv, or combinations thereof	Minimal or doubtful erythema accompanied by papular or papulovesicular response
+	Definite erythema
+ with p, pv, or combinations thereof	Definite erythema accompanied by papular or papulovesicular response
++, +++	Definite erythema and definite edema (++) with vesicles (+++)
+D, ++D, +++D	Definite erythema with or without edema and severe damage to epidermis characterized by crusting, superficial erosions, or oozing (D)

APPENDIX II

DATA LISTINGS

TKL STUDY NO. [redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates					
Subject No.	Screened	1st Applic	Ended	Last Reading #	Completion Status	Days in Study
001	07/20/15	07/20/15	07/24/15	4	C	5
002	07/20/15	07/20/15	07/24/15	4	C	5
003	07/20/15	07/20/15	07/24/15	4	C	5
004	07/20/15	07/20/15	07/24/15	4	C	5
005	07/20/15	07/20/15	07/24/15	4	C	5
006	07/20/15	07/20/15	07/24/15	4	C	5
007	07/20/15	07/20/15	07/24/15	4	C	5
008	07/20/15	07/20/15	07/24/15	4	C	5
009	07/20/15	07/20/15	07/24/15	4	C	5
010	07/20/15	07/20/15	07/24/15	4	C	5
011	07/20/15	07/20/15	07/24/15	4	C	5
012	07/20/15	07/20/15	07/24/15	4	C	5
013	07/20/15	07/20/15	07/24/15	4	C	5
014	07/20/15	07/20/15	07/24/15	4	C	5
015	07/20/15	07/20/15	07/24/15	4	C	5
016	07/20/15	07/20/15	07/21/15	0	L	2
017	07/20/15	07/20/15	07/24/15	4	C	5
018	07/20/15	07/20/15	07/24/15	4	C	5
019	07/20/15	07/20/15	07/24/15	4	C	5
020	07/20/15	07/20/15	07/24/15	4	C	5
021	07/20/15	07/20/15	07/24/15	4	C	5
022	07/20/15	07/20/15	07/24/15	4	C	5
023	07/20/15	07/20/15	07/24/15	4	C	5
024	07/20/15	07/20/15	07/24/15	4	C	5
025	07/20/15	07/20/15	07/24/15	4	C	5
026	07/20/15	07/20/15	07/24/15	4	C	5
027	07/20/15	07/20/15	07/24/15	4	C	5
028	07/20/15	07/20/15	07/24/15	4	C	5
029	07/20/15	07/20/15	07/24/15	4	C	5
030	07/20/15	07/20/15	07/24/15	4	C	5

Key: Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Race
001	64.3	Female	Caucasian
002	63.8	Female	Caucasian
003	57.9	Female	Caucasian
004	40.0	Female	Caucasian
005	70.4	Female	Caucasian
006	57.8	Female	Caucasian
007	63.9	Male	Caucasian
008	56.8	Female	Hispanic
009	75.2	Female	Caucasian
010	47.5	Male	Caucasian
011	42.9	Female	Hispanic
012	68.5	Male	Caucasian
013	48.8	Female	Caucasian
014	53.1	Male	Black
015	24.5	Male	Hispanic
016	22.7	Female	Hispanic
017	41.2	Female	Hispanic
018	58.5	Female	Caucasian
019	42.2	Female	Caucasian
020	45.6	Female	Caucasian
021	30.5	Female	Asian
022	64.4	Female	Caucasian
023	72.2	Female	Caucasian
024	46.3	Female	Caucasian
025	59.0	Female	Black
026	25.4	Male	Black
027	32.5	Male	Black
028	72.3	Female	Caucasian
029	20.9	Female	Black
030	46.2	Female	Caucasian

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Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = SAMPLE NO. 138517

Subject Number	Reading No. 1	2	3	4	Total Score
001	-	-	-	-	0
002	-	-	-	-	0
003	-	-	-	-	0
004	-	-	-	-	0
005	-	-	-	-	0
006	-	-	-	-	0
007	-	-	-	-	0
008	-	-	-	-	0
009	-	-	-	-	0
010	-	-	-	-	0
011	-	-	-	-	0
012	-	-	-	-	0
013	-	-	-	-	0
014	-	-	-	-	0
015	-	-	-	-	0
016	X	X	X	X	
017	-	-	-	-	0
018	-	-	-	-	0
019	-	-	-	-	0
020	-	-	-	-	0
021	-	-	-	-	0
022	?	?	-	-	2
023	-	-	-	-	0
024	-	-	-	-	0
025	-	-	-	-	0
026	-	-	-	-	0
027	-	-	-	-	0
028	-	-	-	-	0
029	-	-	-	-	0
030	-	-	-	-	0

Total Score: 2.0
Normalized Total Score: 0.7

See Table 3.1 for Key to Symbols and Scores

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PRODUCT = R

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = SLS 1.0% LOT# 000844251

Subject Number	Reading No. 1	2	3	4	Total Score
001	?	?	?	+	5
002	-	-	?	+	3
003	-	-	?	+	3
004	?	?	?	+	5
005	-	-	?	+	3
006	?	?	?	+	5
007	-	-	?	+	3
008	-	-	?	+	3
009	-	-	?	+	3
010	-	-	?	+	3
011	-	?	?	+	4
012	-	-	?	+	3
013	-	-	-	+	2
014	?	?	?	+	5
015	-	?	+	+D	6
016	X	X	X	X	
017	-	-	-	+	2
018	-	-	?	+	3
019	-	?	?	+	4
020	-	-	?	+	3
021	-	-	?	+	3
022	?	?	?	+	5
023	-	-	?	+	3
024	?	?	?	+	5
025	-	-	?	?	2
026	-	-	?	+	3
027	-	-	-	?	1
028	+	+	+	+D	9
029	-	-	+	+	4
030	-	-	?	+	3

Total Score: 106.0
Normalized Total Score: 36.6

See Table 3.1 for Key to Symbols and Scores

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PRODUCT = R

5-DAY CUMULATIVE IRRITATION PATCH TEST IN SUBJECTS WITH NORMAL SKIN

PROTOCOL NO. TKL-3500

TALCUM POWDERS

Product 140399 contains 0.0003% Carica Papaya (Papaya) Fruit Extract

TKL STUDY NO. [redacted]

[redacted] **STUDY NO. DCR#** [redacted]

CONDUCTED FOR:

[redacted]

DATE OF FINAL REPORT:

September 9, 2016

TABLE OF CONTENTS

SIGNATURES

This study was conducted in compliance with the requirements of the protocol and TKL's Standard Operating Procedures, and in the spirit of GCP ICH Topic E6.[1] The report accurately reflects the raw data for this study.

_____ _____

Jonathan S. Dosik, MD Date
Dermatologist
Principal Investigator

_____ _____

Michelle Medina Date
Manager, Dermatologic Safety Testing

STATEMENT OF QUALITY CONTROL

The Quality Control Unit of the Dermatological Safety Department conducted a 100% review of all study-related documents. The protocol was reviewed prior to the start of the study, and the medical screening forms and informed consent documents were reviewed in-process of the study. The regulatory binder and study data were reviewed post-study to ensure accuracy. The study report was reviewed and accurately reflects the data for this study.

[1] ICH Topic E6 "Note for guidance on Good Clinical Practices (CPMP/ICH/135/95)" – ICH Harmonised Tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996.

TITLE OF STUDY

5-Day Cumulative Irritation Patch Test in Subjects with Normal Skin

SPONSOR

[redacted]

STUDY MATERIALS

Product Category: Talcum Powders

Sample Number	PDM Number
[redacted]	[redacted]
[redacted]	[redacted]
140399	100000149115/000/000
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

DATE STUDY INITIATED

July 25, 2016

DATE STUDY COMPLETED

July 29, 2016

DATE OF FINAL REPORT

September 9, 2016

INVESTIGATIVE PERSONNEL

Jonathan S. Dosik, MD
Board-certified Dermatologist
Principal Investigator

Michelle Medina
Manager, Dermatologic Safety Testing

CLINICAL SITE

TKL RESEARCH, INC
One Promenade Blvd, Suite 1101
Fair Lawn, NJ 07410

SUMMARY

Ten (10) study materials, Sample Nos. [redacted], 140399, [redacted], [redacted] were evaluated as neat using an occlusive 5-day cumulative irritation patch study to determine their ability to cause irritation to subjects with normal skin. Sodium lauryl sulfate (SLS), 0.2% w/v aqueous solution, applied occlusively served as a positive control. Twenty-seven (27) subjects completed the study. The Dermatologist observed reactions on Study Day 5.

This study determined the following irritation scores for all treated and completed subjects:

Irritation Scores for Products and Positive Control on All Subjects Treated and Completed

Sample No.	Irritation Scores (n=27 All Treated and Completed)		
	Total *	**Normalized ****	**Mean *****
SLS 0.2%	71.0	26.3	0.66 [b]
[redacted]	[redacted]	[redacted]	[redacted]
140399	1.0	0.4	0.01 [a]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

NOTE: Means with the same superscripts are not statistically different at $P<0.05$. The analyses of these data are performed using within subject analysis of variance (ANOVA). Product comparisons were made at the 5% level based on Fisher's least significant differences.

* The Total Irritation Score is the sum of all scores for reactions observed in all subjects at all evaluation times.

** The Normalized Score is the Total Irritation Score for each test product divided by the total number of readings for all subjects and multiplied, first by the number of evaluations, and then by 10 (to normalize to 10 subjects).

*** The Mean Irritation Score for each subject/product is the sum of all scores for the subject/product divided by the number of readings for the subject/product.

**** For Sample No. 140400, 26 subjects are included instead of the 27 subjects for all other products due to a protocol deviation where the evaluator inadvertently did not record the readings for Subject No. 012 during all the evaluations.

All of the tested study materials were statistically significantly less irritating than the positive control, 0.2% SLS. There were no other statistically significant differences between the study materials.

1.0 OBJECTIVE

The objective of the study was to determine the ability of the study materials to cause irritation to the skin of humans under controlled patch study conditions.

2.0 RATIONALE

Cumulative irritancy patch testing is a modified primary irritancy patch test that can detect weak irritants, which require multiple applications to cause a skin reaction. These reactions are due to direct damage to the epidermal cells and no immunologic (allergic) mechanism is involved. This procedure may detect so-called "fatiguing substances" which are mild irritants that cause more strongly positive reactions with successive multiple skin exposure.

3.0 STUDY DESIGN

3.1 STUDY POPULATION

A sufficient number of subjects with normal skin were enrolled to provide 25 completed subjects.

3.1.1 Inclusion Criteria

Individuals eligible for inclusion in the study were those who:

1. Were males or females 18 years of age or older (no more than 20% over age 65), in general good health;
2. Had normal skin;
3. Were free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events (AEs);
4. Were of any skin type or race providing the skin pigmentation allowed discernment of erythema;
5. Had completed a medical screening procedure; and
6. Had read, understood, and signed an informed consent (IC) agreement.

3.1.2 Exclusion Criteria

Individuals excluded from participation were those who:

1. Had any visible skin disease at the study site (back) which, in the opinion of the investigative personnel, would have interfered with the evaluation;
2. Were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results;
3. Were being treated for asthma (non-steroidal was permitted) or experiencing an asthmatic attack;
4. Had psoriasis and/or active atopic dermatitis/eczema;

5 Were females who were pregnant, planning to become pregnant during the study, or breastfeeding;

6. Had a known sensitivity to a cosmetic, skin care products, shampoos, shower gel/body washes, antiperspirants/deodorants, fragrances, soaps, detergents, fabric softeners, dish liquid, sunscreens, fibers, medications, insect repellents, antimicrobials or topical drugs as related to the material being evaluated;

7. Were or may have been immunologically compromised; and/or

8. Were insulin-dependent diabetics.

3.1.3 Informed Consent

A properly executed IC document was obtained from each subject prior to entering the study. The signed IC document is maintained in the study file. In addition, the subject was provided with a copy of the IC document. A sample is included as Appendix III.

3.2 DESCRIPTION OF STUDY

3.2.1 Outline of Study Procedures

The study extended over a 5-day period with 4 evaluations. On Day 1, the study material and the positive control were applied to the designated patch sites. Twenty-four hours later the patches were removed and the sites evaluated following removal of residue by lightly wiping the areas with a tissue. If the skin had not been disrupted, identical patches were applied to the same sites. This was repeated daily for a period of 3 days for a total of 4 applications. The Dermatologist was in attendance for one evaluation visit. The Dermatologist reviewed the raw data at the conclusion of the study.

3.2.2 Study Flow Chart

DAY ACTIVITIES

1 Obtained IC, reviewed completed medical screening form, applied patches

2, 3, 4 Staff removed patches, graded, applied patches

5 Staff removed patches, graded

3.2.3 Method for Grading Responses

The symbols found in the data accompanying this report were used to express the response observed at the time of the examination. Each reaction obtained was assigned a numerical equivalent. See table below.

Symbol	Response	Numerical Equivalent
-	No visible reaction	0
- with p, pv, or combinations thereof	Papular (p) or papulovesicular (pv) response without erythema	0.5

?	Minimal or doubtful erythema (slightly different from surrounding normal skin)	1.0
? with p, pv, or combinations thereof	Minimal or doubtful erythema accompanied by papular or papulovesicular response	1.5
+	Definite erythema	2.0
+ with p pv, or combinations thereof	Definite erythema, accompanied by papular or papulovesicular response	2.5
++, +++	Definite erythema and definite edema (++) with vesicles (+++)	3.0
+D, ++D, +++D	Definite erythema with or without edema and severe damage to epidermis characterized by crusting, superficial erosions, or oozing (D)	3.0

The maximum obtainable individual score was 3.0. When a "++", "+++", "+D", "++D" or "+++D" reaction occurred at any point during the study, further patch application on that subject was terminated with respect to the product involved. An "NP" symbol and a score of 3.0 were assigned to all subsequent days.

A total irritation score for each product was calculated by summing each individual's scores on each of 4 evaluation days. The normalized score per product is the total score divided by the total number of readings for all subjects and multiplied by 4 (the number of days) and by 10 (to normalize to 10 subjects). Since these irritation scores were based on 4 applications of product, no attempt was made to classify these materials as to their irritation potential. A full 21-day cumulative irritation patch evaluation would have to be employed in order to precisely determine the irritation classification of each product.

3.2.4 Evaluation of Responses

All responses were graded by a trained dermatologic evaluator meeting TKL's strict certification requirements to standardize the assignment of response grades.

3.2.5 Statistical Analysis

For the purposes of statistical analysis, irritation scores were reduced to one summary score: the subject's mean irritation score. The analysis was conducted on 2 data sets: first, excluding all subjects who discontinued the study prematurely, and second, including those subjects. Subject's mean irritation scores were analyzed using the analysis of variance (ANOVA) including effects of subject and product. Product comparisons were made at the 5% level based on Fisher's least significant differences (Fisher, R A: *Statistical Methods and Scientific Inference, New York: Hafner Publishing Company, Inc 1956)* [John Wiley & Sons, 1980, 2nd ed]. Mean scores (and standard deviations) were presented in decreasing order of severity by product (See Appendix V).

4.0 STUDY MATERIAL

4.1 STORAGE, HANDLING, AND DOCUMENTATION OF STUDY MATERIAL

Receipt of the material used in this study was documented in a general logbook, which serves as a permanent record of the receipt, storage, and disposition of all study material received by TKL. On

the basis of information provided by the Sponsor, the study material was considered reasonably safe for evaluation on human subjects. A sample of the study material was reserved and will be stored for a period of 6 months. All study material is kept in a locked product storage room accessible to clinical staff members only. At the conclusion of the clinical study, the remaining study material was returned to the Sponsor and the disposition documented in the logbook. Study solutions were discarded after use.

4.2 NATURE OF STUDY MATERIAL

Product Category: Talcum Powders

Sample Number	PDM Number	Test Concentration	Patch Condition	Amount Applied
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
140399	100000149115/000/000	Neat	Occlusive	0.2mL
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Special Instructions: The patch pads were moistened with 0.2mL of distilled water. A sufficient amount of product to cover the patch pad was pressed into the moistened patch pad using a spatula. Study material was applied to the patch pad no longer than 30 minutes prior to patch application. Replacement patches were made for those which began to dry out.

4.3 APPLICATION OF STUDY MATERIAL

The sponsor supplied all study materials except sodium lauryl sulfate. Study solutions were prepared fresh daily, as needed (see Sample Preparation, Appendix I of the protocol [Appendix IV of the report]). A 0.2 mL or g aliquot (or an amount sufficient to cover patch) of the study material/solution was applied to the patches. The patches were applied to the infrascapular area of the back, either to the right or left of the midline according to the randomization schedule (see Randomization, Appendix V of the protocol). Study samples and prepared solutions (if required)

were stored at room temperature. SLS, 0.2% w/v aqueous solution, applied under occlusive conditions served as a positive control.

4.4 PATCH DEFINITIONS

Material evaluated under occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patch is secured with hypoallergenic tape (Micropore), as needed.

Material evaluated under semi-occlusive patch conditions is applied to a 2 cm x 2 cm Webril™ pad. The pad is affixed to the skin with hypoallergenic tape (Micropore).

5.0 INTERPRETATION

Cutaneous irritation accounts for the majority of cases of contact dermatitis. Reactions consist of local inflammatory responses characterized by erythema and/or edema, or an erosive reaction characterized by local tissue destruction or necrosis. These reactions are due to direct damage to the epidermal cells and require no prior sensitization. No immunologic (allergic) mechanism is involved.

To qualify as an "irritant", a substance should evoke inflammation on initial exposure (primary irritation) or on repeated exposure to an identical site (cumulative irritation). An irritant substance will cause dermatitis if it is permitted to act in sufficient concentration for a sufficient length of time. Irritant reactions may develop in all subjects, although individual susceptibility varies greatly.

Cumulative irritancy patch testing can detect weak irritants that require multiple applications to produce skin irritation. During and after first contacts with weak irritants, no visible skin alterations are observed. After repeated contact, the skin gradually becomes erythematous; drying and cracking occur; and later, oozing, crusting, and erosion may develop. An eczematous reaction with papules, vesicles, and edema may also develop.

The procedure employed is a modification of that described by Dr. B. M. Lanman[1] at the Joint Conference on Cosmetic Sciences, April 21-23, 1968 in Washington, DC, and further modified by Phillips, et al[2] and Berger, et al.[3]

6.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) are designed to identify each subject by subject number and initials, and to record demographics, examination results, AEs, and end of study status. Originals or copies of all CRFs, correspondence, study reports, and all source data will be kept on hard-copy file for a minimum of 5 years from completion of the study. Storage is maintained either at a TKL facility in a secured room accessible only to TKL employees, or at an offsite location that provides a secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. Documentation is available for the Sponsor's review on the premises of TKL.

7.0 RESULTS & DISCUSSION

Twenty-seven (27) subjects between the ages of 19 and 71 were enrolled and completed the study. Therefore, the "All Treated" data set and the "Completed" data set contains information on 27 subjects (see Tables 1 and 2 in Appendix I and Data Listings 1 and 2 in Appendix II).
This study determined the following irritation scores for all treated and completed subjects:

Irritation Scores for Products and Positive Control on All Subjects Treated and Completed

Sample No.	Irritation Scores (n=27 All Treated and Completed)		
	Total *	Normalized **	Mean ***
SLS 0.2%	71.0	26.3	0.66 [b]
[redacted]	[redacted]	[redacted]	[redacted]
140399	1.0	0.4	0.01 [a]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

NOTE: Means with the same superscripts are not statistically different at $P<0.05$. The analyses of these data are performed using within subject analysis of variance (ANOVA). Product comparisons were made at the 5% level based on Fisher's least significant differences.

* The Total Irritation Score is the sum of all scores for reactions observed in all subjects at all evaluation times.

** The Normalized Score is the Total Irritation Score for each test product divided by the total number of readings for all subjects and multiplied, first by the number of evaluations, and then by 10 (to normalize to 10 subjects).

*** The Mean Irritation Score for each subject/product is the sum of all scores for the subject/product divided by the number of readings for the subject/product.

**** For Sample No. 140400, 26 subjects are included instead of the 27 subjects for all other products due to a protocol deviation where the evaluator inadvertently did not record the readings for Subject No. 012 during all the evaluations.

There were no adverse events (AEs) reported during the study.

For Sample No. 140400 Subject No. 012 did not receive readings for all four (4) evaluations. The evaluator inadvertently did not record the subject's readings. This is a deviation from the protocol-specified requirement of recording each reading at the time of evaluation. This deviation did not affect the validity of the study.

The Dermatologist was in attendance on Study Day 5.
A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3, Appendix II. A statistical analysis summary is presented in Appendix V.

8.0 CONCLUSION

All of the tested study materials were statistically significantly less irritating than the positive control, 0.2% SLS. There were no other statistically significant differences between the study materials.

9.0 REFERENCES

1 B.M. Lanman, E.B. Elvers and C.J. Howard. "The Role of Human Patch Testing in a Product Development Program" Joint Conference on Cosmetic Sciences, The Toilet Goods Association, Washington, D.C., April 21-23, 1968.

2 L. Philips, M. Steinberg, H.I. Maibach and W.A. Akers. "Comparison of Rabbit and Human Skin Response to Certain Irritants". Toxicol. Appl. Pharmacol. 21.369, 1972.

3 R.S. Berger and J.P. Bowman. "A Reappraisal of the 21-day Cumulative Irritation Test in Man" J. Toxicol. - Cut. & Ocular Toxical. 1 (2). 109-115, 1982.

[redacted]

APPENDIX I

SUMMARY TABLES

TKL Study No. [redacted]

Table 1: Summary of Subject Enrollment and Disposition

	N (%)
Subjects enrolled	27
Subjects completed all phases	27 (100.0)

Note: All percentages are relative to total subjects enrolled.

See data listing 1 for further detail.

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PRODUCT = R

Table 2: Summary of Subject Demographics
All Enrolled Subjects

Age	
N (%) 18 to 44	10 (37.0)
N (%) 45 to 65	12 (44.4)
N (%) 66 and up	5 (18.5)
Mean (SD)	49.6 (16.3)
Median	54.4
Range	19.3 to 71.6
Gender	
N (%) Male	6 (22.2)
N (%) Female	21 (77.8)
Race	
Asian	1 (3.7)
Black	4 (14.8)
Caucasian	16 (59.3)
Hispanic	6 (22.2)

See data listing 2 for further detail.

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TKL Study No.

Table 3: Summary of Dermatologic Response Grades
Number of Subjects by Product

Product = SAMPLE NO. 140399

	Reading No.			
Response	**1**	**2**	**3**	**4**
-	27	27	27	26
?	0	0	0	1
Total evaluable	27	27	27	27

See Table 3.1 for Key to Symbols and Scores

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PRODUCT = R

TKL RESEARCH
TKL Study No.

Table 3: Summary of Dermatologic Response Grades
Number of Subjects by Product

Product = SLS 0.2% LOT# 0012453971

	Reading No.			
Response	**1**	**2**	**3**	**4**
-	27	24	9	0
?	0	2	14	10
+	0	1	4	16
+D	0	0	0	1
Total evaluable	27	27	27	27

See Table 3.1 for Key to Symbols and Scores

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PRODUCT = R

TKL Study No. [redacted]

Table 3.1: Key To Symbols and Scores

Symbol	Response
-	No visable reaction
- with p, pv, or combinations thereof	Papular (p) or papulovesicular (pv)
?	Minimal or doubtful erythema (slightly different from surrounding normal skin)
? with p, pv, or combinations thereof	Minimal or doubtful erythema accompanied by papular or papulovesicular response
+	Definite erythema
+ with p, pv, or combinations thereof	Definite erythema accompanied by papular or papulovesicular response
++, +++	Definite erythema and definite edema (++) with vesicles (+++)
+D, ++D, +++D	Definite erythema with or without edema and severe damage to epidermis characterized by crusting, superficial erosions, or oozing (D)

APPENDIX II

DATA LISTINGS

TKL STUDY NO. [redacted]

Data Listing 1: Subject Enrollment and Disposition

	Study Dates					
Subject No.	Screened	1st Applic	Ended	Last Reading #	Completion Status	Days in Study
001	07/25/16	07/25/16	07/29/16	4	C	5
002	07/25/16	07/25/16	07/29/16	4	C	5
003	07/25/16	07/25/16	07/29/16	4	C	5
004	07/25/16	07/25/16	07/29/16	4	C	5
005	07/25/16	07/25/16	07/29/16	4	C	5
006	07/25/16	07/25/16	07/29/16	4	C	5
007	07/25/16	07/25/16	07/29/16	4	C	5
008	07/25/16	07/25/16	07/29/16	4	C	5
009	07/25/16	07/25/16	07/29/16	4	C	5
010	07/25/16	07/25/16	07/29/16	4	C	5
011	07/25/16	07/25/16	07/29/16	4	C	5
012	07/25/16	07/25/16	07/29/16	4	C	5
013	07/25/16	07/25/16	07/29/16	4	C	5
014	07/25/16	07/25/16	07/29/16	4	C	5
015	07/25/16	07/25/16	07/29/16	4	C	5
016	07/25/16	07/25/16	07/29/16	4	C	5
017	07/25/16	07/25/16	07/29/16	4	C	5
018	07/25/16	07/25/16	07/29/16	4	C	5
019	07/25/16	07/25/16	07/29/16	4	C	5
020	07/25/16	07/25/16	07/29/16	4	C	5
021	07/25/16	07/25/16	07/29/16	4	C	5
022	07/25/16	07/25/16	07/29/16	4	C	5
023	07/25/16	07/25/16	07/29/16	4	C	5
024	07/25/16	07/25/16	07/29/16	4	C	5
025	07/25/16	07/25/16	07/29/16	4	C	5
026	07/25/16	07/25/16	07/29/16	4	C	5
027	07/25/16	07/25/16	07/29/16	4	C	5

Key: Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Race
001	68.1	Female	Caucasian
002	69.2	Female	Caucasian
003	69.5	Male	Caucasian
004	65.3	Female	Caucasian
005	71.6	Female	Caucasian
006	46.4	Female	Caucasian
007	26.0	Female	Hispanic
008	35.6	Female	Hispanic
009	54.4	Female	Asian
010	55.5	Male	Black
011	54.8	Female	Caucasian
012	58.8	Male	Black
013	28.6	Male	Black
014	31.0	Female	Caucasian
015	52.1	Male	Caucasian
016	44.5	Female	Black
017	68.3	Female	Caucasian
018	64.5	Male	Caucasian
019	25.3	Female	Hispanic
020	21.8	Female	Hispanic
021	44.1	Female	Hispanic
022	38.8	Female	Caucasian
023	62.7	Female	Hispanic
024	19.3	Female	Caucasian
025	49.8	Female	Caucasian
026	55.2	Female	Caucasian
027	59.1	Female	Caucasian

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Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = SAMPLE NO. 140399

Subject Number	Reading No. 1	2	3	4	Total Score
001	-	-	-	-	0
002	-	-	-	-	0
003	-	-	-	-	0
004	-	-	-	-	0
005	-	-	-	-	0
006	-	-	-	-	0
007	-	-	-	-	0
008	-	-	-	-	0
009	-	-	-	-	0
010	-	-	-	-	0
011	-	-	-	-	0
012	-	-	-	-	0
013	-	-	-	-	0
014	-	-	-	-	0
015	-	-	-	-	0
016	-	-	-	-	0
017	-	-	-	-	0
018	-	-	-	-	0
019	-	-	-	-	0
020	-	-	-	-	0
021	-	-	-	-	0
022	-	-	-	?	1
023	-	-	-	-	0
024	-	-	-	-	0
025	-	-	-	-	0
026	-	-	-	-	0
027	-	-	-	-	0

Total Score: 1.0
Normalized Total Score: 0.4

See Table 3.1 for Key to Symbols and Scores

Generated on 08/01/16:11:46 by DETAIL2.SAS / Uses: RESP4, PRODLIST
PRODUCT = R

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = SLS 0.2% LOT# 0012453971

Subject Number	Reading No. 1	2	3	4	Total Score
001	-	-	-	?	1
002	-	-	-	?	1
003	-	-	-	?	1
004	-	-	?	+	3
005	-	-	-	?	1
006	-	-	?	+	3
007	-	-	?	+	3
008	-	-	?	+	3
009	-	-	+	+	4
010	-	?	+	+	5
011	-	+	+	+D	7
012	-	-	?	+	3
013	-	-	-	?	1
014	-	-	?	+	3
015	-	-	?	+	3
016	-	-	?	+	3
017	-	-	?	+	3
018	-	-	?	+	3
019	-	?	?	?	3
020	-	-	?	?	2
021	-	-	+	+	4
022	-	-	-	+	2
023	-	-	-	?	1
024	-	-	?	+	3
025	-	-	-	?	1
026	-	-	?	+	3
027	-	-	-	?	1

Total Score: 71.0
Normalized Total Score: 26.3

See Table 3.1 for Key to Symbols and Scores

Generated on 08/01/16:11:46 by DETAIL2.SAS / Uses: RESP4, PRODLIST
PRODUCT = R

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: July 27, 2020

SUBJECT: Carica Papaya (Papaya) Fruit Extract

Anonymous. 2015. Repeated insult patch test (RIPT) - Shelanski method (product containing 0.02% Carica Papaya (Papaya) Extract).

[redacted]

Report Status:	Final Report
Report Date:	April 1, 2015
[redacted] Study Number:	[redacted]
[redacted] Protocol Number:	[redacted]
Study Dates:	February 9, 2015 - March 20, 2015
Study Title:	Repeated Insult Patch Test (RIPT) –Shelanski Method
Test Material:	[redacted]
Sponsor:	[redacted]
Sponsor Representative:	[redacted]
Investigator:	[redacted] Dermatologist

product contains 0.02% Carica Papaya (Papaya) Fruit Extract

APPROVAL SIGNATURES:

[redacted]

Investigator Signature/Date

[redacted]

Good Clinical Practice
Quality Assurance Audit Statement

Clinical Study Number: [redacted]

Start Date: February 9, 2015

Completion Date: March 20, 2015

The clinical study listed above was conducted in accordance with [redacted] Standard Operating Procedures, which incorporate the principles of Good Clinical Practice defined by applicable guidelines and regulations established by U.S. Regulatory Agencies. The conduct of the study was monitored for compliance, and the associated records, including source documents or raw data, were reviewed for documentation practices and accuracy by a Project Manager/Study Director and/or a Quality Assurance Representative. Standard Quality Assurance audit procedures for this final report and study related documents were conducted.

[redacted] ..... [redacted] .....

Quality Assurance Auditor Signature/Date

FINAL REPORT

Repeated Insult Patch Test (RIPT) - Shelanski Method

1.0 OBJECTIVE

The objective of this study was to determine the dermal irritation and sensitization potential of a test material.

2.0 INVESTIGATOR/INVESTIGATIVE SITE

[redacted]
Dermatologist

[redacted]

3.0 SPONSOR REPRESENTATIVE/SPONSOR

[redacted]

[redacted]

4.0 TEST MATERIAL

The following test material was provided by [redacted]. and was received by [redacted]. on February 2, 2015.

Test Material	Test Condition	Patch Type
[redacted]	Dilute to a 10% aqueous solution	Occlusive*

The test material was coded with the following [redacted] identification number:

[redacted]

5.0 STUDY DATES

This study was initiated on February 9, 2015 and was completed on March 20, 2015.

* Occlusive Strip with Flexcon® (Strukmyer LLC, Mesquite,TX or equivalent)

6.0 PANEL SELECTION

Each subject was assigned a permanent [redacted] identification number. All subjects signed an Informed Consent Form in compliance with 21 CFR Part 50: "Protection of Human Subjects" and a HIPAA Authorization Form in compliance with 45 CFR Parts 160 and 164. All subjects completed a Subject Profile/Medical History Form provided by [redacted] prior to the study (Subject Demographics - Appendix 1). Subjects who met the following Inclusion Criteria and none of the Exclusion Criteria were impaneled:

6.1. INCLUSION CRITERIA

a. Subject is male or female between the ages of 18 and 70 years;

b. Subject does not exhibit any skin diseases which might be confused with a skin reaction from the test material;

c. Subject agrees to avoid exposure of the test sites to the sun and to refrain from visits to tanning salons during the course of this study;

d. Subject agrees to refrain from getting patches wet during the course of the study;

e. Subject has signed an Informed Consent in conformance with 21CFR Part 50: "Protection of Human Subjects;"

f. Subject has completed a HIPAA Authorization Form in conformance with 45CFR Parts 160 and 164;

g. Subject is in generally good health and has a current Subject Profile/Medical History on file;

h. Subject is dependable and able to follow directions as outlined in the protocol.

6.2. EXCLUSION CRITERIA

a. Subject is pregnant, nursing, or planning to become pregnant;

b. Subject is currently using any systemic or topical corticosteroids, anti-inflammatory drugs, or antihistamines on a regular basis;

c. Subject reports allergies to cosmetics, toiletries, or personal care products;

d. Subject exhibits any skin disorders, sunburn, scars, excessive tattoos, etc. in the test area;

e. Subject has scheduled, or is planning to undergo, any medical or surgical procedures during the 6 week course of the study.

7.0 TEST METHOD SUMMARY

Prior to the application of the patch, the test area was wiped with 70% isopropyl alcohol and allowed to dry. The test material, which was prepared as described in the Test Material section of the report, was applied to the upper back (between the scapulae) and was allowed to remain in direct skin contact for a period of 24 hours.

Patches were applied to the same site on Monday, Wednesday, and Friday for a total of 9 applications during the Induction Period. This schedule may have been modified to allow for missed visits or holidays. If a subject was unable to report on an assigned test date, the test material was applied on 2 consecutive days during the Induction Phase and/or a makeup day was added at the end of the Induction Phase.

The sites were graded by a [redacted] technician for dermal irritation 24 hours after removal of the patches by the subjects on Tuesday and Thursday and 48 hours after removal of the patches on Saturday, unless the patching schedule was altered as described above.

The sites were graded according to the following scoring system:

Dermal Scoring Scale

0	No visible skin reaction
±	Barely perceptible erythema
1+	Mild erythema
2+	Well defined erythema
3+	Severe erythema and edema
4+	Erythema and edema with vesiculation

If a "2+" reaction or greater occurred, the test material was applied to an adjacent virgin site. If a "2+" reaction or greater occurred on the new site, the subject may not have been patched again during the Induction Phase but may have been challenged on the appropriate day of the study. At the discretion of the Study Director, patch sites with scores less than a "2+" may have been changed.

Following approximately a 2-week rest period, the challenge patches were applied to previously untreated test sites on the back. After 24 hours, the patches were removed by a [redacted] technician and the test sites were evaluated for dermal reactions. The test sites were re-evaluated at 48 and 72 hours. Subjects exhibiting reactions during the Challenge Phase of the study may have been asked to return for a 96-hour reading.

8.0 RESULTS

This study was initiated with 112 subjects. Seven subjects discontinued study participation for reasons unrelated to the test material. A total of 105 subjects completed the study.

Individual dermal scores recorded during the Induction and Challenge Phases appear in Table I.

9.0 ADVERSE EVENTS

No adverse events were reported during the study.

10.0 CONCLUSION

Based on the test population of 105 subjects and under the conditions of this study, the test material identified as [redacted] did not demonstrate a potential for eliciting dermal irritation or sensitization.

11.0 RETENTION

Test materials and all original forms of this study will be retained by [redacted] as specified in [redacted] Standard Operating Procedures 30.6 and 30.6C, unless designated otherwise by the Sponsor.

[redacted]

TABLE I

Summary of Dermal Scores

Test Material: [redacted]

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	±	±d	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0

d = Dryness

TABLE I
(Continued)

Summary of Dermal Scores

Test Material: [redacted]

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	Discontinued							
29	0	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0	0	0	0
38	0	0	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	X	0*
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	1+	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	X	Disc	

X = Subject Absent
Disc = Discontinued
*No reaction was observed at the 96 hour evaluation.

TABLE I
(Continued)

Summary of Dermal Scores

Test Material: [redacted]

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	0	0	0	0	0	0	0	0	0	0	0
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0	0	0	0	0
59	0	0	0	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0	±	±	0	0	0
61	0	0	0	0	0	0	0	0	0	0	0	0
62	0	0	0	0	0	0	0	0	0	0	0	0
63	0	0	0	0	0	0	0	0	0	0	0	0
64	0	0	0	0	0	0	0	0	0	0	0	0
65	0	Discontinued										
66	0	0	0	0	0	0	0	0	0	0	0	0
67	0	0	0	0	0	0	0	0	0	0	0	0
68	0	0	0	0	0	0	0	0	0	0	0	0
69	0	0	0	0	0	0	0	0	0	0	0	0
70	0	0	0	0	0	0	0	0	0	0	0	0
71	0	0	0	0	0	0	0	0	0	0	0	0
72	0	0	0	0	0	0	0	0	0	0	0	0
73	0	0	0	0	0	0	0	0	0	0	0	0
74	0	0	0	0	0	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0	0	0	0	0	0

[redacted]

TABLE I
(Continued)

Summary of Dermal Scores

Test Material: [redacted]

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
76	0	0	0	0	0	0	0	0	0	0	0	0
77	0	0	0	0	0	0	0	0	0	0	0	0
78	0	0	0	0	0	0	0	0	0	0	0	0
79	0	0	0	0	0	0	0	0	0	0	0	0
80	0	0	0	0	0	0	0	0	0	0	0	0
81	0	0	0	0	0	0	0	0	0	0	0	0
82	0	0	0	0	0	0	0	0	0	0	0	0
83	0	0	0	0	0	0	0	0	0	0	0	0
84	0	0	0	0	0	0	0	0	0	0	0	0
85	0	0	0	0	0	0	0	0	0	0	0	0
86	0	0	0	0	0	0	0	0	0	0	0	0
87	0	0	0	0	0	0	0	0	0	0	0	0
88	0	0	0	0	0	0	0	0	0	0	0	0
89	0	0	0	0	0	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0	0	0	0	0	0
91	0	0	0	0	0	0	0	0	0	0	0	0
92	0	0	0	0	0	0	0	0	0	0	0	0
93	0	0	0	0	0	0	0	0	0	0	0	0
94	0	0	0	0	0	0	±	0	0	0	0	0
95	0	0	0	0	0	0	0	0	0	0	0	0
96	0	0	0	0	0	0	0	0	0	0	0	0
97	0	0	0	0	0	0	0	0	0	0	0	0
98	0	0	0	0	0	0	0	0	X	0	0	0
99	0	0	0	0	0	0	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0	0	0	0	0

X = Subject Absent

TABLE I
(Continued)

Summary of Dermal Scores

Test Material: [redacted]

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
101	0	0	0	0	Discontinued							
102	0	0	0	0	0	0	0	0	0	0	0	0
103	0	0	0	0	0	0	2+C	0	0	0	0	0
104	0	0	0	0	0	0	0	0	X	0	0	0
105	0	0	0	0	0	0	0	0	0	0	0	0
106	0	0	0	0	0	0	0	0	0	0	0	0
107	0	0	0	0	Discontinued							
108	0	0	0	0	0	0	0	0	0	0	0	0
109	0	0	0	0	0	0	0	0	0	0	0	0
110	Discontinued											
111	0	0	0	Discontinued								
112	0	0	0	0	0	0	0	0	0	0	0	0

X = Subject Absent
C = Changed Site

[redacted]

Appendix I

Subject Demographics

Subject Number	Subject Initials	Age	Sex
1	LG	67	F
2	AM	51	M
3	MS	49	M
4	AM	49	F
5	VH	32	F
6	DH	46	F
7	DM	28	M
8	ER	57	F
9	MP	58	F
10	MC	59	F
11	KW	56	M
12	WG	68	F
13	FP	60	F
14	RP	63	M
15	SR	67	F
16	AH	66	M
17	AA	60	M
18	AR	48	F
19	CA	55	M
20	NS	46	F
21	BS	60	F
22	JT	25	M
23	MB	50	M
24	PA	42	M
25	MC	58	M
26	ES	63	M
27	RM	56	M
28	EA	56	F

Subject Number	Subject Initials	Age	Sex
29	MR	55	F
30	NS	39	F
31	DP	50	F
32	JQ	54	F
33	RG	46	M
34	SC	55	M
35	SH	65	F
36	MS	22	F
37	CS	45	F
38	GA	68	F
39	RA	55	F
40	LR	60	M
41	JA	21	F
42	JM	65	M
43	DK	50	M
44	RC	58	F
45	SP	31	F
46	SS	28	F
47	KP	63	F
48	KS	55	F
49	HJ	50	F
50	EM	59	M
51	SJ	29	F
52	VR	64	F
53	DM	54	F
54	KA	53	F
55	MJ	27	F
56	CC	59	F

Appendix I

Subject Demographics
(Continued)

Subject Number	Subject Initials	Age	Sex
57	SH	59	F
58	ND	54	F
59	JA	50	F
60	PB	50	F
61	ST	31	F
62	SR	60	F
63	JP	57	F
64	LB	47	F
65	LD	28	F
66	TM	46	F
67	CP	39	F
68	ML	49	F
69	MW	68	F
70	JP	23	F
71	MT	25	F
72	PA	51	M
73	JH	32	F
74	FR	50	F
75	MF	50	F
76	CY	59	F
77	LD	52	F
78	TW	42	F
79	TT	64	F
80	OH	52	M
81	NT	37	F
82	BE	58	F
83	KP	54	M
84	SB	67	F

Subject Number	Subject Initials	Age	Sex
85	AF	28	F
86	SD	34	F
87	SK	45	F
88	PC	61	F
89	DM	44	M
90	JM	33	F
91	DH	66	M
92	JB	60	F
93	CS	51	F
94	MR	47	M
95	LF	51	F
96	JM	35	M
97	MC	51	F
98	FG	49	M
99	VD	58	F
100	RD	66	M
101	SL	23	F
102	SA	20	M
103	KS	26	M
104	TW	34	M
105	SS	23	F
106	EW	25	F
107	DC	33	F
108	EM	23	F
109	LK	65	F
110	VM	60	F
111	AC	31	M
112	DP	63	F

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: September 24, 2020

SUBJECT: Carica Papaya (Papaya) Fruit Extract

TKL Research, Inc. 2019. Repeated insult patch test (product containing 0.0075% Carica Papaya (Papaya) Fruit Extract).

KGL LLC. 2019. Photocontact allergenicity assay (product containing 0.0075% Carica Papaya (Papaya) Fruit Extract).

KGL LLC. 2019. Human phototoxicity bioassay (product containing 0.0075% Carica Papaya (Papaya) Fruit Extract).

Cantor Research Laboratories, Inc. 2005. 100 Human subject repeat insult patch test (product containing 0.0586% Carica Papaya (Papaya) Fruit Extract).

Product 053 contains 0.0075% Carica Papaya (Papaya) Fruit Extract

REPEATED INSULT PATCH STUDY

TKL STUDY NO. DS101019

[redacted]

DATE OF FINAL REPORT:

April 19, 2019

[redacted]

201.587.0500 • www.tklresearch.com

TKL Research, Inc. One Promenade Boulevard, Suites 1101/1201, Fair Lawn, NJ 07410

TABLE OF CONTENTS

APPENDICES

I SUMMARY TABLES
II DATA LISTINGS
III INFORMED CONSENT DOCUMENT

SIGNATURES

This study was conducted in compliance with the requirements of the protocol and TKL's Standard Operating Procedures, and in the spirit of GCP ICH Topic E6.[1] The report accurately reflects the raw data for this study.

Jonathan S. Dosik Digitally signed by Jonathan S. Dosik Date: 2019.04.19 09:54:40 -04'00'

April 19, 2019

Jonathan S. Dosik, MD
Board Certified Dermatologist
Principal Investigator

Date

Tina LaRosa Digitally signed by Tina LaRosa Date: 2019.04.19 09:54:50 -04'00'

April 19, 2019

Tina LaRosa
Director, Dermatologic Safety Operations

Date

STATEMENT OF QUALITY CONTROL

The Quality Control Unit of the Dermatological Safety Department conducted a 100% review of all study-related documents. The protocol was reviewed prior to the start of the study, and the medical screening forms and informed consent documents were reviewed in-process of the study. The regulatory binder and study data were reviewed post-study to ensure accuracy. The study report was reviewed and accurately reflects the data for this study.

[1] ICH Topic E6 "Note for guidance on Good Clinical Practices (CPMP/ICH/135/95)" – ICH Harmonised Tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996.

TITLE OF STUDY

Repeated Insult Patch Study

[redacted]

STUDY MATERIALS

Product Code	Description
[redacted] Study # 0119113 MF# [redacted] 053 Batch # [redacted] 055	SPF 50 Lotion
[redacted] Study # 0119112 MF# [redacted] 057 Batch # [redacted] 121	SPF 50 Lotion

DATE STUDY INITIATED

January 28, 2019

DATE STUDY COMPLETED

March 7, 2019

DATE OF FINAL REPORT

April 19, 2019

INVESTIGATIVE PERSONNEL

Jonathan S. Dosik, MD – Board Certified Dermatologist
Principal Investigator

Tina LaRosa
Director, Dermatologic Safety Operations

CLINICAL SITE

TKL RESEARCH, INC
1255 Broad Street
Bloomfield, NJ 07003

SUMMARY

Two (2) study materials, MF# [redacted]053, and MF# [redacted]057, were evaluated neat to determine their potential to cause irritation and/or sensitization to the skin of volunteer subjects with normal skin using a repeated insult patch study under occlusive conditions. One hundred nineteen (119) subjects completed Induction and all 119 subjects completed the study.

Under the conditions employed in this study, there was no evidence of induced skin irritation and/or sensitization to the study materials, MF# [redacted]053, and MF# [redacted]057.

1.0 OBJECTIVE

The objective of this study was to determine the ability of the study materials to cause irritation and/or sensitization by repeated topical applications to the skin of humans under controlled patch study conditions.

2.0 RATIONALE

Substances that come into contact with human skin need to be evaluated for their propensity to cause skin irritation and/or sensitization. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to confirm that a particular test article can be applied safely to human skin without significant risk of local adverse reactions.

Repeated insult patch evaluation is a modified predictive patch study that can detect weak sensitizers that require multiple applications to induce a cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure.

3.0 STUDY DESIGN

3.1 STUDY POPULATION

One hundred twenty-six (126) volunteer subjects between the ages of 25 and 70 were enrolled to provide 100 completed subjects. Forty-five (45) subjects (35.7%) were male and 81 subjects (64.3%) were female. The majority of subjects were Black (81, 64,3%), 44 subjects (34.9%) were Caucasian, and a subject (0.8%) were of Other Race. One hundred nineteen (119) subjects (94.4%) completed the Induction Phase. One hundred nineteen (119) subjects (94.4%) completed the Challenge Phase, therefore 119 subjects completed the study. In the absence of any sensitization reaction in this sample size (with 119 evaluable subjects completed), a 95% upper confidence bound on the population rate of sensitization would be 1.5%.

3.1.1 Inclusion/Exclusion Criteria

One hundred twenty-six (126) subjects met all the Inclusion criteria and none of the Exclusion criteria.

3.1.2 Informed Consent

Prior to entering the study, a properly executed Informed Consent (IC) and medical screener forms were obtained from all 126 subjects. The signed IC form is maintained in the study file. In addition, each subject was provided with a copy of the IC form (see IRB approved IC Appendix III).

3.2 DESCRIPTION OF STUDY

3.2.1 Outline of Study Procedures

Study Material Preparation
All of the study materials received from the sponsor for this study were stored at room temperature. Prior to patch preparation, the study materials were shaken well. Each study material was applied to

the Webril patch pad in the amount of 0.2 mL. Each subject received 0.2 mL of each of the two (2) study materials and 0.2 mL of the positive control 0.2% SLS.

The Induction Phase consisted of a series of nine (9) consecutive applications of each study material under occlusive conditions and subsequent evaluations of the application sites. Fresh patches were applied on Mondays, Wednesdays, and Fridays for 3 consecutive weeks and were removed by the subjects approximately 24 hours after application. The subjects returned to the test facility at approximately 48-hour intervals to have the sites evaluated using the 8-point integer scoring system detailed in Section 3.2.3. Once all evaluations were made, identical patches of the same study material were then applied to the same sites. Patches applied on Friday were to be removed on Saturday and the sites evaluated on Monday, 72 hours after application

Subjects who were absent once during the Induction Phase received a make-up (MU) patch on the last induction visit. The MU applications were graded 48 hours later at the MU visit, or were recorded as no ninth grading (N9G). Subjects who missed the ninth evaluation (N9G) but had 9 patch applications were considered to have completed the Induction Phase. A total of 119 subjects (94.4%) completed the Induction Phase.

Subjects required 8 induction readings and 9 applications. The applications were to be conducted by the clinical staff and the subject was to remove the patch prior to being the rest phases of this study.

Rest Period
One hundred nineteen (119) subjects started a rest period of approximately 10-14 days. During this period, subjects did not have any of the study materials applied and were advised to contact TKL if any reaction, changes in their health, or change in medications occurred during the Rest Period.

Challenge Phase
At the Challenge Phase, 119 subjects were evaluable and completed the Induction Phase and 119 subjects were patched with identical patches to those used during induction applied to sites previously unexposed to the study material. The patches were removed 24 hours after application by the clinical staff. The sites were graded at 24, 48, and 72 hours after application. Following a negative induction, a 48/72-hour sequence of "0/3", "1/3", "2/3", or "3/3" would have resulted in an additional reading to be performed at the 96-hour interval.

Post Challenge patch removal 119 subjects were evaluated at the 24hr and 72hr challenge evaluations and completed the study. None of the subjects experienced reactions during the challenge evaluations in response to study materials, [redacted] Study # 0692-053 and [redacted] Study # 0692-057.

Due to the minimal reactions observed during the Challenge Phase, there was no requirement for a Rechallenge Phase. The Board-Certified Dermatologist reviewed all Challenge grades to determine the sensitization results.

To have been considered a completed case, a subject must have had 9 applications of the study material and no fewer than 8 subsequent readings during induction, and a single application and 2 readings during challenge. Only completed cases were used to assess sensitization. A total of 119 subjects (94.4%) were considered to be completed and assessed for sensitization during this study.

Rechallenge
There was no Rechallenge Phase required for this study.

3.2.2 Study Flow Chart

WEEK 1

DAY	ACTIVITIES
1[1]	Staff obtains informed consent, reviews completed medical screening form, applies patches
2	Subject removes patches
3	Staff grades sites, applies patches
4	Subject removes patches
5	Staff grades sites, applies patches
6	Subject removes patches

WEEK 2

DAY	ACTIVITIES
1	Staff grades sites, applies patches
2-6	Same as Week 1

WEEK 3

1-6	Same as Week 2

WEEK 4

1	Staff grades sites; applies make-up (MU) induction patches, if required
2	Subject removes MU induction patches
3	Staff grades MU induction sites at MU visit
2-7	Rest period

WEEK 5

1-7	Rest period

WEEK 6

1	Staff applies patches
2	Subject removes patches
3	Staff grades sites
4	Staff grades sites

[1] Study flow starting with Week 1, Day 1, will be altered when enrollment occurs other than on Monday. Study flow could be altered when a holiday occurs during the study or enrollment is other than on Monday.

3.2.3 Definitions Used for Grading Responses

The symbols found in the scoring scales below were used to express the response observed at the time of examination:

- = No reaction
? = Minimal or doubtful response, slightly different from surrounding normal skin
+ = Definite erythema, no edema
++ = Definite erythema, definite edema
+++ = Definite erythema, definite edema and vesiculation

SPECIAL NOTATIONS

E = Marked/severe erythema
S = Spreading of reaction beyond patch site (ie, reaction where material did not contact skin)
p = Papular response > 50%
pv = Papulovesicular response > 50%
D = Damage to epidermis: oozing, crusting and/or superficial erosions
I = Itching
X = Subject absent
PD = Patch dislodged
NA = Not applied
NP = Not patched (due to reaction achieved)
N9G = No ninth grading

3.2.4 Evaluation of Responses

All responses were graded by a trained dermatologic evaluator meeting TKL's strict certification requirements to standardize the assignment of response grades.

4.0 NATURE OF STUDY MATERIALS

4.1 STUDY MATERIAL DESCRIPTION

Product ID Code	Description	Amount Applied	Concentration Applied
MF# [redacted]053	SPF 50 Lotion	0.2 mL	Neat
MF# [redacted]057	SPF 50 Lotion	0.2 mL	Neat
0.2% SLS	OmniPure LOT# 17E025203	0.2 mL	0.2% w/v aqueous solution

Receipt of the two (2) study materials used in this study was documented in a general logbook, which serves as a permanent record of the receipt, storage, and disposition of all test articles received by TKL. On the basis of information provided by the Sponsor, the test articles were considered safe for evaluation on human subjects. All study materials were kept in a locked product storage room

accessible to clinical staff members only. At the conclusion of the clinical study, the remaining test articles were to be returned to the Sponsor and the disposition documented in the logbook. A sample of each study material will be retained for a period of 6 months.

4.3 APPLICATION OF STUDY MATERIALS

All study materials were supplied by the sponsor. An aliquot of 0.2 mL of the study material (neat) was used to cover the 2 cm x 2 cm patch. Fresh patches were applied to the infrascapular area of the back, left of the midline during Induction and the right of the midline during the Challenge Phase. Sodium lauryl sulfate, 0.2% aqueous solution, supplied by TKL was utilized as an irritant control patch.

4.4 DESCRIPTION OF PATCH CONDITIONS

All study materials were evaluated neat under occlusive patch conditions using a 2 cm x 2cm Webril™ pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patch was applied without air dry and secured with hypoallergenic tape (Micropore), as needed.

5.0 INTERPRETATION OF TEST MODEL

Sensitization is characterized by an acute allergic contact dermatitis. Typical sensitization reactions begin with an immunologic response in the dermis resulting in erythema, edema formation, and secondary epidermal damage (vesiculation), sometimes extending beyond the patch site and often accompanied by itching. Sensitization reactions tend to be delayed. The reaction typically becomes evident between 24 and 48 hours, peaks at 48-72 hours and subsequently subsides. The reaction is often greater at 72 hours than at 48 hours. The severity of the reaction is generally greater during the challenge phase of a Repeated Insult Patch Test (RIPT) than that seen during induction.

Irritant reactions are characterized as a non-immunologic, localized, superficial, exudative, inflammatory response of the skin due to an externally applied material. The typical initial reaction does not develop much edema or vesiculation but results in scaling, drying, cracking, oozing, crusting, and erosions. The reaction is usually sharply delineated, not spreading beyond the patch site. Irritant reactions are typically evident by 24 hours and diminish over the next 48-72 hours. Removal of the offending agent results in gradual improvement of the epidermal damage. The reaction seen at 72 hours is, therefore, less severe than that seen at 48 hours. Finally, the severity of the reaction experienced in the challenge phase is generally similar to that seen during induction.

If the results of the study indicate the likelihood of sensitization, the recommended practice is to rechallenge the subjects who have demonstrated questionable reactions to confirm that these reactions are, indeed, associated with the test article. The rechallenge test will be conducted based on consultation with the Sponsor.

6.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) were designed to identify each subject by subject number and initials, and to record demographics, examination results, AEs, and end of study status. Originals or copies of all CRFs, correspondence, study reports, and all source data will be kept on hard-copy file for a minimum of 5 years from completion of the study. Storage was maintained at either a TKL facility in a secured room accessible only to TKL employees, or at an offsite location, which provides a

secure environment with burglar/fire alarm systems, camera detection, and controlled temperature and humidity. Documentation is available for the Sponsor's review on the premises of TKL Research, Inc.

7.0 RESULTS AND DISCUSSION

7.1 SUBJECT ACCOUNTABILITY AND DEMOGRAPHICS

One hundred twenty-six (126) female and male subjects between the ages of 25 and 70 were enrolled (see Table of Demographics, Table 1) and 119 completed the study (see Table of Subject Accountability, Table 2).

The following tables summarize subject demographics (Table 1) and accountability including enrollment and disposition (Table 2):

Table 1: Table of Demographics

Age:	**(N):**	**%:**
18 to 44	18	14.3%
45 to 65	88	69.8%
66 and up	20	15.9%
Gender:	**(N):**	**%:**
Male	45	35.7%
Female	81	64.3%
Race:	**(N)**	**%:**
Black	81	64.3%
Caucasian	44	34.9%
Other	1	0.8%

Source: Table 2, Appendix I

Table 2: Table of Subject Overall Study Accountability

Number enrolled:		126
Number discontinued:		7
Lost to follow-up:	7	
Number completed:		119

Source: Table 1, Appendix I

7.1.2 Protocol Deviations

There were no protocol deviations reported during this study.

7.2 Response of Subjects to Study Material and Control Articles

A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3, Appendix II.

7.2.1 Study Material

Study Material MF# [redacted]053: One hundred nineteen (119) subjects completed the Induction Phase. During the Induction Phase, 117 subjects (98.3%) experienced no reaction (-) in response to the study material. One (1) subject (0.8%) experienced minimal or doubtful response (?) in response to the study material. One (1) subject (0.8%) experienced definite erythema, no edema (+) in response to the study material. One hundred nineteen (119) subjects entered the Challenge Phase and experienced no reaction (-) in response to the study material during the 48hr and 72hr evaluations.

Study Material MF# [redacted]057: One hundred nineteen (119) subjects completed the Induction Phase. During the Induction Phase, 117 subjects (98.3%) experienced no reaction (-) in response to the study material. One (1) subject (0.8%) experienced minimal or doubtful response (?) in response to the study material. One (1) subject (0.8%) experienced definite erythema, no edema (+) in response to the study material. One hundred nineteen (119) subjects entered the Challenge Phase and experienced no reaction (-) in response to the study material during the 48hr and 72hr evaluations.

See Table 3 Data Listing 3, Appendix II for more details.

8.0 ADVERSE EVENTS

There were no adverse events (AEs) reported during this study.

9.0 CONCLUSION

Under the conditions employed in this study, there was no evidence of induced skin irritation and/or sensitization to the study materials, MF# [redacted]053, and MF# [redacted]057.

10.0 REFERENCES

Schwartz L, Peck SM. The patch test in contact dermatitis. Publ Health Pep 1944; 59:2.

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[am/bp] K:RIPT\MC[redacted]019\DS101019-R

APPENDIX I

SUMMARY TABLES

Table 1: Summary of Subject Enrollment and Disposition

	N (%)
Subjects enrolled	126
Subjects completed induction phase	119 (94.4)
Subjects completed all phases	119 (94.4)
Total subjects discontinued	7 (5.6)
Lost to follow-up	7 (5.6)

Note: All percentages are relative to total subjects enrolled.

See data listing 1 for further detail.

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Table 2: Summary of Subject Demographics
All Enrolled Subjects

Age	
N (%) 18 to 44	18 (14.3)
N (%) 45 to 65	88 (69.8)
N (%) 66 and up	20 (15.9)
Mean (SD)	55.5 (10.2)
Median	56.5
Range	25.6 to 70.8
Sex	
N (%) Male	45 (35.7)
N (%) Female	81 (64.3)
Race	
Black	81 (64.3)
Caucasian	44 (34.9)
Other	1 (0.8)
Ethnicity	
Hispanic/Latino	14 (11.1)
Not Hispanic/Not Latino	112 (88.9)

See data listing 2 for further detail.

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Table 3: Summary of Dermatologic Response Grades
Number of Subjects by Product

Product = SPF 50 Lotion [redacted] 0692-053

	Induction Reading										Challenge Phase		
Response	1	2	3	4	5	6	7	8	9	Make Up	48hr	72hr	96hr(*)
-	118	114	114	114	116	116	114	116	115	27	119	119	
?	1	2	1	0	0	0	0	0	0	0	0	0	
+	0	0	0	1	1	1	1	1	0	0	0	0	
Total evaluable	119	116	115	115	117	117	115	117	115	27	119	119	
Number absent	4	5	5	4	2	2	4	2	4		0	0	
Number discontinued	3	5	6	7	7	7	7	7	7		7	7	

Maximum Elicited Response During Induction
All Subjects Completing Induction (N=119)

Response	n(%) Subjects
-	117 (98.3%)
?	1 (0.8%)
+	1 (0.8%)

(*) when required

See Table 3.1 for Key to Symbols and Scores

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TKL Study No. DS101019

Table 3.1: Key To Symbols and Scores

Score or Symbol	Response or Description of Reaction
	Erythema Results
-	No reaction
?	Minimal or doubtful response, slightly different from surrounding normal skin
+	Definite erythema, no edema
++	Definite erythema, definite edema
+++	Definite erythema, definite edema and vesiculation
	Additional Comments
X	Reading not performed due to missed visit or subject discontinuation
D	Damage to epidermis: oozing, crusting and/or superficial erosions
E	Marked/severe erythema
I	Itching
p	Papular response >50%
pv	Papulovesicular response >50%
S	Spreading of reaction beyond patch site
NP	Not patched due to reaction achieved
PD	Patch dislodged
N9G	No ninth grading
NA	Not applied

APPENDIX II

DATA LISTINGS

Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
001	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
002	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
003	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
004	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
005	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
006	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
007	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
008	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
009	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
010	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
011	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
012	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
013	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
014	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
015	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
016	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
017	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
018	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
019	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
020	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
021	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
022	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
023	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
024	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
025	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
026	01/28/19	01/28/19	--	02/04/19	I	L	8
027	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
028	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
029	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
030	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
031	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
032	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
033	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
034	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
035	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
036	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
037	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
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041	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
042	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
043	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
044	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
045	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
046	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
047	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
048	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
049	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
050	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
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052	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
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056	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
057	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
058	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
059	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
060	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
061	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
062	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
063	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
064	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
065	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
066	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
067	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
068	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
069	01/28/19	01/28/19	--	02/01/19	I0	L	5
070	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
071	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
072	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
073	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
074	01/28/19	01/28/19	--	02/08/19	I3	L	12
075	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
076	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
077	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
078	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
079	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
080	01/28/19	01/28/19	--	02/06/19	I2	L	10
081	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
082	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
083	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
084	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
085	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
086	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
087	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
088	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
089	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
090	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
091	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
092	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
093	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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Data Listing 1: Subject Enrollment and Disposition

	Study Dates						
Subject No.	Screened	1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days in Study
094	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
095	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
096	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
097	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
098	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
099	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
100	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
101	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
102	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
103	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
104	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
105	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
106	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
107	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
108	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
109	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
110	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
111	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
112	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
113	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
114	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
115	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
116	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
117	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
118	01/28/19	01/28/19	--	02/01/19	I0	L	5
119	01/28/19	01/28/19	--	02/04/19	I1	L	8
120	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
121	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
122	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
123	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
124	01/28/19	01/28/19	--	02/01/19	I0	L	5
125	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39
126	01/28/19	01/28/19	03/04/19	03/07/19	C	C	39

Key:
Last Reading # (I=Induction Phase, C=Challenge Phase)
Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal, V=Protocol violation, AE=Adverse event, O=Other)

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Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Ethnicity	Race
001	64.3	Male	Not Hispanic/Not Latino	Black
002	63.1	Male	Not Hispanic/Not Latino	Black
003	58.3	Female	Not Hispanic/Not Latino	Black
004	56.3	Male	Not Hispanic/Not Latino	Black
005	66.2	Male	Not Hispanic/Not Latino	Black
006	51.6	Female	Not Hispanic/Not Latino	Black
007	60.2	Male	Not Hispanic/Not Latino	Black
008	61.7	Male	Not Hispanic/Not Latino	Black
009	49.8	Female	Not Hispanic/Not Latino	Black
010	55.6	Female	Not Hispanic/Not Latino	Black
011	61.9	Male	Not Hispanic/Not Latino	Black
012	61.5	Female	Not Hispanic/Not Latino	Black
013	46.8	Female	Not Hispanic/Not Latino	Black
014	61.8	Female	Not Hispanic/Not Latino	Black
015	69.5	Male	Hispanic/Latino	Caucasian
016	60.9	Female	Not Hispanic/Not Latino	Black
017	51.8	Male	Not Hispanic/Not Latino	Black
018	53.0	Female	Not Hispanic/Not Latino	Black
019	56.8	Female	Not Hispanic/Not Latino	Black
020	70.2	Male	Not Hispanic/Not Latino	Black
021	61.6	Male	Not Hispanic/Not Latino	Black
022	70.4	Male	Not Hispanic/Not Latino	Caucasian
023	40.9	Male	Not Hispanic/Not Latino	Caucasian
024	58.9	Female	Not Hispanic/Not Latino	Caucasian
025	52.5	Female	Not Hispanic/Not Latino	Caucasian
026	53.3	Male	Not Hispanic/Not Latino	Black
027	58.1	Female	Not Hispanic/Not Latino	Black
028	67.6	Female	Not Hispanic/Not Latino	Caucasian
029	64.2	Male	Not Hispanic/Not Latino	Black
030	59.5	Female	Not Hispanic/Not Latino	Black
031	48.7	Female	Not Hispanic/Not Latino	Black
032	61.3	Female	Not Hispanic/Not Latino	Black
033	64.9	Male	Not Hispanic/Not Latino	Black
034	60.6	Female	Not Hispanic/Not Latino	Caucasian
035	68.2	Female	Not Hispanic/Not Latino	Black
036	48.0	Female	Not Hispanic/Not Latino	Black/Hawaiian/Pacific Islander
037	48.9	Female	Not Hispanic/Not Latino	Black

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Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Ethnicity	Race
038	45.7	Male	Not Hispanic/Not Latino	Black
039	49.1	Female	Not Hispanic/Not Latino	Black
040	65.8	Female	Not Hispanic/Not Latino	Caucasian
041	64.5	Female	Not Hispanic/Not Latino	Caucasian
042	41.8	Female	Not Hispanic/Not Latino	Caucasian
043	49.5	Female	Not Hispanic/Not Latino	Caucasian
044	53.5	Female	Not Hispanic/Not Latino	Caucasian
045	68.5	Female	Not Hispanic/Not Latino	Caucasian
046	42.3	Male	Hispanic/Latino	Caucasian
047	62.3	Female	Not Hispanic/Not Latino	Caucasian
048	57.4	Male	Not Hispanic/Not Latino	Black
049	47.8	Female	Not Hispanic/Not Latino	Caucasian
050	51.6	Male	Not Hispanic/Not Latino	Caucasian
051	56.6	Male	Not Hispanic/Not Latino	Caucasian
052	55.8	Female	Not Hispanic/Not Latino	Caucasian
053	46.9	Female	Not Hispanic/Not Latino	Caucasian
054	70.8	Male	Not Hispanic/Not Latino	Black
055	50.5	Male	Not Hispanic/Not Latino	Black
056	53.0	Female	Not Hispanic/Not Latino	Black
057	39.2	Male	Not Hispanic/Not Latino	Black
058	53.0	Female	Not Hispanic/Not Latino	Black
059	50.1	Female	Not Hispanic/Not Latino	Black
060	65.7	Female	Not Hispanic/Not Latino	Caucasian
061	66.5	Male	Not Hispanic/Not Latino	Black
062	67.1	Male	Not Hispanic/Not Latino	Black
063	51.6	Female	Hispanic/Latino	Caucasian
064	63.3	Female	Not Hispanic/Not Latino	Black
065	62.2	Female	Not Hispanic/Not Latino	Black
066	65.7	Female	Not Hispanic/Not Latino	Black
067	69.5	Male	Not Hispanic/Not Latino	Caucasian
068	56.9	Male	Not Hispanic/Not Latino	Black
069	54.4	Female	Not Hispanic/Not Latino	Caucasian
070	56.8	Female	Not Hispanic/Not Latino	Black
071	28.4	Female	Not Hispanic/Not Latino	Black
072	43.6	Female	Not Hispanic/Not Latino	Black
073	54.1	Female	Not Hispanic/Not Latino	Black
074	56.9	Female	Not Hispanic/Not Latino	Caucasian

Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Ethnicity	Race
075	54.4	Male	Not Hispanic/Not Latino	Black
076	69.9	Female	Hispanic/Latino	Caucasian
077	65.8	Male	Not Hispanic/Not Latino	Black
078	70.4	Female	Not Hispanic/Not Latino	Black
079	51.9	Female	Not Hispanic/Not Latino	Black
080	53.1	Male	Not Hispanic/Not Latino	Black
081	59.9	Female	Not Hispanic/Not Latino	Black
082	33.8	Female	Not Hispanic/Not Latino	Black
083	44.2	Male	Not Hispanic/Not Latino	Black
084	69.8	Female	Not Hispanic/Not Latino	Black
085	64.0	Female	Not Hispanic/Not Latino	Black
086	54.2	Female	Not Hispanic/Not Latino	Black
087	67.4	Female	Not Hispanic/Not Latino	Black
088	69.9	Male	Hispanic/Latino	Caucasian
089	69.2	Male	Hispanic/Latino	Caucasian
090	34.5	Female	Not Hispanic/Not Latino	Caucasian
091	66.0	Female	Not Hispanic/Not Latino	Caucasian
092	55.2	Male	Not Hispanic/Not Latino	Caucasian
093	59.4	Male	Hispanic/Latino	Caucasian
094	61.1	Female	Not Hispanic/Not Latino	Black
095	55.0	Male	Not Hispanic/Not Latino	Caucasian
096	52.1	Male	Not Hispanic/Not Latino	Caucasian
097	63.2	Female	Not Hispanic/Not Latino	Black
098	42.8	Male	Not Hispanic/Not Latino	Black
099	70.1	Female	Not Hispanic/Not Latino	Caucasian
100	35.2	Female	Hispanic/Latino	Caucasian
101	42.5	Female	Not Hispanic/Not Latino	Black
102	51.8	Female	Not Hispanic/Not Latino	Black
103	66.5	Male	Not Hispanic/Not Latino	Black
104	52.9	Male	Not Hispanic/Not Latino	Black
105	51.6	Female	Not Hispanic/Not Latino	Black
106	48.8	Female	Not Hispanic/Not Latino	Black
107	61.5	Female	Not Hispanic/Not Latino	Black
108	56.3	Female	Hispanic/Latino	Caucasian
109	56.2	Female	Hispanic/Latino	Caucasian
110	51.0	Female	Not Hispanic/Not Latino	Caucasian
111	62.3	Male	Not Hispanic/Not Latino	Black

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Data Listing 2: Subject Demographics

Subject No.	Age	Gender	Ethnicity	Race
112	64.4	Female	Not Hispanic/Not Latino	Black
113	52.0	Male	Not Hispanic/Not Latino	Black
114	37.9	Female	Not Hispanic/Not Latino	Black
115	25.6	Female	Hispanic/Latino	Caucasian
116	27.3	Male	Hispanic/Latino	Caucasian
117	48.9	Female	Hispanic/Latino	Caucasian
118	57.6	Female	Not Hispanic/Not Latino	Black
119	33.9	Female	Hispanic/Latino	Caucasian
120	52.1	Female	Not Hispanic/Not Latino	Black
121	60.4	Female	Not Hispanic/Not Latino	Black
122	56.9	Female	Not Hispanic/Not Latino	Black
123	57.2	Female	Not Hispanic/Not Latino	Caucasian
124	30.7	Female	Not Hispanic/Not Latino	Black
125	38.2	Female	Not Hispanic/Not Latino	Black
126	45.4	Male	Not Hispanic/Not Latino	Black

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[redacted]
TKL Study No. DS101019

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = SPF 50 Lotion [redacted] 0692-053

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
001	-	-	-	-	-	-	-	-	-		-	-	
002	-	-	-	-	-	-	-	X	-	-	-	-	
003	-	-	-	-	-	-	-	-	-		-	-	
004	-	-	-	-	-	-	-	-	-		-	-	
005	-	-	-	-	-	-	-	-	-		-	-	
006	-	-	-	-	-	-	-	-	-		-	-	
007	-	-	-	-	-	-	-	-	-		-	-	
008	-	-	-	-	-	-	-	-	-		-	-	
009	-	-	-	-	-	-	X	-	-	-	-	-	
010	-	-	-	X	-	-	-	-	-	N9G	-	-	
011	-	-	-	-	-	-	-	-	-		-	-	
012	-	-	-	-	-	-	-	-	-		-	-	
013	-	-	-	-	-	X	-	-	-	-	-	-	
014	-	-	-	-	-	-	-	-	-		-	-	
015	-	-	-	-	-	-	-	-	-		-	-	
016	-	X	-	-	-	-	-	-	-	-	-	-	
017	-	-	-	-	-	-	-	-	-		-	-	
018	-	-	-	-	-	-	-	-	-		-	-	
019	-	-	-	-	-	-	-	-	-		-	-	
020	-	-	-	-	-	-	-	-	-		-	-	
021	-	-	-	-	-	-	-	-	-		-	-	
022	-	-	-	-	-	-	-	-	-		-	-	
023	-	-	-	-	-	-	-	-	N9G		-	-	

See Table 3.1 for Key to Symbols and Scores

MU = Make-up reading for missed induction visit

(*) When required
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[redacted]
TKL Study No. DS101019

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = SPF 50 Lotion [redacted] 0692-053

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
024	-	-	-	-	-	-	-	-	N9G		-	-	
025	-	-	-	-	-	-	-	-	-		-	-	
026	-	X	X	X	X	X	X	X	X		X	X	
027	-	X	-	-	-	-	-	-	-	-	-	-	
028	-	-	-	-	-	-	-	-	-		-	-	
029	-	-	-	-	-	-	-	-	-		-	-	
030	-	-	-	-	-	-	-	-	-		-	-	
031	-	-	-	-	-	-	-	-	-		-	-	
032	-	-	-	-	-	-	-	-	-		-	-	
033	-	-	-	-	-	-	-	-	-		-	-	
034	-	-	-	-	-	-	-	-	-		-	-	
035	-	-	-	-	-	-	-	-	-		-	-	
036	-	-	-	-	-	-	-	-	-		-	-	
037	-	-	-	-	-	-	-	-	-		-	-	
038	-	-	-	-	-	-	-	-	-		-	-	
039	-	-	-	-	-	-	-	-	-		-	-	
040	-	-	-	-	-	-	-	-	-		-	-	
041	-	-	-	-	-	-	-	-	-		-	-	
042	-	-	-	-	-	-	-	-	-		-	-	
043	-	-	-	-	-	-	-	-	-		-	-	
044	-	-	-	-	-	-	-	-	-		-	-	
045	-	-	-	-	-	-	-	-	-		-	-	
046	-	-	X	-	-	-	-	-	-	-	-	-	

(*) When required
Generated on 03/12/19:15:56 by DETAIL.SAS/USES: RESPONSE, PRODLIST

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = SPF 50 Lotion [redacted] 0692-053

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
047	?	?	?	+	+	+	+	+	N9G		-	-	
048	-	-	-	-	-	-	X	-	-	-	-	-	
049	-	-	-	-	-	-	-	-	-		-	-	
050	-	-	-	-	-	-	-	-	-		-	-	
051	-	-	-	-	-	-	-	-	-		-	-	
052	-	-	X	-	-	-	-	-	-	-	-	-	
053	-	-	-	-	-	-	-	-	-		-	-	
054	-	-	-	-	-	-	-	-	-		-	-	
055	-	-	-	-	-	-	-	-	-		-	-	
056	-	-	-	-	-	-	-	-	-		-	-	
057	-	-	-	-	-	-	-	-	N9G		-	-	
058	X	-	-	-	-	-	-	-	-	-	-	-	
059	-	-	-	-	-	-	-	-	-		-	-	
060	-	-	X	-	-	-	-	-	-	-	-	-	
061	-	-	-	-	-	-	-	-	-		-	-	
062	-	-	-	-	-	-	-	-	-		-	-	
063	-	-	-	-	-	-	-	-	-		-	-	
064	-	-	-	-	-	-	-	-	-		-	-	
065	-	-	-	-	-	-	-	-	-		-	-	
066	-	-	-	-	-	-	-	-	-		-	-	
067	-	-	-	-	-	-	-	-	-		-	-	
068	-	-	-	-	-	-	-	-	-		-	-	
069	X	X	X	X	X	X	X	X	X		X	X	

(*) When required
Generated on 03/12/19:15:56 by DETAIL.SAS/USES: RESPONSE, PRODLIST

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = SPF 50 Lotion [redacted] 0692-053

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
070	-	-	-	-	-	-	-	-	-		-	-	
071	-	-	-	-	-	-	-	-	-		-	-	
072	-	-	-	-	-	-	-	-	-		-	-	
073	-	-	-	-	-	-	-	-	-		-	-	
074	-	-	-	X	X	X	X	X	X		X	X	
075	-	-	-	-	-	-	-	-	-		-	-	
076	-	-	-	-	-	-	-	-	-		-	-	
077	-	-	-	-	-	-	-	-	-		-	-	
078	-	-	-	-	-	-	-	-	-		-	-	
079	-	-	-	-	-	-	-	-	-		-	-	
080	-	-	X	X	X	X	X	X	X		X	X	
081	-	-	-	-	-	-	-	-	-		-	-	
082	-	-	-	-	-	-	-	-	-		-	-	
083	-	-	-	-	-	X	-	-	-	-	-	-	
084	-	-	-	-	-	-	-	-	-		-	-	
085	-	-	-	-	-	-	-	-	-		-	-	
086	-	X	-	-	-	-	-	-	-	-	-	-	
087	-	-	-	-	-	-	-	-	-		-	-	
088	-	-	-	-	-	-	-	-	-		-	-	
089	-	-	-	-	-	-	-	-	-		-	-	
090	-	-	-	-	-	-	-	-	-		-	-	
091	-	-	-	-	-	-	X	-	-	-	-	-	
092	-	-	-	-	-	-	-	-	-		-	-	

(*) When required
Generated on 03/12/19:15:56 by DETAIL.SAS/USES: RESPONSE, PRODLIST

[redacted]

Data Listing 3: Dermatologic Response Grades
By Product and Subject

Product = SPF 50 Lotion [redacted] 0692-053

Subject No.	Induction Reading										Challenge Phase		
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
093	-	-	-	-	-	-	-	-	-		-	-	
094	-	-	-	-	-	-	-	-	-		-	-	
095	-	?	X	-	-	-	-	-	-	-	-	-	
096	-	-	-	-	-	-	-	-	-		-	-	
097	-	-	-	-	-	-	-	-	-		-	-	
098	-	-	-	-	-	-	-	-	-		-	-	
099	-	-	-	-	-	-	-	-	-		-	-	
100	-	-	-	-	-	-	-	X	-	-	-	-	
101	-	X	-	-	-	-	-	-	-	-	-	-	
102	-	-	-	-	X	-	-	-	-	-	-	-	
103	-	-	-	-	X	-	-	-	-	-	-	-	
104	-	-	-	X	-	-	-	-	-	-	-	-	
105	-	-	-	X	-	-	-	-	-	-	-	-	
106	-	-	X	-	-	-	-	-	-	-	-	-	
107	-	-	-	X	-	-	-	-	-	-	-	-	
108	-	-	-	-	-	-	-	-	-		-	-	
109	-	-	-	-	-	-	-	-	-		-	-	
110	-	-	-	-	-	-	-	-	-		-	-	
111	X	-	-	-	-	-	-	-	-	-	-	-	
112	-	-	-	-	-	-	-	-	-		-	-	
113	X	-	-	-	-	-	-	-	-	-	-	-	
114	-	-	-	-	-	-	X	-	-	-	-	-	
115	-	-	-	-	-	-	-	-	-		-	-	
116	-	-	-	-	-	-	-	-	-		-	-	
117	-	-	-	-	-	-	-	-	-		-	-	
118	X	X	X	X	X	X	X	X	X		X	X	
119	-	X	X	X	X	X	X	X	X		X	X	
120	-	X	-	-	-	-	-	-	-	-	-	-	
121	-	-	-	-	-	-	-	-	-		-	-	
122	-	-	-	-	-	-	-	-	-		-	-	
123	X	-	-	-	-	-	-	-	-	-	-	-	
124	X	X	X	X	X	X	X	X	X		X	X	
125	-	-	-	-	-	-	-	-	-		-	-	
126	-	-	-	-	-	-	-	-	-		-	-	

(*) When required
Generated on 03/12/19:15:56 by DETAIL.SAS/USES: RESPONSE, PRODLIST

KGL
SKIN STUDY CENTER

Product contains 0.0075% Carica Papaya (Papaya) Fruit Extract

Final Report for

[redacted]

KGL Study # 8490

[redacted] #0119094

PHOTOCONTACT ALLERGENICITY ASSAY
Sample: Sunscreen Lotion SPF 50 coded [redacted]055
(tested as supplied; under occlusive patch)
MF# [redacted]053

Submitted by:

Stuart R. Lessin, MD

March 8, 2019
Date

Statement of Compliance and Quality Control

The above signature of the Principal Investigator affirms that (1) the study was conducted in compliance with the IRB-approved protocol and the International Council on Harmonization Good Clinical Practices, (2) all study related documents underwent quality control review in accordance with the standard operating procedures of KGL Skin Study Center to ensure the accuracy of the data, (3) the clinical study report was fully reviewed and accurately reflects the results of the study.

[redacted]

The names of the KGL Skin Study Center, KGL, Inc., or KGL LLC, any officer, employee, or collaborating scientist are not to be used for any advertising, promotional, or sales purposes without the written consent of the KGL Skin Study Center, KGL

[redacted]

TEL. 610-544-1715 KGL LLC • 505 PARKWAY • BROOMALL, PA • 19008 FAX. 610-544-6305
WWW.KGLSKINSTUDYCENTER.COM

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[redacted]

I. BACKGROUND

Patch testing is an established diagnostic procedure used to identify skin sensitizing substances [1]. Dilute substances are applied to small areas of skin under occlusion (i.e., a patch) for variable periods of time. In clinical practice, patch testing is performed with common skin sensitizing substances over 1-2 days and results in positive reactions at a rate greater than 0.5% to 1.0% [2]. In product safety testing of new substances or formulations, repeat insult patch testing (RIPT) is performed over 1-5 weeks.

The Photocontact Allergenicity Assay is a RIPT designed to detect the photoallergic potential of topically applied substances on human skin and combines artificial ultraviolet (UV) exposure from a solar simulator with patch testing [3, 4]. Both UVA (320 nm – 410 nm) & UVB (280 nm – 320 nm) radiation can photoactivate topically applied substances on the skin. When processed by the immune system, photoactivated compounds are capable of inducing a type IV cell-mediated (delayed) hypersensitivity reaction (allergic photocontact dermatitis). The assay consists of an induction phase, a rest phase, a challenge phase, and a re-challenge phase for positive responders.

II. OBJECTIVES

This test was designed to assess the photosensitization (photocontact allergenicity) potential of any preparation designed for topical use by means of repeat insult patch testing [3, 4].

III. EXPERIMENTAL DESIGN

Principal Investigator: Stuart R. Lessin, M.D. – Board Certified Dermatologist

Project Technician: Melanie Chappell

Test Facility: KGL Skin Study Center
505 Parkway Drive, Broomall, PA 19008
(610) 544-1715

Study Sponsor [redacted]

Study Contact: [redacted]

Investigational Review Board: IntegReview IRB
3815 S. Capital of Texas Hwy, Suite 320
Austin, TX 78704

Design of Study

This was an open-label, single-arm (cell), non-randomized, evaluator-blinded RIPT wherein the test product and UV radiation (UVR) from a solar simulator were administered under an occlusive dressing to the same designated test site over the mid or lower back area repeatedly for six 24-hour induction exposures over a three week period (induction phase). This was followed by 10 days of no applications (rest phase) and then a single challenge to a naive skin site (challenge phase) on a minimum of 25 subjects. In subjects who developed a positive or questionable response to the challenge, a second challenge (re-challenge phase) may have been performed within 14 days after the initial challenge to confirm or rule out the development of photocontact sensitization. The test product was applied to the skin of each subject. The evaluator graded the level of irritation at the test site and was blinded as to the identity of the test product.

Study Dates

January 21, 2019 – February 22, 2019

Test Material

The test material used in this study was supplied by the sponsor and labeled as Sunscreen Lotion SPF 50 coded [redacted]055. The test material was tested as supplied under occlusive patching.

Pre-Study

Recruitment of prospective subjects was accomplished by telephone contact. Candidate subjects were assigned an appointment time at the testing facility. During this visit, the following was performed:

- Informed Consent Form
- Medical History and Concomitant Medications
- Childbearing Potential
- Inclusion/Exclusion

Study Schedule

Study Procedures	Visit 1	Visit 2-12	Visit 12	Visit 13	Visit 14	Visit 15
	BASELINE (DAY 1)	DAYS 2-19	DAY 29	DAYS 30	DAY 32	DAY 33
Informed Consent	X					
Medical History	X					
Collect/Record Concomitant Medications	X					
Eligibility Assessment	X**					
MED Determination	X					
Product Application (Mondays/Thursday)	X*	X*				
UVR (Tuesday/Friday)		X				
Induction Phase Patch Site Assessment		X				
Challenge Phase Test Material Application			X			
Challenge Phase UVR				X		
Challenge Phase Patch Site Grading					X	X**

*Test Material applied for 24 hours on Mondays/Thursdays

** Initial and final visit evaluated by Board Certified Dermatologist

Procedures

Screening (Day -7 to Day 1)

After the subject provided written informed consent, the following procedures were completed in the order listed:

1. Obtained demographic information and medical history, including information on all medications used within the past 30 days. This included herbal therapies, vitamins, and all over-the-counter as well as prescription medications.
2. Focused skin exam of test sites for any scars, moles, or other blemishes that could interfere with the study.
3. Reviewed inclusion/exclusion criteria.

Minimal Erythema Dose (MED) Determination (Day 1-2)

MED

On Day 1, each subject received a series of five UVR exposures in 25% increments from a xenon arc solar simulator (see below). The starting exposure time (minimum UV dose) for each series was selected based on the subject's Fitzpatrick Skin Type. The exposures were 1 cm diameter circular areas on one side of the lower back. The subject's MED was the shortest exposure time (of the five) that produced a minimally visible faint erythema 20 to 24 hours later. Thus, the MED was recorded on day 2.

Light Source

The light source was a 150-watt compact xenon arc solar simulator (Solar Light Company) equipped with a UV-reflecting dichroic mirror and a 1 mm thick Schott WG320 filter to produce simulation of the solar spectrum (SSR waveband). A 1 mm thick UG11 filter was added to reduce residual visible and heat wavelengths. The SSR waveband was used to determine the individual MED. For the challenge phase, a 1 mm thick Schott WG345 filter was added to eliminate the UVB component (290-320 nm) and to produce a continuous broadband UVA extending from 320 to 410 nm. Total UVR and UVA irradiance at skin level was measured with a calibrated ILT 1400 Radiometer (International Light Technologies, Inc.) and UVR doses (J/cm2) were correlated to exposure times and recorded in the CRFs. The size of the irradiated field at skin level was approximately a 1 cm diameter circle. Total irradiance at skin level was 97.5 mW/cm.^{2} The UVA intensity was 45.0 mW/cm^2.

Induction Phase (Day 1 – Day 19)

Approximately 40 mg of the test material Sunscreen Lotion SPF 50 coded [redacted]055 (tested as supplied)was spread uniformly onto a 2 x 2 cm square (10 mg/cm^2) of non-absorbing cotton cloth (Webril) using micropipettes or plastic tuberculin syringes and placed on the subject's lower back. The site was then covered with an occlusive tape and the entire patch fastened to the skin with Scanpor Tape to ensure intimate contact with the skin. The patch was left in place for approximately 24 hours. At the end of this period, the patch was removed and the site immediately exposed to two minimal erythema doses (MED's) from a xenon arc solar simulator. This sequence of test product application followed by exposure to two MED's 24 hours later was repeated to the same test site for a total of six exposures (two exposures per week for three weeks). If a severe dermatitis (see induction phase assessment) developed on the induction site, the test product was applied to a nearby area and irradiated as described above at least once before returning to the original site. This "site move" allowed the original site to recover from the acute UV reaction.

Rest Period (Day 20-28)

No exposure to the test product or UVR occurred during the rest period that lasted for approximately 10 days after the last induction patch.

Challenge Phase (Day 29 – Day 33)

The subjects were challenged in a naive site on the opposite side of the back. Approximately 40 mg of the test product Sunscreen Lotion SPF 50 coded [redacted]055 (tested as supplied) was applied to a fresh skin site measuring 2 x 2 cm under occlusive dressing for 24 hours followed by exposure to ½ MED of solar simulated radiation plus 4 J/cm2 of UVA from the filtered xenon arc solar simulator with the Schott WG345 filter to eliminate sunburning waves (UVB). An un-irradiated site treated with the test product served as a "dark" control. The sites were examined at 48 and 72 hours after irradiation for evidence of photocontact sensitization. If a reaction developed during the challenge phase, the subject was asked to participate in a re-challenge test to clarify or investigate in more detail the nature of the reaction seen at challenge, as indicated in the consent form. The board-certified dermatologist evaluated the final results at 48 hours.

No rechallenge phase was performed during the course of this study.

Assessment of Dermatitis during Induction Phase

Levels of dermatitis arising during the induction phase were assessed according to the International Contact Dermatitis Research Group (ICDRG) scale (0-4) (see scale below) [5].

ICDRG SCORING SCALE
0 = no dermatitis
1 = mild dermatitis (mild erythema)
2 = brisk dermatitis (erythema with edema, spreading beyond the borders of the patch, with or without vesiculation)
3 = severe dermatitis (erythema with large vesiculobullous reaction)

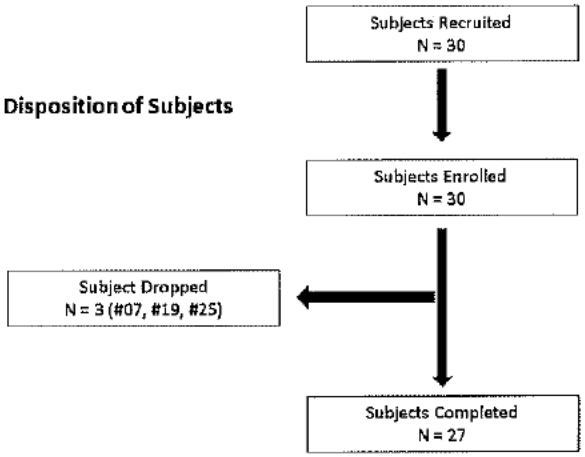
Assessment and Grading Possible Allergic Reactions during the Challenge Phase

Reactions that arose during the challenge phase, which were beyond those seen in the induction phase, were graded according to the following ICDRG scale:

SCORING SCALE
0 = not sensitized
1 = mild sensitization (mild erythema)
2 = moderate irritation (erythema with edema, spreading beyond the borders of the patch, with or without vesiculation)
3 = strong sensitization (erythema with large vesiculobullous reaction)

IV. RESULTS

A. Panelist Accountability



Thirty (30) subjects who satisfied the inclusion/exclusion criteria were enrolled into the study; twenty-seven (27) subjects completed this investigation as outlined in the standard study protocol.

- Subjects #07, #19, and #25: dropped due to failure to maintain the study schedule.

B. Demographic Data

There were eighteen (18) females and twelve (12) males between the ages of 32 and 70 years enrolled in the study. The demographic data is shown in Table 1 below.

TABLE 1

Subject Demographic Data			
Subject Number	**Age**	**Gender**	**Race**
01	49	F	C
02	67	F	C
03	65	M	C
04	44	F	C
05	68	M	C
06	64	F	C
07*	54	M	C
08	65	M	C
09	32	F	C
10	38	F	C
11	69	F	C
12	69	F	C
13	53	M	C
14	60	M	C
15	59	F	C
16	54	M	C
17	65	M	C
18	69	M	C
19*	54	M	C
20	62	F	C
21	50	F	C
22	48	F	C

Subject Demographic Data (cont.)			
Subject Number	Age	Gender	Race
23	36	F	C
24	44	F	C
25*	55	F	C
26	62	M	C
27	61	M	C
28	50	F	C
29	70	F	C
30	56	F	C

*Dropped C = Caucasian

C. Adverse Events

There were no adverse events and no serious adverse events during the course of this study.

D. Protocol Deviations

There were no protocol deviations that occurred during this study.

E. Photocontact Allergenicity Results

No unexpected reactions were seen in any of the subjects during the study. The results are shown in Table 2.

TABLE 2

Sunscreen Lotion SPF 50 coded [redacted]055 (tested as supplied; under occlusive patch)				
Subject Number	48 Hour Reading 2/21/19 Irradiated	48 Hour Reading 2/21/19 Unirradiated	72 Hour Reading 2/22/19 Irradiated	72 Hour Reading 2/22/19 Unirradiated
01	0	0	0	0
02	0	0	0	0
03	0	0	0	0
04	0	0	0	0
05	0	0	0	0
06	0	0	0	0
07*	--	--	--	--
08	0	0	0	0
09	0	0	0	0
10	0	0	0	0
11	0	0	0	0
12	0	0	0	0
13	0	0	0	0
14	0	0	0	0
15	0	0	0	0
16	0	0	0	0
17	0	0	0	0
18	0	0	0	0
19*	--	--	--	--
20	0	0	0	0
21	0	0	0	0
22	0	0	0	0
23	0	0	0	0
24	0	0	0	0
25*	--	--	--	--
26	0	0	0	0
27	0	0	0	0
28	0	0	0	0
29	0	0	0	0
30	0	0	0	0

*Dropped

V. CONCLUSION

Under the conditions of this test, the test sample –Sunscreen Lotion SPF 50 coded [redacted] 055– did not possess a detectable photocontact-sensitizing potential in human skin.

VI. REFERENCES

1. Zug KA, Warshaw EM, Fowler JF Jr, Maibach HI, Belsito DL, Pratt MD, et al. Patch-test results of the North American Contact Dermatitis Group 2005-2006 [Erratum in: Dermatitis 2009;20:300; Marks J, added]. Dermatitis 2009;20:149-60.

2. Wentworth AB, Yiannias JA, Keeling JH, Hall MR, Camilleri MJ, Drage LA, et al. Trends in patch-test results and allergen changes in the standard series: A Mayo Clinic 5-year retrospective review (January 1, 2006, to December 31, 2010). J Am Acad Dermatol 2014;70:269-75.

3. Kaidbey, KH and Kligman AM: Photomaximization test for identifying photoallergic contact sensitizers. Contact Dermatitis, 6: 161-169, 1980.

4. Kaidbey, KH and Kligman AM: Identification of contact photosensitizers by human assay. In "Current concepts in cutaneous toxicity, edited by V.A. Drill and P. Lazar. Academic Press Inc., pp. 55-68, New York, NY, 1980.

5. Ivens U, O'Goshi K, Serup J. Allergy patch test reading from photographic images: disagreement on ICDRG grading but agreement on simplified tripartite reading. Skin Res Technol. 2007 Feb;13(1):110-3

6. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol 124:869-71,1988.

7. Berger DS: Specification and design of solar ultraviolet simulators. J Invest Dermtol. 53: 192-199, 1969.

[redacted]

KGL
SKIN STUDY CENTER

Final Report for

[redacted]

KGL Study #8489
[redacted] Study #0119095

HUMAN PHOTOTOXICITY BIOASSAY
Sample: Sunscreen Lotion SPF 50 coded [redacted]055
(tested as supplied under occlusive patch)
MF# [redacted]053

Submitted by: Product contains 0.0075% Carica Papaya (Papaya) Fruit Extract

Stuart R. Lessin, MD

January 31, 2019
Date

Statement of Compliance and Quality Control

The above signature of the Principal Investigator affirms that (1) the study was conducted in compliance with the IRB-approved protocol and the International Council on Harmonization Good Clinical Practices, (2) all study related documents underwent quality control review in accordance with the standard operating procedures of KGL Skin Study Center to ensure the accuracy of the data, (3) the clinical study report was fully reviewed and accurately reflects the results of the study.

[redacted]

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[redacted]

I. BACKGROUND

Patch testing is an established diagnostic procedure used to identify skin sensitizing substances [1]. Dilute substances are applied to small areas of skin under occlusion (i.e., a patch) for variable periods of time. In clinical practice, patch testing is performed with common skin sensitizing substances over 1-2 days and results in positive reactions at a rate greater than 0.5% to 1.0% [2]. In product safety testing of new substances or formulations, repeat insult patch testing (RIPT) is performed over 1-5 weeks.

The Human Phototoxicity Bioassay is designed to detect the phototoxicity potential of topically applied substances on human skin and combines artificial ultraviolet (UV) exposure from a solar simulator with patch testing [3, 4]. Topically applied substances can interact with sunlight and become photo-activated by the UV radiation (UVR). Both UVA (320 nm – 410 nm) & UVB (280 nm – 320 nm) can photoactivate a compound. The direct, non-immunological effects of photoactivation results in phototoxicity and are similar to an irritancy reaction.

II. OBJECTIVE

This test was designed to assess the phototoxicity potential of any substance intended for topical use in human skin [3, 4].

III. EXPERIMENTAL DESIGN

Principal Investigator: Stuart R. Lessin, M.D. – Board Certified Dermatologist

Project Technician: Melanie Chappell

Test Facility: KGL Skin Study Center
505 Parkway Drive, Broomall, PA 19008
(610) 544-1715

Study Sponsor: [redacted]

Study Contact: [redacted]

Investigational Review Board: IntegReview IRB
3815 S. Capital of Texas Hwy, Suite 320
Austin, TX 78704

A. Design of Study

This was an open-label, single-arm (cell), non-randomized, evaluator-blinded RIPT. The procedure involved a one-time 24-hour occluded application of the test material Sunscreen Lotion SPF 50 coded [redacted]055 (tested as supplied) to duplicate sites on the lower back area (Days1-2) followed by a single exposure to UV radiation (UVR) (Day 2) on a minimum of 20 subjects. The duplicate site served as an unirradiated control. One additional site served as an irradiated control. Sites were assessed immediately after UV irradiation as well as 24 hours and 48 hours post UVR (Days 3-4).

B. Study Dates

January 14, 2019 – January 17, 2019

C. Pre-Study

Recruitment of prospective subjects was accomplished by telephone contact. Candidate subjects were assigned an appointment time at the testing facility. During this visit, written informed consent was obtained and the following was performed:

- Medical History and Concomitant Medications
- Inclusion/Exclusion
- Completed childbearing potential if female.

D. Study Schedule

Day:	Monday 1	Tuesday 2	Wednesday 3	Thursday 4
MED UVR** Exposure	X			
Test Material Application	X			
Test Material Removed		X		
UVR Exposure		X G*	G	G**

(G) Grading immediately after UVR (G*) and at 24 hours and 48 hours post UVR.** Initial and final visit evaluated by Board Certified Dermatologist

E. Procedures

Screening (Day -7 to Day 1)

After the subject provided written informed consent, the following procedures were performed in the order listed:

1. Obtained demographic information and medical history, including information on all medications used within the past 30 days which included herbal therapies, vitamins, and all over-the-counter as well as prescription medications.
2. Focused skin exam of test sites for any scars, moles, or other blemishes that can interfere with the study.
3. Reviewed the inclusion/exclusion criteria.

Minimal Erythema Dose (MED) Determination (Day 1 – 2)

On Day 1, each subject received a series of five UVR exposures in 25% increments from a xenon arc solar simulator. The starting exposure time (minimum UV dose) for each series was selected based on the subject's Fitzpatrick skin type. The exposures were 1 cm diameter circular areas on one side of the lower back. The subject's MED was the shortest exposure time (of the five) that produced a minimally visible faint erythema 20 to 24 hours later. Thus, the MED was recorded on Day 2.

Patch Testing (Day 1 – 2)

On Day 1, approximately 40 mg of the test material Sunscreen Lotion SPF 50 coded [redacted] 055 (tested as supplied) was delivered to duplicate skin sites measuring 2 x 2 cm each using a 1 ml plastic tuberculin syringe. The patch test sites were placed on the opposite side of the back from the MED determination sites. The patch test sites were then covered by equal squares of non-woven cotton cloth (Webril, Curity). The patches were then fastened to the skin with occlusive tape (Blenderm, 3M) and further secured to the skin with Scanpor tape. The patches were worn for 24 hours and removed on Day 2. One set of patches received UVR on Day 2 while the other set did not and served as unirradiated control. One additional patch without any test material was similarly taped to an adjacent area of the back, received UVR on Day 2, and served as an irradiated control.

UVR Exposure (Day 2)

On Day 2, the MED test sites were evaluated and the site that showed detectable erythema from the least dose was taken as the MED and was documented for each subject. All patches were removed and any residual test material was wiped from the skin with dry gauze. One duplicate test site was immediately exposed to 10 J/cm^2 of longwave ultraviolet (UVA) plus 0.5 MED of full spectrum solar-simulated radiation. The other patch test site served as un-irradiated control.

The adjacent skin site with the additional blank Webril patch was exposed to the same dose of UVA plus 0.5 MED's and served as an irradiated control. Reactions were graded immediately, 24 hours, and 48 hours after irradiation.

UVR Light Source

This was a 150-watt compact xenon arc solar simulator (Solar Light Company - see reference #6) equipped with a UV-reflecting dichroic mirror and a 1 mm thick Schott WG320 filter to produce simulation of the solar spectrum (SSR waveband). A 1 mm thick UG11 filter was added to reduce residual visible and heat wavelengths. The SSR waveband was used to determine the individual MED. A 1 mm thick Schott WG345 filter was then added to eliminate the UVB component (290-320 nm) and to produce a continuous broadband UVA extending from 320 to 410 nm. Total UVR and UVA irradiance at skin level was measured with a calibrated ILT 1400 Radiometer (International Light Technologies, Inc.) and UVR doses (J/cm^2) were correlated to exposure times and recorded in the CRFs. The size of the irradiated fields at skin level was approximately a 1 cm diameter circle.

Total irradiance at skin level as measured with the calibrated IL UVR Radiometer was 75.0 mW/cm^2. The UVA irradiance was 45.0 mW/cm^2.

Evaluation Phase (Day 3 – Day 4):

A phototoxic material produces either a wheal-and-flare response immediately after exposure or intense erythema and edema 24-48 hours later.

The presence of a wheal-and-flare within 2-3 minutes after irradiation was recorded, if present. Delayed erythema was evaluated using the five-point International Contact Dermatitis Research Group (ICDRG) scale (0-4) (see scale below) [7].

Assessment of MED During Pre-Patch Testing Phase

Assessment of erythema present at the UVR test sites was utilized to determine the MED.

Assessment of Immediate Phototoxicity Reaction during UVR Exposure Phase

Assessment for the presence of a wheal-and-flare reaction within 2-3 minutes after UV irradiation was utilized to determine immediate phototoxicity.

Assessment of Delayed Phototoxicity Reaction during Evaluation Phase

The 5-point ICDRG grading scale (0-4) of skin irritation was utilized to evaluate test sites at 24 hours and 48 hours.

ICDRG SCORING SCALE
0 = normal skin
1 = minimal visible erythema with ill-defined borders
2 = deeper erythema with clear distinct borders
3 = intense erythema and edema (an elevated lesion)
4 = vesicles, erosions or blisters

F. Test Product Handling and Accountability

The test product was received in good condition by our Quality Assurance Department and was checked against the submission form for (1) amount, (2) product number or code, and (3) product container. The test product was inventoried and kept in a secure, environmentally-controlled product storage room and kept at room temperature during the course of the study.

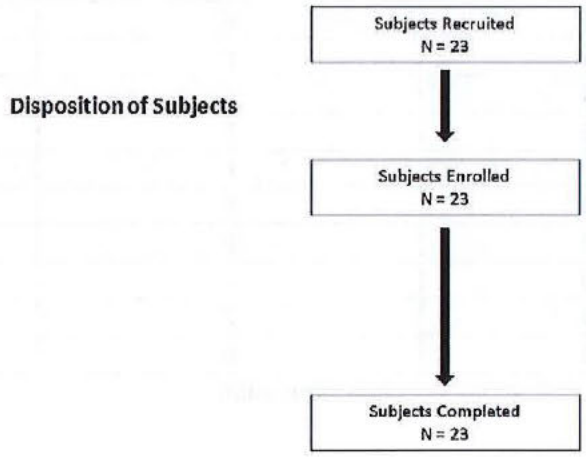
All remaining test material will be returned to the sponsor under separate cover via a trackable method following submission of the final written report to the Sponsor.

G. Recording of Data and Handling of Study Documents

All case report forms (CRFs) were provided by the Investigator. All CRFs were completed in real time during the subject's visit. All study related documents were kept under secure lock in the technician's office during the course of the study. Copies of the CRFs will be retained by the Investigator as well as the original signed informed consent.

IV. RESULTS

A. Panelist Accountability



Twenty-three (23) subjects who satisfied the inclusion/exclusion criteria were enrolled into the study; twenty-three (23) subjects completed this investigation as outlined in the standard study protocol.

B. Demographic Data

There were twenty (20) females and three (3) males between the ages of 20 to 70 years in this study. The demographic data is shown in Table 1 below.

TABLE 1

Subject Demographic Data			
Subject Number	Age	Gender	Race
01	68	M	C
02	66	M	C
03	22	F	C
04	37	F	C
05	36	F	C
06	38	F	C
07	65	F	C
08	70	F	C
09	61	M	C
10	66	F	C
11	49	F	C
12	39	F	C
13	44	F	C
14	65	F	C
15	65	F	C
16	69	F	C
17	39	F	C
18	37	F	C
19	59	F	C
20	63	F	C
21	20	F	C
22	27	F	C
23	49	F	C

C = Caucasian

C. Adverse Events

There were no adverse events and no serious adverse events during the course of this study.

D. Protocol Deviations

There were no protocol deviations that occurred during this study.

E. Phototoxicity Bioassay Results

No unexpected reactions were seen in any of the subjects during the study. The results are shown in Table 2 through Table 4.

TABLE 2

INDIVIDUAL EVALUATIONS IMMEDIATELY POST EXPOSURE Sunscreen Lotion SPF 50 coded [redacted]055 (tested as supplied)			
Subject Number	Treated Unirradiated Site	Treated Irradiated Site	UV Irradiated Plain Cotton Webril (control site)
01	0	0	0
02	0	0	0
03	0	0	0
04	0	0	0
05	0	0	0
06	0	0	0
07	0	0	0
08	0	0	0
09	0	0	0
10	0	0	0
11	0	0	0
12	0	0	0
13	0	0	0
14	0	0	0
15	0	0	0
16	0	0	0
17	0	0	0
18	0	0	0
19	0	0	0
20	0	0	0
21	0	0	0
22	0	0	0
23	0	0	0

TABLE 3

INDIVIDUAL EVALUATIONS 24 HOURS POST EXPOSURE Sunscreen Lotion SPF 50 coded [redacted]055 (tested as supplied)			
Subject Number	Treated Unirradiated Site	Treated Irradiated Site	UV Irradiated Plain Cotton Webril (control site)
01	0	0	0
02	0	0	0
03	0	0	0
04	0	0	0
05	0	0	0
06	0	0	0
07	0	0	0
08	0	0	0
09	0	0	0
10	0	0	0
11	0	0	0
12	0	0	0
13	0	0	0
14	0	0	0
15	0	0	0
16	0	0	0
17	0	0	0
18	0	0	0
19	0	0	0
20	0	0	0
21	0	0	0
22	0	0	0
23	0	0	0

TABLE 4

INDIVIDUAL EVALUATIONS 48 HOURS POST EXPOSURE Sunscreen Lotion SPF 50 coded [redacted]055 (tested as supplied)			
Subject Number	Treated Unirradiated Site	Treated Irradiated Site	UV Irradiated Plain Cotton Webril (control site)
01	0	0	0
02	0	0	0
03	0	0	0
04	0	0	0
05	0	0	0
06	0	0	0
07	0	0	0
08	0	0	0
09	0	0	0
10	0	0	0
11	0	0	0
12	0	0	0
13	0	0	0
14	0	0	0
15	0	0	0
16	0	0	0
17	0	0	0
18	0	0	0
19	0	0	0
20	0	0	0
21	0	0	0
22	0	0	0
23	0	0	0

V. CONCLUSION

Under the conditions of this test, the test sample – Sunscreen Lotion SPF 50 coded [redacted]55– does not possess a detectable phototoxic potential in human skin.

VI. REFERENCES

1. Zug KA, Warshaw EM, Fowler JF Jr, Maibach HI, Belsito DL, Pratt MD, et al. Patch-test results of the North American Contact Dermatitis Group 2005-2006 [Erratum in: Dermatitis 2009;20:300; Marks J, added]. Dermatitis 2009;20:149-60.

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100 HUMAN SUBJECT REPEAT INSULT PATCH TEST SKIN IRRITATION/SENSITIZATION EVALUATION (OCCLUSIVE PATCH)

Product contains 0.0586% Carica Papaya (Papaya) Fruit Extract

Date: May 26, 2005

CR Ref. No.: RIPT.C0415-A1.O.100.DERM.TRLI

Sponsor: [redacted]

1.0 Objective: Consumer products or raw materials designed for consistent reapplication to areas of the skin may, under proper conditions, prove to be contact sensitizers or irritants in certain individuals. It is the intention of a Repeat Insult Patch Test (RIPT) to provide a basis for evaluation of this irritation/ sensitization (allergenicity) potential if such exists.

2.0 Reference: The method is modified to test 100 panelists and not the 200 cited in the reference Appraisal of the Safety of Chemicals in Food, Drugs and Cosmetics, published by The Association of Food and Drug Officials of The United States. The method also employs nine inductive patchings and not the ten cited in the reference.

3.0 Test Material:

3.1 Test Material Description:

On April 15, 2005 one test sample labeled [redacted] Lotion/Body Butter, Formula No. 598-154X, Batch 598154X was received from Tanning Research Laboratories, Inc. and assigned CR Lab No. C0415-A1.

3.2 Handling: Upon arrival at Cantor Research Laboratories, Inc., the test material is assigned a unique laboratory code number and entered into a daily log identifying the lot number, sample description, sponsor, date and test requested.
Samples are retained for a period of three months beyond submission of final reports unless otherwise specified by the sponsor or, if sample is known to be in support of governmental applications, representative retained samples are kept two years beyond final report submission.

Sample disposition is conducted in compliance with appropriate federal, state and local ordinances.

3.3 Test Material Evaluation Prerequisite:

Prior to induction of a human test panel, animal toxicology, microbiology and other in-vivo or in-vitro performance spectra may be required to assess the feasibility of commencement as dictated by an Institutional Review Board (IRB) described in Section 4.0.

3.3.1 Sponsor purports that prior to sample submission to Cantor Research Laboratories, Inc., the following tests were conducted with no adverse results and that the test data are on file on their premises and have not been made available to Cantor Research Laboratories, Inc., personnel:

- CTFA Preservative Efficacy Test or equivalent
- 90 Day Accelerated Stability and Container Compatibility Study

4.0 Institutional Review Board:

Reference: CFR Title 21 Part 56, Subparts A, B, C, and D. The IRB of Cantor Research Laboratories, Inc., consists of five or more individuals, chosen from within the company for technical expertise and from the local community for lay interaction. The list of IRB members is kept on file at Cantor Research Laboratories, Inc., and is available for inspection during the hours of operation.

5.0 Panel Selection:

5.1 Standards for Inclusion in a Study:

- Individuals who are not currently under a doctor's care.
- Individuals free of any dermatological or systemic disorder which would interfere with the results, at the discretion of the Investigator.
- Individuals free of any acute or chronic disease that might interfere with or increase the risk of study participation.
- Individuals who will complete a preliminary medical history form mandated by Cantor Research Laboratories, Inc., and are in general good health.

- Individuals who will read, understand and sign an informed consent document relating to the specific type of study they are subscribing. Consent forms are kept on file and are available for examination on the premises of Cantor Research Laboratories, Inc., only.
- Individuals able to cooperate with the Investigator and research staff, willing to have test materials applied according to the protocol, and complete the full course of the study.

5.2 Standards for Exclusion from a Study:

- Individuals under 18 years of age.
- Individuals who are under doctor's care.
- Individuals who are currently taking any medication (topical or systemic) that may mask or interfere with the test results.
- Subjects with a history of any acute or chronic disease that might interfere with or increase the risk of study participation.
- Individuals diagnosed with chronic skin allergies.
- Female volunteers who indicate that they are pregnant or nursing.

5.3 Recruitment:

Panel selection is accomplished by advertisements in local periodicals, community bulletin boards, phone solicitation, electronic media or any combination thereof.

5.4 Informed Consent and Medical History Forms:

An informed consent was obtained from each volunteer prior to initiating the study describing reasons for the study, possible adverse effects, associated risks and potential benefits of the treatment and their limits of liability. Panelists signed and dated the informed consent document to indicate their authorization to proceed and acknowledge their understanding of the contents. Each subject was assigned a permanent identification number and completed an extensive medical history form. These forms along with the signed consent forms, are available for inspection on the premises of Cantor Research Laboratories, Inc., only. Reference 21 CFR Ch. 1 Part 50, Subpart B.

6.0 Population Demographics:

Number of subjects enrolled		109
Number of subjects completing study		107
Age Range		19 – 70
Sex	Male	32
	Female	77
Race	Caucasian	64
	Hispanic	19
	Asian	2
	African American	24

7.0 Equipment:

- Patch Description: Parke-Davis Hypoallergenic Readi Bandages (20 x 20 mm Webril affixed to the center of a 40 x 40 mm adhesive bandage) or the equivalent.
- 1 ml volumetric syringe without a needle.

8.0 Procedure:

- Subjects are requested to bathe or wash as usual before arrival at the facility.
- 0.2 ml or 0.2 g of the test material is dispensed onto the occlusive, hypoallergenic patch.
- The patch is then applied directly to the skin of the infrascapular regions of the back, to the right or left of the midline and the subject is dismissed with instructions not to wet or expose the test area to direct sunlight.
- After 24 hours the patch is removed by the panelist at home.
- This procedure is repeated until a series of nine consecutive 24 hour exposures have been made for every Monday, Wednesday and Friday for three consecutive weeks.
- In the event of an adverse reaction, the area of erythema and edema is measured. The edema is estimated by the evaluation of the skin with respect to the contour of the unaffected normal skin. Reactions are scored just before applications two through nine and the next test date following application nine. Clients are notified immediately in the case of adverse reaction and determination is made as to treatment program if necessary.
- Subjects are then given a 10 - 14 day rest period after which a challenge or retest dose is applied once to a previously unexposed test site. The retest dose is equivalent to any one of the original nine exposures. Reactions are scored 24 and 48 hours after application.
- Comparison is made between the nine inductive responses and the retest dose.

- At the end of the study, the consulting Dermatologist reviewed this data and confirmed the stated conclusions.

9.0 Results: Please refer to attached Table.

10.0 Observations: No adverse reactions of any kind were noted during the course of this study. Fifty two subjects completing this study were self-described as having sensitive skin.

11.0 Archiving: All raw data sheets, technician's notebooks, correspondence files, and copies of final reports are maintained on premises of Cantor Research Laboratories, Inc., in limited access storage files marked "Archive" for five years after completion of the study. A duplicate disk copy of final reports is separately archived in a bank safe deposit vault.

12.0 Conclusions: The test material (CR Lab No.: C0415-A1; Client No.: [redacted] Lotion/Body Butter, Formula No. 598-154X, Batch 598154X) when tested under occlusive conditions as described herein, may be considered as a **NON-PRIMARY IRRITANT** and a **NON-PRIMARY SENSITIZER** (NON-ALLERGENIC) to the skin according to the reference.

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Dermatologist

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Technician

Christine M. Bremer, B.S.
Technician

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Quality Assurance Supervisor

5/26/05
Date

TABLE
SUMMARY OF RESULTS
(OCCLUSIVE PATCH)

CR Lab No.: C0415-A1
Client No.: [redacted] Lotion/Body Butter, Formula No. 598-154X, Batch 598154X

No.	Subject ID	RACE	SEX	Response									Chall.		Score
				1	2	3	4	5	6	7	8	9	24 HR	48 HR	
1*	03-6638	C	M	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
2	03-6071	H	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
3*	03-6276	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
4	03-6085	H	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
5*	03-6479	A	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
6*	03-6526	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
7	03-6679	C	M	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
8	03-6433	AA	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
9*	03-6061	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
10	03-6678	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
11	03-6107	AA	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
12*	03-6030	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
13	03-6416	AA	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
14*	03-6463	C	F	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
15	03-6065	C	M	0	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
16*	03-6176	AA	F	0	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
17	03-6793	AA	F	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
18*	03-6757	C	F	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
19*	03-6052	A	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
20	03-6529	C	M	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
21	03-6372	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
22*	03-6720	AA	F	0	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
23*	03-6770	C	F	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
24*	03-6171	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
25	03-6668	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
26*	03-6055	C	F	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
27*	03-6450	C	F	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
28	03-6308	C	M	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
29*	03-6088	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
30	03-6583	H	F	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
31*	03-6076	C	F	0	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
32	03-6080	C	F	0	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0

TABLE (CONT'D)
SUMMARY OF RESULTS
(OCCLUSIVE PATCH)

CR Lab No.: C0415-A1
Client No.: [redacted] Lotion/Body Butter, Formula No. 598-154X, Batch 598154X

No.	Subject ID	RACE	SEX	Response									Chall.		Score
				1	2	3	4	5	6	7	8	9	24 HR	48 HR	
33*	03-6656	AA	M	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
34*	03-6098	AA	F	0	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
35	03-6794	C	F	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
36	03-6378	C	M	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
37*	03-6509	AA	F	0	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
38	03-6020	C	F	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
39	03-6258	H	F	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
40*	03-6281	H	M	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
41	03-6282	H	M	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
42	03-6431	AA	M	0	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
43*	03-6316	C	F	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
44*	03-6375	C	M	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
45	03-6541	C	F	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
46	03-6168	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
47	03-6235	AA	M	0	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
48*	03-6597	AA	F	0	0	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
49*	03-6204	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
50	03-6672	C	M	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
51	03-6144	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
52*	03-6418	C	M	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
53*	03-6183	H	M	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
54*	03-6615	H	M	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
55	03-6368	C	F	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
56	03-6089	H	F	0	S/0	S/0	S/0	S/0	Dc	Dc	Dc	Dc	Dc	Dc	NA
57	03-6391	AA	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
58*	03-6045	H	M	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
59*	03-6747	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
60*	03-6003	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
61	03-6395	AA	M	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
62	03-6078	C	M	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
63	03-6784	AA	F	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
64	03-6496	C	M	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0

TABLE (CONT'D)
SUMMARY OF RESULTS
(OCCLUSIVE PATCH)

CR Lab No.: C0415-A1
Client No.: [redacted] Lotion/Body Butter, Formula No. 598-154X, Batch 598154X

No.	Subject ID	RACE	SEX	Response									Chall.		Score
				1	2	3	4	5	6	7	8	9	24 HR	48 HR	
65*	03-6610	C	F	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
66	03-6039	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
67*	03-6040	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
68*	03-6545	AA	F	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
69*	03-6028	C	F	S/0	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	Dc	NA
70*	03-6153	C	F	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
71*	03-6721	AA	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
72*	03-6643	C	F	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
73*	03-6718	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
74*	03-6184	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
75	03-6787	AA	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
76	03-6077	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
77*	03-6422	C	M	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
78*	03-6500	AA	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
79	03-6518	C	F	0	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
80	03-6165	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
81	03-6687	C	M	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
82*	03-6458	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
83*	03-6081	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
84	03-6009	H	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
85	03-6038	H	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
86	03-6169	H	M	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
87	03-6274	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
88*	03-6034	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
89*	03-6573	AA	M	0	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
90	03-6037	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
91	03-6539	H	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
92	03-6565	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
93*	03-6635	AA	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
94	03-6162	H	M	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
95	03-6356	H	M	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0

TABLE (CONT'D)
SUMMARY OF RESULTS
(OCCLUSIVE PATCH)

CR Lab No.: C0415-A1
Client No.: [redacted]otion/Body Butter, Formula No. 598-154X, Batch 598154X

No.	Subject ID	RACE	SEX	Response 1	2	3	4	5	6	7	8	9	Chall. 24 HR	48 HR	Score
96	03-6173	H	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
97*	03-6264	H	M	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
98	03-6298	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
99	03-6148	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
100*	03-6164	H	M	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
101	03-6492	C	M	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
102*	03-6376	C	M	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
103	03-6538	C	M	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
104	03-6174	C	F	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
105	03-6062	C	F	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
106*	03-6278	AA	F	0	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
107*	03-6314	AA	F	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
108	03-6501	AA	M	0	0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0
109	03-6255	C	F	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	S/0	0.0

* Panelist self-described as having sensitive skin

Evaluation Period:

This study was conducted from April 18, 2005 through May 25, 2005.

Scoring Scale and Definition of Symbols Shown In Table:

0 - No evidence of any effect

? - (Barely perceptible) minimal faint (light pink) uniform or spotty erythema

1 - (Mild) pink uniform erythema covering most of contact site

2 - (Moderate) pink\red erythema visibly uniform in entire contact area

3 - (Marked) bright red erythema with accompanying edema, petechiae or papules

4 - (Severe) deep red erythema with vesiculation or weeping with or without edema

D - Patch eliminated due to reaction

Dc - Discontinued due to absence of subject on application date

M - Patch applied to an adjacent site after strong test reaction

NA - Score is not calculated for subjects discontinued before challenge

S - Skin stained from pigment in product

T - Tan

NOTE: All technical employees of Cantor Research Laboratories, Inc. are required to take and pass a visual discrimination examination conducted by a Board Certified Ophthalmologist using the Farnsworth-Munsell 100 Hue Test as published; which determines a person's ability to discern color against a black background. This test was additionally modified to include a flesh tone background more nearly approaching actual use conditions, wherein erythematous skin is graded according to intensity.

Concentration of Use by FDA Product Category – Papaya-Derived Ingredients*

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

Ingredient	Product Category	Maximum Concentration of Use
Carica Papaya (Papaya) Fruit Extract	Powders (dusting and talcum)	0.0003%
Carica Papaya (Papaya) Fruit Extract	Hair conditioners	0.0006%
Carica Papaya (Papaya) Fruit Extract	Hair sprays Pump spray	 0.00023%
Carica Papaya (Papaya) Fruit Extract	Hair dyes and colors	0.008%
Carica Papaya (Papaya) Fruit Extract	Lipstick	0.000002-0.02%
Carica Papaya (Papaya) Fruit Extract	Bath soaps and detergents	0.015-0.25%
Carica Papaya (Papaya) Fruit Extract	Deodorants Not spray Aerosol	 0.005% 0.0008%
Carica Papaya (Papaya) Fruit Extract	Shaving cream	0.0025%
Carica Papaya (Papaya) Fruit Extract	Other shaving preparations	0.01%
Carica Papaya (Papaya) Fruit Extract	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.02%
Carica Papaya (Papaya) Fruit Extract	Depilatories	0.01%
Carica Papaya (Papaya) Fruit Extract	Face and neck cream Not spray	 0.000085-0.02%
Carica Papaya (Papaya) Fruit Extract	Body and hand products Not spray Not spray or powder	 0.01% 0.02%
Carica Papaya (Papaya) Fruit Extract	Suntan products Not spray Pump spray	 0.01% 0.01%
Carica Papaya (Papaya) Fruit Extract	Indoor tanning preparations	0.00025%
Carica Papaya (Papaya) Fruit Extract	Other suntan preparations	0.01%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey but no uses were reported.

Information collected in 2018

Table prepared October 24, 2018

Corrected July 13, 2020: added hair conditioners; high concentration in depilatories changed from 0.05% to 0.01%

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: June 1, 2020

SUBJECT: Draft Report: Safety Assessment of *Carica papaya* (Papaya)-Derived Ingredients as Used in Cosmetics (draft prepared for the June 8-9, 2020 CIR Expert Panel meeting)

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

Composition - In the Composition section where BITC is discussed, the following additional information from reference 5 should be added: "Papaya leaves and green fruits contain toxicants such as benzyl isothiocyanate (BITC) that can cause irritation of the mucus epithelial membrane. Munguti et al. (2006) reported that soaking in water and heat treatment destroys such toxic compounds in papaya and other plants."