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

Status:	Draft Report for Panel Review
Release Date:	February 21, 2020
Panel Meeting Date:	March 16-17, 2020

The Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The 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.

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Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Priya Cherian, Scientific Analyst/Writer
Date: February 21, 2020
Subject: Draft Report on Papaya-derived ingredients

Enclosed is the Draft Report on 5 papaya-derived ingredients. The attached report (*papaya032020rep*) includes the following unpublished data that were received from the Council:

1) Use concentration data (*papaya032020data1*)
2) Manufacturing and impurities data on a Carica Papaya (Papaya) Fruit Extract (*papaya032020data2*)
3) Physical and chemical properties of a Carica Papaya (Papaya) Fruit Extract (*papaya032020data3*)

Also included in this package for your review are the CIR report history (*papaya032020hist*), flow chart (*papaya032020flow*), literature search strategy (*papaya032020strat*), ingredient data profile (*papaya032020prof*), and updated 2020 FDA VCRP data (*papaya032020fda*). Comments provided by the Council on the SLR were received and addressed (*papaya032020pcpc*).

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

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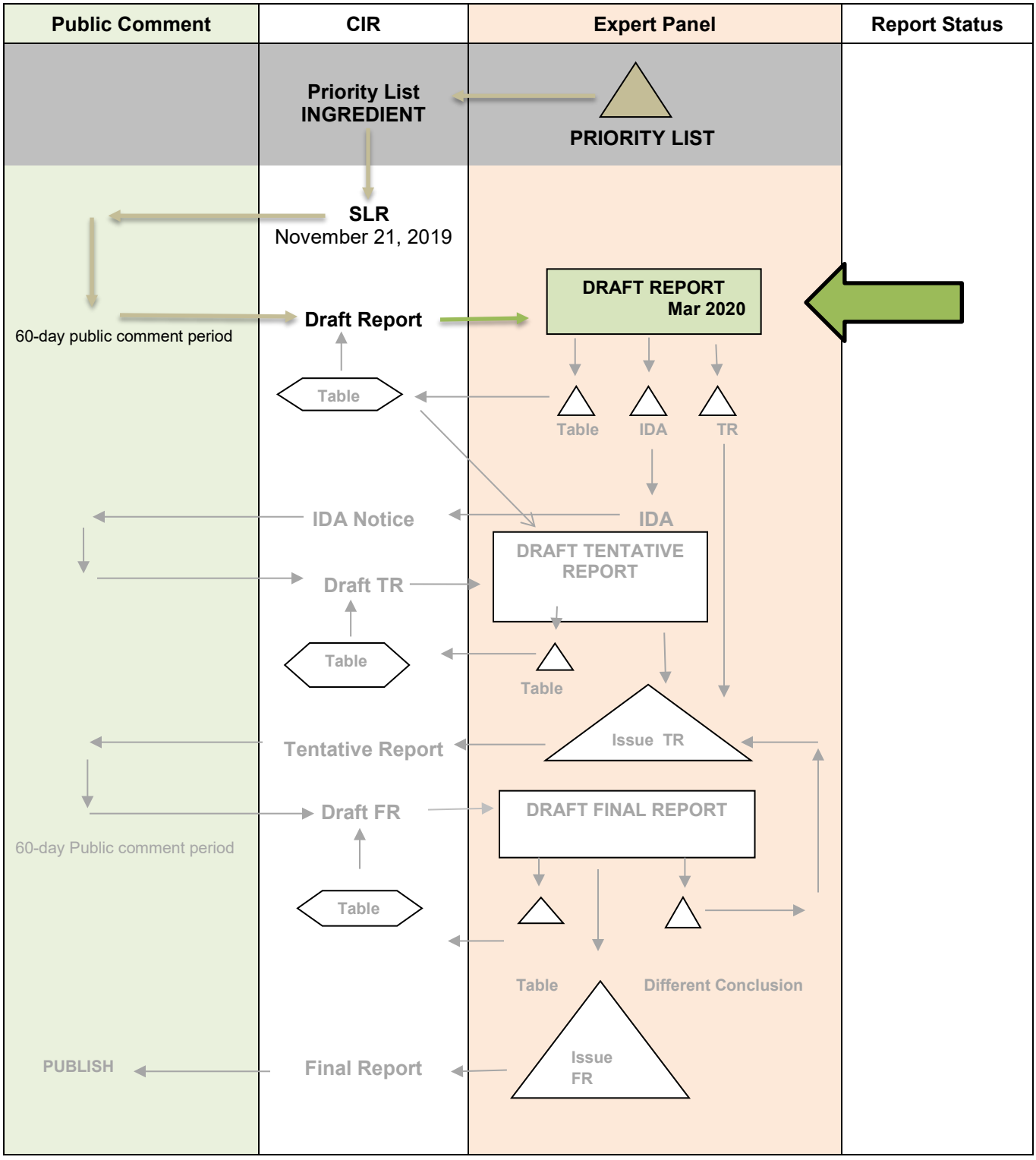
SAFETY ASSESSMENT FLOW CHART

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

MEETING March 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

March 2020
-Panel reviews Draft Report

Papaya-derived ingredients Data Profile – March 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																	
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)
- Scifinder (https://scifinder.cas.org/scifinder)

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)

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

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

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 Panel has previously reviewed the safety of a *Carica papaya*-derived ingredient. In 2017, CIR published a safety assessment of plant-derived oils, 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 CIR typically evaluates, is provided on the CIR website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Although the seeds of *Carica-papaya* are not an ingredient being reviewed in this report, information regarding these seeds has been included as it may be helpful in determining the safety of the *Carica papaya*-derived ingredients. The relevancy of this data has yet to be determined by the Panel.

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, CIR is reviewing the potential toxicity of each of the botanical ingredients as a whole, complex mixture; CIR is not reviewing the potential toxicity of the individual constituents.

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 (INC) terminology (e.g., Carica Papaya (Papaya) Leaf Extract) will be used.

CHEMISTRY

Definition and Plant Identification

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. The skin of unripe fruit is smooth and green.[5] 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.

Physical and Chemical Properties

According to a supplier, a mixture of Carica Papaya (Papaya) Fruit Extract (CAS No. 84012-30-6), glycerin, and water is a water-soluble liquid that is clear in color.[6] A mixture of Carica Papaya (Papaya) Leaf Extract (CAS No. 84012-30-6), glycerin, and water is also a liquid, is completely soluble in water, and is a light to medium amber in color.[7] Other available physical and chemical properties of these two ingredients are described in Table 2.

Methods of Manufacturing

The majority of the methods below are general to the processing of *Carica papaya*, and it is unknown if they apply to cosmetic ingredient 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.[8] 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.[9] 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.[10] 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.[11] 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

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.[12] A study was performed in order to evaluate the chemical composition of the unripe pulp of *Carica papaya*.[13] 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.[14] 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.[15] A single papaya fruit contains approximately 25 g of latex.[16] 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;[5] 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.[15] 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.[5] 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.[5] 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.[5] BITC content decreases from 109 µg BITC/g when papaya fruit is green, to 10 µg BITC/g 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.[17] According to another study, extracts of unripe *Carica papaya* fruit contained terpenoids, alkaloids, flavonoids, carbohydrates, glycosides, saponins, and steroids.[18]

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.[19]

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.[20] Carpaine is a major alkaloid found in various parts of papaya, but is primarily found in leaves.[21] 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). Carpaine concentration in dry leaves was found to range from 0.02 to 0.31%. Papaya leaves also contain toxins, such as BITC.[5]

Impurities

Carica Papaya (Papaya) Fruit Extract

Heavy metals testing was performed on the concentrate of a Carica Papaya (Papaya) Fruit Extract in a safflower oil base.[8] 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).

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).[22] The results of a concentration of use survey conducted by the Council in 2018 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.[23] 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%.[23] 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.[24-27] 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.[24,26] 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.[26] 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.[28-30]

The *Carica papaya*-derived ingredients are not restricted from use in any way under the rules governing cosmetic products in the European Union.[31]

Non-Cosmetic

Carica papaya fruit is commonly known for its food use and nutritional value throughout the world.[32] 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.[33] 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.[5] 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.[34] Other reported effects of leaf extracts include: antifungal, anti-inflammatory, and antioxidant properties.[18,35] The extracts have also been researched for the management of burn injuries.[36] The milky juice of *Carica papaya* fruit, when extracted and dried, is used as

chewing gum, toothpaste, and meat tenderizer.[18] 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.[37] In ayurvedic medicine, the *Carica papaya* fruit is used for treatment of digestive ailments, as well as ringworm and psoriasis.[32] The fruit is also reported to be used as an abortifacient, laxative, diuretic, anti-inflammatory and antibacterial agent.

TOXICOKINETICS

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.[38] No mortality was observed in male Wistar rats given up to 1500 mg/kg of a methanolic *Carica papaya* leaf extract via gavage.[39] 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.[40] No mortalities were observed when a methanolic *Carica papaya* leaf extract was given to Wistar mice in doses of up to 3200 mg/kg.[41]

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/day), orally, for 42 days.[38] Wistar rats given a methanolic *Carica papaya* leaf extract (400 mg/kg bw/d) via gavage for 28 days 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.[39] No extract-related effects were noted when green *Carica papaya* leaf extract (up to 2000 mg/kg/day) was given to Sprague-Dawley rats for 28 days via gavage.[15] Similarly, no adverse effects were reported when Wistar mice were given a methanolic *Carica papaya* leaf extract (up to 3200 mg/kg/day) for 60 days.[41] 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 years.[42] 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.[43] 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).[44] 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.[45] 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.[46] Treated rats were given 500 mg/kg bw extract orally for 21 days. 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 days.[39] 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.[47] Rats (10 rats/group) were given 50, 100, or 800 mg/kg bw/day 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/day) to male albino mice (6/group) for 10 to 30 days via gavage caused a significant decrease in sperm count and sperm motility when compared to the control animals that were given water only.[48] The potential reproductive effects of an

aqueous alkaloid extract of *Carica papaya* seeds was studied in male Wistar rats (5 rats/group).[49] Each rat was dosed orally (route of administration not stated) with the extract daily, for 3 days, with doses of either 10, 50, or 150 mg/kg/day, 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/day 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.[50] 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/day for 150 days. No treatment-related adverse effects were observed; fertility, semen quality, and hematological parameters were similar among treated and control groups.

CARCINOGENICITY

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).[51] 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).[52] Two groups of mice were subcutaneously injected with purified r Cari p 1 (10 µg antigen/animal) emulsified in an adjuvant. Seven days 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

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

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-year-old woman without a history of atopic disease of drug allergy developed a maculopapular symmetric exanthematous rash approximately 2 days after taking throat lozenges containing papaya juice.[53] 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 weeks of this treatment. Four weeks 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.[52] 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.[54] 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.[55] 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.[56] 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.[57] 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 Kd molecular size range, were detected in most extracts. Putative chitinases appeared in papaya (30-35 Kd) and latex (35-45 Kd). 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 Kd) and latex (6-10, 20, and 35-45 Kd). All of these specific IgE-binding components, except for the 6- to 10 Kd and 20 Kd 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 Kd, 23- to 28 Kd, and 50- to 70 Kd 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 CIR 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 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 days. Wistar rats given a methanolic *Carica papaya* leaf extract (400 mg/kg bw/d) via gavage for 28 days 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 days 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 days. 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 years. 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 days. 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 days. 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/day) was given to male albino mice for 10 to 30 days. The potential reproductive effects of an aqueous alkaloid extract of *Carica papaya* seeds (10, 50, and 150 mg/kg/day) 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/day. 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/day, for 150 days. 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.

A 55-year-old woman without a history of atopic disease or drug allergy developed a rash 2 days 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 days 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 Kd) and latex (35-45 Kd). In latex-fruit allergic patient sera, reactive proteins were located in both papaya (30-35 Kd) and latex (6-10, 20, and 30-45 Kd). No reactive bands were observed in sera of patients with latex allergy only, however, high molecular size bands were observed in the control group.

DISCUSSION

To be developed.

CONCLUSION

To be determined.

TABLES

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

Ingredient/CAS No.	Definition & Structure	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. Physical and Chemical Properties

Property	Value	Reference
Carica Papaya (Papaya) Fruit Extract (in glycerin and water)		
Physical Form	Liquid	9
Color	Yellowish-brown to brown	9
Odor	Characteristic	6
pH	3.0 – 5.0	9
Density/Specific Gravity (@ 25 ºC)	1.05 - 1.15	6
Boiling Point (ºC)	290	6
Water Solubility	Complete	6
Carica Papaya (Papaya) Leaf Extract (in glycerin and water)		
Physical Form	Liquid	7
Color	Light to medium amber	7
Odor	Characteristic	7
Density/Specific Gravity (@ 25 ºC)	1.05 - 1.15	7
Boiling Point (ºC)	290	7
Water Solubility	Complete	7

Table 3. Potential fragrance allergen evaluation of a Carica Papaya (Papaya) Fruit Extract[8]

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

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	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*	*0.0025 – 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	NR	NR
Hair-Coloring	4	NR	NR	0.008; 0.005[b]	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

	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	[38]
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.	[39]
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 days.	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.	[40]
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.	[41]

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-day 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.	[38]
Carica papaya leaf extract (methanolic) 0, 100, 200, and 400 mg/kg bw/d	male Wistar rats; 8/group	28-day 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.	[39]
green *Carica papaya* leaf extract (aqueous) 10, 140, and 2000 mg/kg/day	Sprague-Dawley rats; 10 /sex/group	28-day 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 week 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.	[15]
Carica papaya leaf extract (methanolic) 200, 400, 800, 1600, and 3200 mg/kg/day	Wistar strain mice; 30 males/group	60-day 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.	[41]
		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 months of feeding, two mice of each sex from each group were sacrificed and subjected to complete gross pathologic examinations. All animals remaining at 24 months were killed and examined.	No significant changes in final body weights were noted in any groups from the tenth week through the twentieth month. After the twentieth month, 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.	[42]

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.	[43]
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 weeks 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 one week. 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.	[44]
Carica papaya leaf extract (aqueous)	Wistar rats	6 females/group	0, 60 mg/kg, or 120 mg/kg/day	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.	[45]

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/day	The test group was administered a single daily dose of the extract, orally, for 21 days 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.	[46]
Carica papaya leaf extract (methanolic extract)	Wistar rats	8 males/group	100, 200, and 400 mg/kg bw/day	Test animals were dosed for 28 days 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.	[39]
Carica papaya seed extract (aqueous extract)	albino Swiss mouse	6 males/group	50 mg/kg bw/day; 0.1 mL controls were given distilled water only	Mice were dosed via gavage for either 10, 20 or 30 days. Animals were sacrificed post-treatment for evaluation.	A significant decline ($P < 0.001$) of sperm count was noted in mice after 10 to 30 days 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 days 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.	[48]
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/day; controls given corn oil	Treatments were given orally for 3 days; 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 day papaya showed no pregnancies, whereas female rats mated with male rats treated with corn oil delivered an average of 9 pups after a 21-day gestation period. One female rat mated with male rats treated with 10 mg/kg/day papaya daily for 3 days delivered only 4 pups.	[49]
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/day; controls given corn oil	Animals were dosed for 3 days and used for semen analysis and testes histopathology. Method of oral administration was not stated. Twenty-four hours 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.	[49]
Carica papaya seed extract (aqueous extract)	Sprague-Dawley rats	10 females/group	GI and GII: 50, 100 and 800 mg/kg bw/day	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.	[47]

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/day	Rats were dosed via gavage for 150 days. 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.	[50]

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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

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 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	0.05%
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

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: December 18, 2019

SUBJECT: Papaya-Derived Ingredients

Anonymous. 2019. Carica Papaya (Papaya) Fruit Extract: Manufacturing process and impurities.

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

- **Carica Papaya (Papaya) Fruit Extract**

Manufacturing Process:

The **fresh/dried fruit** is extracted with specified **eluent(s) under appropriate temperature conditions,** to yield a **concentrate.** The concentrate containing the phytochemical constituents is then blended with the desired diluent(s) and preservation system to produce the final ingredient. The ingredient is evaluated for physiochemical properties according to the specification requirements for the batch to be released. In addition, the concentrate is also evaluated for contaminants and physiochemical properties as needed.

Typical eluents include Water, Butylene Glycol, Carthamus Tinctorius (Safflower) Seed Oil, Glycerin, and Propylene Glycol.

Heavy Metal & Pesticides/ Allergens/ Impurities:

The following heavy metal testing was conducted on the concentrate in an safflower oil base:

	Heavy Metal	Detection	Reporting Limit	Heavy Metal	Detection	Reporting Limit
Heavy metals:	Antimony	Not Detected	0.005 mg/l	Iron	Not Detected	0.1 mg/l
	Arsenic	Not Detected	0.01 mg/l	Lead	Not Detected	0.0025 mg/l
	Cadmium	Not Detected	0.001 mg/l	Mercury	Not Detected	0.0002 mg/l
	Chromium	Not Detected	0.002 mg/l	Nickel	Not Detected	0.002 mg/l

There were no residual pesticides detected. (Parameters: 8081 GCS Pesticides and 8141 GCS, O/P Pesticides)

The following Allergen testing was conducted on the concentrate in an alcohol base:

	Fragrance Ingredient	Threshold	Fragrance Ingredient	Threshold
Presence of the 26 allergens defined by the 7th amendment to the EU Cosmetic Directive:	Amyl Cinnamal	<1ppm-0.0001%	Anise Alcohol	<1ppm-0.0001%
	Benzyl Alcohol	<1ppm-0.0001%	Benzyl Cinnamate	<1ppm-0.0001%
	Cinnamyl Alcohol	<1ppm-0.0001%	Farnesol	<1ppm-0.0001%
	Citral	<1ppm-0.0001%	Butylphenyl Methylpropional	<1ppm-0.0001%
	Eugenol	<1ppm-0.0001%	Linalool	<1ppm-0.0001%
	Hydroxycitronellal	<1ppm-0.0001%	Benzyl Benzoate	<1ppm-0.0001%
	Isoeugenol	<1ppm-0.0001%	Citronellol	<1ppm-0.0001%
	Amylcinnamyl Alcohol	<1ppm-0.0001%	Hexyl Cinnamal	<1ppm-0.0001%
	Benzyl Salicylate	<1ppm-0.0001%	Limonene	<1ppm-0.0001%
	Cinnamal	<1ppm-0.0001%	Methyl l2-octynoate	<1ppm-0.0001%
	Hydroxyisohexyl 3-Cyclohexene Carboxaldehyde	<1ppm-0.0001%	Alpha-Isomethyl Inone (Other Name: Methyl Lonone Gamma)	<1ppm-0.0001%
	Coumarin	<1ppm-0.0001%	Evernia Prunastri (Oak Moss) Extract	Not Detected
	Geraniol	<1ppm-0.0001%	Evernia Furfuracea (Tree Moss) Extract	Not Detected

*The given values correspond to the limit of determination OR *Results have been calculated form highest reported values published.

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: December 19, 2019

SUBJECT: Carica Papaya (Papaya) Fruit Extract

Anonymous. 2019. Summary information: Carica Papaya (Papaya) Fruit Extract.

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

December 2019

Summary Information - Carica Papaya (Papaya) Fruit Extract

Ripe papaya fruit pulp is extracted with water.

Because the material is heated to 100 ° C, the enzymes are denatured, so there is NO enzymatic activity.

Specifications

Physicochemical Control	Specification
Form	Liquid
Colour	Yellowish-brown to brown
Odor	Characteristic of the fruit
Total solids	3.00% (minimum)
Total ash	0.1%
pH	3.00 to 5.00
Solubility	Water soluble

Personal Care Products Council
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Memorandum

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

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

DATE: December 12, 2019

SUBJECT: Scientific Literature Review: Safety Assessment of *Carica papaya* (Papaya)-Derived Ingredients as Used in Cosmetics (release date: November 21, 2019)

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

Key Issues

More information about the potential of papaya to cause Type 1 allergic reactions should be included in this report, such as the 2018 paper entitled: "Cari p 1, a Novel Polygalacturonase Allergen From Papaya Acting as Respiratory and Food Sensitizer" found at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6016011/pdf/fpls-09-00823.pdf.

DART - The two year study in mice (reference 39) indicates that a 3-generation study in mice was also completed. The 3-generation study is available at https://digital.library.unt.edu/ark:/67531/metadc1025733/m2/1/high_res_d/4718658.pdf and should be added to the DART section.

Additional Considerations

Introduction - Regarding the CIR report on plant oils, it should be made clear that the report was published in 2017.

It would be better to be more specific and call papain an enzyme or protein, rather than a "chemical".

Physical and Chemical Properties - Please indicate that both extracts described in this section are in Glycerin and Water.

Methods of Manufacturing - It should also be stated that by definition, Carica Papaya (Papaya) Fruit Water is a product of distillation.

Methods of Manufacturing, Carica Papaya (Papaya) Leaf Extract - It should be stated that in reference 10, the surface of the leaves were sterilized by putting them in a 0.1% solution of mercuric chloride.

Composition - The following sentence does not belong in the Composition section. "(Papain may induce immunoglobulin E (IgE)-mediated allergic reactions through oral, respiratory, or dermal routes of exposure.)".

Cosmetic Use - The European inventory of cosmetic ingredients (most recent version available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2019.121.01.0001.01.ENG&toc=OJ:L:2019:121:TOC) does not include limitations. The inventory is just a list of labeling names. Restrictions are found in the European cosmetic regulations. COSING is an internet tool that includes both the inventory and the European Cosmetic Regulations. Please revise the following sentence as it implies that the inventory includes restrictions: "The Carica papaya-derived ingredients described in this report are listed in the European Union inventory with no restrictions of use in cosmetic products." This sentence is cited to reference 29 entitled: "The influence of particle size" , which is not the correct reference.

DART - The studies on seed extract are presented at the end of the second paragraph and in the last paragraph of this section. They do not need to be presented twice.

Summary - In the first paragraph, please correct: "is flavonoids" (to "isoflavonoids")

Please include the plant part of the extract used in the rat acute oral toxicity study in which the LD_{50} was 2520 mg/kg, and in the study in male rats treated with 100, 200 or 400 mg/kg bw for 28-days.

Table 2 - Please include the solvents in which these ingredients are sold.

Table 5 - At what doses were the histopathological effects observed in the kidneys, heart and kidneys (reference 36)?

Please correct "administrated" (to "administered")

In the summary of the 2-year study of papaya fruit in mice, it is not correct to state that the number of animals/sex were not specified. Table 1 of the study indicates that were 75 males and 75 females in each dose group. The interim sacrifices completed in this study should be described in the Method column. The Results column states "None of the animals died during the study". For a 2-year study with so many mice that was completed in 1971, this is highly implausible. See table VI in the report; there were multiple deaths in this study, but the deaths were not related to treatment.

Table 6 - In the description of the test article studied in reference 44, it should be made clear that the papaya seeds were first extracted with petroleum ether, then the petroleum ether was further extracted with ethanol.