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

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All interested persons are provided 60 days from the above date (January 20, 2020) to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; 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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INTRODUCTION

This scientific literature review is the initial step in preparing 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*), with the exception of Carica Papaya (Papaya) Fruit (for which no function is reported), the *Carica papaya*-derived ingredients in this safety assessment are reported to function as skin conditioning agents in cosmetic products (Table 1).[1] The Panel has previously reviewed the safety of a *Carica papaya*-derived ingredient. In 2017, the CIR Expert Panel reviewed the safety of plant-derived oils; the Panel concluded that the 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. Although papain is not among the ingredients reviewed in this report, information regarding this chemical 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

This tropical plant is a member of the Caricaceae family that originated in central America.[3] The papaya 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.[4] 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, the trees are cultivated in Florida.

Physical and Chemical Properties

Carica Papaya (Papaya) Fruit Extract is a water-soluble liquid that is clear in color.[5] Carica Papaya (Papaya) Leaf Extract is also a liquid that is completely soluble in water, and is light to medium amber in in color.[6] Other available physical and chemical properties of these two ingredients are described in Table 2.

Methods of Manufacturing

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

Fresh fruits of papaya were first cut into small pieces, dried, and ground with a blender into powder form.[7] This process was followed by soaking and stirring of the powder in absolute ethanol (200 g/500 mL ethanol) for 3 days. The papaya fruit extract was filtered, and the residue was re-extracted twice using ethanol, and the pooled extract was then vacuum-dried at 40 ºC. According to the same study, an aqueous papaya fruit extract was prepared by a maceration process. The filtrate was subjected to a lyophilization process using a freeze dryer system.

A different *Carica papaya* fruit extract was prepared by first obtaining the matured, fresh, unripe fruit.[8] The fruit was then peeled and the seeds were discarded. One-hundred grams of the fruit was soaked in 100 mL of distilled water and incubated at room temperature for 72 h.

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.[9] 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.[10] 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.

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.[11] A study was performed in order to evaluate the chemical composition of the unripe pulp of *Carica papaya*.[12] 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.[13] Results indicated that unripe papaya has the most carbohydrates, vitamins, and proteins, 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 compounds, including 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.[14] A single papaya fruit contains approximately 25 g of latex.[15] Papain is found in the fruit,[4] 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.[14] (Papain may induce immunoglobin E (IgE)-mediated allergic reactions through oral, respiratory, or dermal routes of exposure.[4]) Cysteine peptidases 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.[4] 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.[4] 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.[4] 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.[7] According to another study, extracts of unripe *Carica papaya* fruit contained terpenoids, alkaloids, flavonoids, carbohydrates, glycosides, saponins, and steroids.[16]

Carica Papaya Fruit Juice

The major constituents of a *Carica papaya* fruit juice were reported as lipids, and n-butyric, n-hexanoic, n-octanoic, myristic, palmitic, stearic, linoleic, linolenic, vaccenic, and oleic acids.[17]

Carica Papaya Leaf Extract

A methanolic extract of *Carica papaya* leaf extract was found to contain polyphenols and tannins, flavonoids, saponins, terpenoids, glycosides, alkaloids, and high amounts of glycosides.[18] Carpaine is a major alkaloid found in various parts of papaya,

but is primarily found in leaves.[19] In a study, 29 samples of *Carica papaya* leaves were used to examine relative carpaine concentration. The assay involved pressurized 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.[4]

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 2019 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 337 cosmetic products (176 leave-on products, 160 rinse-off products; Table 3).[20] 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.[21] 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%.[21] 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.[22-25] 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.[22,24] Carica Papaya (Papaya) Fruit Extract is reportedly used in deodorant sprays 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.[24] 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 (3 reported uses). 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.[26-28]

The *Carica papaya*-derived ingredients described in this report are listed in the European Union inventory with no restrictions of use in cosmetic products.[29]

Non-Cosmetic

Carica papaya fruit is commonly known for its food and nutritional value throughout the world.[30] Ripe papaya fruits are typically eaten raw, but are also used in jams, jelly, marmalade, puree, wine, nectar, juice, mixed beverages, ice cream, baby food, and pies.[31] 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.[4] 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.[32] Other reported effects of the leaf extract include: antifungal, anti-inflammatory, and antioxidant properties.[16,33] The extracts have also been researched for the management of burn injuries.[34] The milky juice of *Carica papaya* fruit, when extracted and dried, is used as chewing gum, toothpaste, and meat tenderizers.[16] 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.[35] In ayurvedic medicine, the *Carica papaya* fruit is used for treatment of digestive ailments, as well as ringworm and psoriasis.[30] 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 4.

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.[8] No mortality was observed in male Wistar rats given up to 1500 mg/kg of a methanolic *Carica papaya* leaf extract via gavage.[36] 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 aqueous *Carica papaya* leaf extract.[37] No mortalities were observed when a methanolic *Carica papaya* leaf extract was given to Wistar mice in doses of up to 3200 mg/kg.[38]

Short-Term and Chronic Toxicity Studies

The short-term and chronic oral studies summarized below are described in Table 5**.**

No signs of toxicity were observed when Wistar albino rats were given *Carica papaya* fruit extract (up to 250 mg/kg/day), orally, for 42 days.[8] 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.[36] 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.[14] 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.[38] A study was performed in order to evaluate the toxicity of irradiated and non-irradiated papaya fruit given to Swiss white mice for 2 years.[39] All papaya fruit-treated groups received a diet consisting of 15% papaya (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 6.

The effect of ripe papaya 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.[40] No signs of fetal or maternal toxicity were observed in any of the treatment groups. 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.[41] 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.[42] 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.[36] 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.[43] 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.[44] Results showed that oral administration of *Carica papaya* seed extract prevents fertilization, reduces sperm cell counts, promotes sperm cell degeneration, and induces 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.[45] 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.[46] Fertility, semen quality, and hematological parameters were similar among treated and control groups.

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.[45] 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.[43] The potential reproductive effects of an aqueous alkaloid extract of *Carica papaya* seeds was studied in male Wistar rats (5 rats/group).[44] 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.[46] 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).[47] The extract significantly inhibited the proliferative responses of 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.

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 were found in the published literature, and unpublished data were not submitted

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*, these ingredients function as skin-conditioning agents in cosmetic products. The *Carica papaya* plant contains many bioactive phytochemicals, such as phenolic acids, flavonoids, is flavonoids, saponins, phytosterols, and alkaloids. These phytochemicals vary based on specific parts of the plant.

According to 2019 VCRP survey data, the ingredient with the most reported uses is Carica Papaya (Papaya) Fruit Extract, which is reported to be used in 337 cosmetic products (176 leave-on products, 160 rinse-off products). 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 *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 papayas given to Swiss white mice for 2 years. All papaya-treated groups received a diet consisting of 15% papaya (irradiated or non-irradiated). No treatment-related clinical, hematological, pathological, or behavioral abnormalities were noted.

The effect of ripe papaya 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. 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 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.

DATA NEEDS

CIR is seeking physical properties, method of manufacturing, and additional data on the composition and impurities of the *Carica papaya*-derived ingredients described in this report as used in cosmetic formulations. Additional toxicological data, specifically dermal irritation and sensitization data on these cosmetic ingredients, at or above maximum use concentrations, are also being sought in order to help the CIR Expert Panel assess the safety of the use of these ingredients.

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		
Physical Form	Liquid	
Color	Clear	5
Odor	Characteristic	5
Density/Specific Gravity (25 ºC)	1.05 - 1.15	5
Boiling Point (ºC)	290	5
Water Solubility	Complete	5
Refractive Index (25 ºC)	1.39 – 1.50	5
Carica Papaya (Papaya) Leaf Extract		
Physical Form	Liquid	6
Color	Light to medium amber	6
Odor	Characteristic	6
Density/Specific Gravity (25 ºC)	1.05 - 1.15	6
Boiling Point (ºC)	290	6
Water Solubility	Complete	6
Refractive Index (25 ºC)	1.39 – 1.50	6

Table 3. Frequency (2019)[20] and concentration (2018)[21] 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*	**9**	**NR**	**337**	**0.000002 – 0.25**	**5**	**NR**
Duration of Use						
Leave-On	*1*	*NR*	*176*	*0.000002 – 0.02*	2	*NR*
Rinse-Off	*8*	*NR*	*160*	*0.0025 – 0.25*	3	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*1*	*NR*	NR	*NR*
Exposure Type						
Eye Area	NR	NR	12	NR	NR	NR
Incidental Ingestion	NR	NR	7	0.000002 – 0.02	NR	NR
Incidental Inhalation-Spray	1[a]	NR	63[a]; 64[b]	0.00023 - 0.01; 0.00025 – 0.01[a]; 0.02[b]	1[a]; 1[b]	NR
Incidental Inhalation-Powder	NR	NR	3; 64[b]	0.0003; 0.000085 – 0.02[b]; 0.02[c]	1[b]	NR
Dermal Contact	5	NR	290	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 4. 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	[8]
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.	[36]
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.	[37]
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.	[38]

Table 5. 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.	[8]
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.	[36]
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; administrated 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.	[14]
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.	[38]
Chronic Studies				
Irradiated and non-irradiated papaya fruit	Swiss white mice; 75/group (number of animals/sex not specified)	2-year study; 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 received stock feed	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. None of the animals died during the study and there were no treatment-related clinical or behavioral signs. Two animals per group of each sex were sacrificed after 3, 6, 12 and 18 months. All of the animals remaining at 24 months were killed and examined. When compared to the control groups, there were no treatment-related changes in hematological and clinical chemistry, or gross pathology.	[39]

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

Table 6. 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.	[40]
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.	[41]
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.	[42]
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.	[36]

Table 6. 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)	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.	[43]
Carica papaya seed extract (ethanolic alkaloid extract)	Rat (Wistar)	5 males/group	10, 50, 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.	[44]
Carica papaya seed extract (ethanolic alkaloid extract)	Rat (Wistar)	5 males/group	10, 50, 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.	[44]
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.	[45]
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.	[46]

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