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# Safety Assessment of *Punica granatum* (Pomegranate)-Derived Ingredients as Used in Cosmetics

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## ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 18 *Punica granatum* (pomegranate)-derived ingredients. Most of these ingredients are reported to function as skin conditioning agents in cosmetic products. The Panel reviewed the available data to determine the safety of these ingredients. Industry should use good manufacturing practices to limit impurities. The Panel concluded that 9 *Punica granatum* (pomegranate) ingredients derived from the fruit, juice, pericarp, and seed are safe in cosmetics in the practices of use and concentration described in this safety assessment. However, the Panel also concluded that the available data on the remaining 9 *Punica granatum* (pomegranate)-derived ingredients are insufficient to make a determination of safety under the intended conditions of use in cosmetic formulations.

## INTRODUCTION

This assessment of the safety of the following 18 *Punica granatum*-derived ingredients is based on the data contained in this report.

Punica Granatum Extract <sup>‡</sup>	Punica Granatum Fruit Water
Punica Granatum Bark Extract	Punica Granatum Juice Extract
Punica Granatum Bark/Fruit Extract	Punica Granatum Leaf Cell Extract
Punica Granatum Callus Culture Extract	Punica Granatum Peel Extract
Punica Granatum Flower Extract	Punica Granatum Pericarp Extract
Punica Granatum Fruit Extract	Punica Granatum Seed
Punica Granatum Fruit Juice	Punica Granatum Seed Cell Culture Lysate
Punica Granatum Fruit/Root/Stem Powder	Punica Granatum Seed Extract
Punica Granatum Fruit/Sucrose Ferment Filtrate	Punica Granatum Seed Powder

<sup>‡</sup> Ingredient has been deleted from the Dictionary, but uses are currently reported.

Most of the *Punica granatum*-derived ingredients detailed in this safety assessment are reported to function in cosmetics as skin conditioning agents, while some are reported to have other functions, such as abrasives and antioxidants, according to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*; see Table 1).<sup>1</sup>

It should be noted that Punica Granatum Extract, which was defined as an extract of the “whole plant,” is no longer listed in the *Dictionary*; trade names that were associated with this ingredient are now included for monographs associated with plant part specific ingredient names, as suppliers have indicated that extracts are not made from the “whole plant.” However, Punica Granatum Extract is still included in the list of ingredients named in this report because it has the highest number of uses reported in the US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database, and because concentration of use data are still associated with this name.

*Punica granatum*, commonly referred to as pomegranate, has been used as a source of Unani and Chinese medicines.<sup>2</sup> Investigations into the antioxidant activity of various extracts derived from parts of *Punica granatum* are numerous; however, the Panel is not evaluating these claims as these are not related to the safety of the use of these ingredients in cosmetic products.<sup>3-8</sup>

In 2017, the Panel published a safety assessment of Punica Granatum Seed Oil and Hydrogenated Punica Granatum Seed Oil, and concluded that these ingredients are safe in the present practices of use and concentration.<sup>9</sup> The Panel also previously reviewed the safety of Punica Granatum Sterols, and concluded that this phytosterol ingredient is safe in the present practices of use and concentration.<sup>10</sup>

Essential oils, oleoresins (solvent free), and natural extracts (including distillates) derived from *Punica granatum* Linnaeus are generally recognized as safe (GRAS) for their intended use in foods for human and animal consumption according to the US FDA. Additionally, the pomegranate fruit, fruit juice, and seeds are consumed as food or beverages, and daily exposure from such consumption would result in much larger systemic exposures than those from use in cosmetic products. Accordingly, the focus of this safety assessment will be on data relevant to the use of *Punica granatum*-derived ingredients in cosmetics, with specific focus on topical exposure when available.

Botanicals, such as *Punica granatum*-derived ingredients, may contain hundreds of constituents. In this assessment, the Panel is reviewing the potential toxicity of each of the *Punica granatum*-derived ingredients as a whole, complex mixture. The Panel is not reviewing the potential toxicity of the individual constituents.

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 the Panel typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (<https://www.cir-safety.org/supplementaldoc/preliminary-search->

[engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline](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.

**Note:** In many of the published studies, it is not known how the substance being tested compares to the cosmetic ingredient. Therefore, if it is not known whether the substance being discussed is a cosmetic ingredient, the test substance will be identified as “pomegranate...” or “*Punica granatum* ...” (e.g., “pomegranate seed extract” or “*Punica granatum* fruits”); if it is known that the substance is a cosmetic ingredient, the *Dictionary* nomenclature “Punica Granatum...” (e.g., “Punica Granatum Seed Extract” or “Punica Granatum Fruit Extract”) will be used.

## **CHEMISTRY**

### **Definition and Plant Identification**

The definitions and functions of the *Punica granatum*-derived ingredients included in this report are provided in Table 1. The *Punica granatum*-derived ingredients, with the exception of Punica Granatum Fruit/Sucrose Ferment Filtrate and Punica Granatum Seed Cell Culture Lysate, are generically associated with the CAS number 84961-57-9; there are no CAS numbers associated with these exceptions.<sup>1</sup> The raw materials for the ingredients in this report are obtained from the deciduous shrub or small tree, *Punica granatum*.<sup>11</sup> These trees can grow to 6 to 10 m (20 to 30 ft) tall. *Punica granatum* trees are native to Afghanistan, Iran, Iraq, Turkey, the Russian Federation, Tajikistan, Turkmenistan, and India.<sup>12</sup> In the US, the trees are cultivated in Arizona and California.<sup>11</sup>

Table 2 lists the generic definitions of the parts of plants that are most pertinent to the ingredients in this report.<sup>1</sup> The fruit produced by the tree are nearly round and are 2.5 to 5 inches wide with a non-edible, tough, leathery peel or rind, and are light to deep pink or red in color.<sup>11</sup> The fruit interior is separated into compartments by membranous walls and white spongy tissue. The compartments are filled with transparent sacs containing fleshy, tart pulp, known as arils, that are red, pink, or white in color. The seeds in the arils represent approximately half of the weight of the whole fruit.

### **Chemical Properties**

#### **Punica Granatum Fruit Extract**

A supplier reported that Punica Granatum Fruit Extract prepared in water is a light to medium pink liquid with a characteristic odor.<sup>13</sup> At 25° C, the pH is 3.3 and the specific gravity is 0.99. This ingredient is soluble in any proportion in water.

Another supplier reported that a tradename mixture containing 20% Punica Granatum Fruit Extract was a clear to slightly hazy liquid with a specific gravity of 1.015 - 1.035 and a pH (direct) of 5.5 - 7.5.<sup>14</sup>

#### **Punica Granatum Pericarp Extract**

A supplier reported that a tradename mixture containing glycerin, water, and 0.1% - 1% Punica Granatum Pericarp Extract was yellowish to red-brown with a density (at 20 °C) of 1.176 - 1.232 g/ml.<sup>15</sup> Another supplier reported a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids) was a light brown to brown liquid with a pH of 3.1 - 5.1 and a specific gravity of 1.0 - 1.1.<sup>16</sup>

### **Methods of Manufacturing**

#### **Punica Granatum Fruit Extract**

A supplier reported that Punica Granatum Fruit Extract is produced through the mechanical processing (grinding/milling) of whole *Punica granatum* fruits followed by aqueous extraction at a specific pH, temperature, and duration.<sup>17</sup> The supplier incorporates this extract into a tradename mixture by dilution in butylene glycol, addition of phenoxyethanol and tetrasodium ethylenediaminetetraacetic acid (EDTA), filtration, and quality control. The final tradename mixture contains 20% Punica Granatum Fruit Extract.

Another supplier reported that Punica Granatum Fruit Extract is produced by extracting fresh or dried fruit with specified eluent(s) under appropriate temperature conditions to yield a concentrate.<sup>13</sup> Typical eluents include water, butylene glycol, carthamus tinctorius (safflower) seed oil, glycerin, and propylene glycol. The concentrate containing phytochemical constituents is then blended with the desired diluent(s) and preservation system to produce the final ingredient.

#### **Punica Granatum Pericarp Extract**

A supplier reported that a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids) is produced by extracting the dried raw material with a 50% ethanolic solution prior to filtering, concentrating, and incorporating 30% butylene glycol solution.<sup>16</sup>

Another supplier reported that Punica Granatum Pericarp Extract (3.1%) in a tradename mixture is produced by water extraction and heating for 1 h at 110 °C.<sup>18</sup> The same supplier reported that Punica Granatum Pericarp Extract (2.5%) in a different tradename mixture is produced by hydroglycolic extraction of the dried pericarp and heating for 1 h at 110 °C.<sup>19</sup>

### Punica Granatum Seed Powder

A supplier reported that Punica Granatum Seed Powder is produced by grinding and sieving pomegranate seeds prior to decontaminating through heat or gamma-rays.<sup>20</sup>

#### **Composition/Impurities**

The main classes of phytochemicals identified from pomegranate (various plant parts) are as follows: ellagitannins, gallotannins, and derivatives; flavonoids; lignans; triterpenoids and phytosterols; fatty acids and lipids; organic acids and phenolic acids; alkaloids, including pelletierine (mainly found in bark); and other compounds, such as catechol and coumestrol.<sup>21,22</sup> Specifically, the triterpenes ursolic acid and oleanolic acid are reported to be constituents of pomegranate leaves, bud, fruits, flowers and seeds.<sup>23</sup> Gallic acid is reported to be a constituent of pomegranate peel, pomegranate juice, pomegranate fruit, and pomegranate flowers. The major constituents of pomegranate pericarp are reported to be hydrolysable ellagitannins (up to 28%) and other polyphenols.<sup>24</sup> The main biologically active constituents of pomegranate root and stem bark are alkaloids (0.5% to 0.9%) and tannins (up to 22% in bark).<sup>24</sup> Yields of constituents have been found to be dependent on solvent types, with polar solvents having a greater ability to extract antioxidants when compared to non-polar solvents.<sup>4,5,25</sup> Pomegranates grown in different conditions and locations may have varying composition levels in different plant parts.<sup>6</sup> Table 3 describes the total phytochemical contents of pomegranate extracts by plant part.<sup>3,6,26-29</sup>

### Punica Granatum Flower Extract

The tannin content of a pomegranate flower extract used in a wound healing efficacy study was 48.7%.<sup>30</sup> The test material was extracted with ethanol. Analyses of methanol extracts of a flower extract characterized a total of 57 phenolic compounds.<sup>31</sup>

The gallic acid and ellagic acid contents of an ethyl acetate soluble fraction of a methanolic extract of pomegranate flower extract were 2.00 mg/g and 68.80 mg/g, respectively.<sup>2</sup> A methanolic extract, and the water-soluble fraction of the methanolic extract, quantified ellagic acid content as 18.85 mg/g and 10.88 mg/g, respectively.

### Punica Granatum Fruit Extract

A food-grade pomegranate fruit extract that was produced from whole pomegranate fruit was standardized to contain 70% polyphenols total, including 30% punicalagins.<sup>32</sup> Other constituents of the extract included not more than 5% ellagic acid and 0.3% gallic acid. Analyses of methanol extracts of a patented pomegranate fruit extract characterized a total of 71 phenolic compounds, including 64 tannins.<sup>31</sup>

A supplier reported that a pomegranate extract contained 20% Punica Granatum Fruit Extract, ~40% butylene glycol, ~40% water, 1% phenoxyethanol, and 0.1% tetrasodium EDTA.<sup>33</sup> This supplier has certified that this product does not contain the 26 allergenic flavors or fragrances restricted by the European Union, nor does it contain pesticides exceeding US Environmental Protection Agency limits. Heavy metals, lead, arsenic, cadmium, microbial content, yeast and mold, and gram-negative bacteria were below detection limits.<sup>14</sup>

Another supplier reported that Punica Granatum Fruit Extract concentrate in an alcohol base had 0.013 mg/l cadmium.<sup>13</sup> Antimony, arsenic, chromium, iron, lead, mercury, and nickel were below levels of detection. No residual pesticides were detected. The 26 fragrance allergens defined by the European Union Cosmetic Regulations were below threshold levels in a concentrate of Punica Granatum Fruit Extract concentrate in an alcohol base.

### Punica Granatum Leaf Extract

A chromatogram of an acetyl acetate extract of pomegranate leaves identified the following constituents: punicalin, ellagic acid derivate, galloyl-hexahydroxydiphenyl-glucose, castalagin derivatives, granatin B, ellagic acid rhamnoside, kaempferol-3-O-glucoside, kaempferol-arabinoside, and a kaempferol derivative.<sup>34</sup>

### Punica Granatum Peel Extract

The major constituents of aqueous pomegranate peel extract were reported as punicalagin, punicalin, ellagic acid, gallic acid, quercetin, luteolin, kaempferol, and naringenin.<sup>35</sup> Ellagic acid, punicalagin  $\alpha$ , and punicalagin  $\beta$  contents of a methanolic pomegranate peel extract were 2.75 mg/g, 3.52 mg/g, and 5.04 mg/g, respectively.<sup>2</sup> A methanolic extract of pomegranate peel used in a wound healing efficacy study contained 34.03% gallic acid and 3.31% catcechin.<sup>36</sup>

### Punica Granatum Pericarp Extract

A supplier reported that a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids) contains tannin and sugar.<sup>16</sup> The heavy metals content is not more than 20 ppm and the arsenic content is not more than 2 ppm.

### Punica Granatum Seed Extract

The fatty acid composition of an ethanol extract of pomegranate seed is described in Table 4.<sup>3</sup>

An ethanolic extract of pomegranate seeds was found to contain triterpenoids, steroids, glycosides, saponins, tannins, alkaloids, and flavonoids.<sup>37</sup> No further details were provided.

Total phenolic content of pomegranate seed extracts was dependent on the solvent type used during extraction.<sup>5</sup> Methanol and water yielded the highest amount of phenolic compounds (27.93 and 22.61 mg/l seed extract, respectively), followed by acetone (3.41 mg/l), butanol (0.57 mg/l), ethyl acetate (0.37 mg/l), and hexane (0.29 mg/l).

#### Punica Granatum Seed Powder

The gross chemical components of pomegranate seed powder are protein (13.66%), fat (29.6%), ash (1.49%), fiber (39.36%), carbohydrate (13.12%), phenolics (0.25%), and moisture (5.82%).<sup>38</sup> Vitamin content includes thiamine (0.930 mg/100g), riboflavin (0.146 mg/100g), L-ascorbic acid (3.02 mg/100g),  $\alpha$ -tocopherol (1.35 mg/100 g), and retinol (0.089 mg/100 g).

### USE

#### **Cosmetic**

The safety of the cosmetic ingredients included in this assessment is evaluated based on data received from the US 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 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.

Although no longer listed in the *Dictionary*, 2020 VCRP survey data indicate that of the ingredients included in this report, Punica Granatum Extract has the most reported uses in cosmetic products, with a total of 334; the majority of the uses are in leave-on skin care products (Table 5).<sup>39</sup> Punica Granatum Fruit Extract has the second greatest number of reported uses in this safety assessment with 188 uses; the majority of these uses are also in leave-on skin care products. The results of the concentration of use survey conducted in 2017 by the Council indicated that Punica Granatum Seed Extract is used at up to 0.3% (in leave-on cuticle softeners).<sup>40,41</sup> Survey data from 2019 indicate that Punica Granatum Extract and Punica Granatum Fruit Extract are used at up to 0.13% (in moisturizing preparations) and 0.1% (in face and neck and night skin preparations), respectively. Punica Granatum Fruit Juice is used at up to 0.1% (in makeup preparations). Ingredients with no reported uses in the VCRP or by the Council are listed in Table 6.

*Punica granatum*-derived ingredients may be used in products that can be incidentally ingested or come into contact with mucous membranes; for example, Punica Granatum Seed Extract is reported to be used in lipstick at up to 0.11%.<sup>40,41</sup> Additionally, some ingredients have been reported to be used in products that may come into contact with the eyes; for example, Punica Granatum Fruit Extract is used at up to 0.018% in eye shadows. Moreover, some ingredients have been reported to be used in spray and powder products that could possibly be inhaled; for example, Punica Granatum Extract is used in a face and neck spray at 0.001% and Punica Granatum Fruit Juice is used in a face powder at 0.01%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters  $> 10 \mu\text{m}$ , with propellant sprays yielding a greater fraction of droplets/particles below  $10 \mu\text{m}$  compared with pump spray.<sup>42-45</sup> 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.<sup>42,43</sup> 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.<sup>46-48</sup>

The *Punica granatum*-derived ingredients described in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.<sup>49</sup>

#### **Non-Cosmetic**

In the US, the essential oils, oleoresins (solvent-free) and natural extractives (including distillates) from *Punica granatum* L. (pomegranate) are GRAS for their use in food intended for human consumption and in animal drugs, feeds, and related products according to 21CFR182.20 and 21CFR582.20, respectively. Minimum quantities of pomegranate juice have been established for use in juice, flavored beverages, and jellies (21CFR101.30 and 21CFR150.140).

Because of antioxidant and anti-inflammatory properties, the extracts of various parts of *Punica granatum* have been researched for use as alternative or therapeutic treatments (as herbal medicines or dietary supplements) for burn injuries and other dermal wounds, canker sores and oral hygiene, neurodegenerative conditions, convulsions, management of diabetes and weight, acute pancreatitis, acute lung injury, myocardial infarctions and other cardiovascular protection, and various cancers.<sup>3,4,8,23,27,30,34,36,37,50-60</sup> The juice and peel extracts have also been researched for use as antifungal and antibacterial treatments.<sup>61-65</sup>

### TOXICOKINETICS STUDIES

No relevant toxicokinetics studies on *Punica granatum*-derived ingredients were found in the published literature, and unpublished data were not submitted. 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**

#### **Oral**

##### **Punica Granatum Fruit Extract**

In separate experiments performed by the same researchers, groups of 6 male and 6 female Wistar rats and Swiss albino mice received a single dose of pomegranate fruit extract (solvent not reported; the extract was standardized to contain 70% polyphenols, including 30% punicalagins) at 0, 50, 500, or 5000 mg/kg bw via gavage.<sup>32</sup> The oral LD<sub>50</sub> was determined to be greater than 5000 mg/kg bw for both species. No adverse effects were observed during the 14-day observation period, and no gross pathological abnormalities were observed during necropsy in both the rats and mice.

##### **Punica Granatum Pericarp Extract**

A supplier reported that the oral LD<sub>50</sub> for a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids) was greater than 2000 mg/kg in mice.<sup>16</sup> No further details were provided.

##### **Punica Granatum Seed Extract**

An ethanolic extract of pomegranate seeds was administered orally to 5 groups of 6 fasted NMRI male mice.<sup>37</sup> Doses were 2000, 3000, or 5000 mg/kg. No mortalities were observed in any dose level. No further details were provided.

### **Short-Term Toxicity Studies**

#### **Oral**

##### **Punica Granatum Peel Extract**

In a 15-day study, groups of 7 male Wistar rats received pomegranate peel extract by gavage at 250 mg/kg/d bw as a control and at up to 500 mg/kg/d bw in treatment groups induced with oral candidiasis.<sup>63</sup> At the end of the treatment period, macroscopic examination of the oral cavity and the tongue tissues and histopathological examinations of the tongue tissues were performed. No adverse effects from the test material were observed in the rats.

#### **Intranasal**

##### **Punica Granatum Fruit Extract**

The toxic effects of an ethanolic pomegranate fruit extract was studied in a 35 day intranasal study in groups of 10 male Wistar rats.<sup>66</sup> The rats received 0, 0.4, 1.2, or 7 mg/kg lyophilized extract in each nasal cavity with a microsyringe. The controls received saline solution. The rats were weighed and feed consumption was measured every 7 days. At the end of the treatment period, biochemical and histopathology samples were analyzed and organs were weighed. No statistically significant differences in mean animal weight or feed consumption were observed. There were no clinical signs of toxicity. The only biochemical effect noted was an increase in creatinine values in the highest dose group (7 mg/kg), but these values were still within the normal range and there was no indication of kidney damage in the histopathology samples. No treatment-related effects were observed in any dose group.

### **Subchronic Toxicity Studies**

#### **Oral**

##### **Punica Granatum Fruit Extract**

The toxicity of a pomegranate fruit extract was investigated in a 90-day oral toxicity study in Wistar rats in accordance with the Organization for Economic Co-operation and Development (OECD) test guideline (TG) 408.<sup>32</sup> Groups of 10 male and 10 female rats received 0, 60, 240, or 600 mg/kg bw/day pomegranate fruit extract (solvent not reported; the extract was standardized to contain 70% polyphenols, including 30% punicalagins) via gavage. Two additional groups of animals that received 0 and 600 mg/kg/day of the extract were recovery groups that were observed for 28 days after the initial 90-day treatment period. Clinical observations, body weight and feed consumption measurements, clinical pathology, and macroscopic and microscopic examinations of tissues from over 40 sites (including ovaries and uteri in females and testes and epididymides in males) were performed on all animals.

All animals survived until scheduled necropsies in both the 90-day study group and the recovery group. No adverse effects were observed during clinical observations. No treatment-related biologically significant effects were noted on body weight or body weight gain, feed consumption, in urinalysis parameters, in hematology parameters, in serum chemistry parameters, in absolute or relative organ weights, or in macroscopic or microscopic findings at any dose tested. No treatment-related effects were reported in the recovery groups. The no-observed-adverse-effect-level (NOAEL) for pomegranate fruit extract was determined to be 600 mg/kg/day.<sup>32</sup>

### **Chronic Toxicity Studies**

No relevant chronic toxicity studies were found in the published literature, and unpublished data were not submitted.

## **DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES**

### **Punica Granatum Fruit Extract**

Abnormal sperm were observed 5 weeks after male Balb/C mice were treated with a hydroalcoholic pomegranate fruit extract in a sperm-shape abnormality assay.<sup>67</sup> Route of exposure was not defined. The extract was tested at doses of 0, 7, 70, or 700 mg/kg bw in groups of 5 mice. There was a dose-dependent increase in sperm with amorphous and hookless head. The frequency of abnormal sperm was significant ( $p < 0.05$ ) at doses  $\geq 70$  mg/kg bw.

### **Oral**

### **Punica Granatum Fruit Juice Extract and Punica Granatum Seed Extract**

The potential effects of pomegranate seed extract (described as husk extract) and pomegranate juice extract on chondrogenesis and osteogenesis in developing embryos was investigated in female Balb/c mice.<sup>68</sup> Both test materials were extracted in water. Groups of 10 pregnant mice received the seed extract (1.0 g/kg suspended in 0.2 ml distilled water), the juice extract (3.3 ml/kg suspended in 0.2 ml distilled water), a mixture of both extracts, or distilled water daily in an oral dietary supplement between days 8 and 18 of gestation. On day 19 of gestation, the embryos were weighed and the length of the femur, tibia, and the ossification zones were measured by stereomicroscopy. The bone calcium content of the femurs of the pregnant mice was also measured.

Body weight gains of the pregnant mice were not affected by the test material. The pregnant mice that received the pomegranate extracts had an increase in bone calcium content, with a statistically significant increase ( $p < 0.05$ ) in the group that received pomegranate juice extract. The fetuses from the mixed extract group did have significantly reduced body weights and crown-rump lengths; these effects were not observed in the pomegranate seed extract only and pomegranate juice extract only treatment groups. Significantly increased femur lengths and osteogenesis indices were observed in all extract-exposed groups. No craniofacial abnormalities or limb defects were reported during gross observations, and no pathological changes, including necrosis, abnormal cells, or congestion in longitudinal section of fetuses were observed. The liver and kidneys of the fetuses and the dams were within normal parameters.<sup>68</sup>

### **Punica Granatum Fruit Juice**

The effects of pomegranate juice on sperm quality, spermatogenic cell density, antioxidant activity, and testosterone levels were studied in male Wistar rats.<sup>7</sup> Groups of 7 rats received 0.25 ml pomegranate juice with 0.75 ml distilled water, 0.50 ml pomegranate juice with 0.50 ml distilled water, 1 ml pomegranate juice, or 1 ml distilled water via gavage daily for 7 weeks. Body weights, reproductive organ weights, spermatogenic cell density, sperm characteristics, levels of antioxidant vitamins (A, C, and E), testosterone, lipid peroxidation, and antioxidant activities (glutathione, glutathione peroxidase, and catalase) were recorded. Analyses were done only once at the end of the study. There were no statistically significant effects on body weights in the treated groups when compared to the control group. Weights of testes, epididymides, seminal vesicles, prostate glands, and Cowper glands were higher in the treated groups when compared to the controls, but the differences were not statistically significant. A significant ( $p < 0.05$ ) decrease in malondialdehyde level and marked increases in glutathione, glutathione peroxidase and catalase activities, and vitamin C levels were observed in rats treated with different doses of pomegranate juice. Increases in epididymal sperm concentration, sperm motility, spermatogenic cell density, diameter of seminiferous tubules, germinal cell layer thickness, and a decreased abnormal sperm rate were observed with pomegranate juice consumption when compared to the controls.

## **GENOTOXICITY**

### **In Vitro**

### **Punica Granatum Fruit Extract**

The genotoxicity of a hydroalcoholic extract of pomegranate fruit (including peel) was assessed in an Ames study using *Salmonella typhimurium* strain TA100, with and without S9 metabolic activation.<sup>67</sup> The extract was tested at 0, 0.45, 1, 2, and 4 mg/plate. The higher doses of the extract induced significant increases of revertants (2 mg/plate,  $p < 0.05$ ; 4 mg/plate,  $p < 0.01$ ); the results of the lower doses tested were comparable with negative controls. The positive control yielded expected results.

The same pomegranate fruit extract (described above) was tested at concentrations up to 18 mg/ml in *Saccharomyces cerevisiae* strain D7.<sup>67</sup> The extract did not induce gene-conversion events, but an increased frequency of reverse mutations was observed in a dose-dependent manner, with and without metabolic activation. Statistical significance at the doses these effects occurred was not provided.

In mutagenic studies of a hydroalcoholic pomegranate fruit extract, Chinese hamster ovary (CHO) cells were tested with and without metabolic activation at concentrations of 0, 1, 50, 110, 230, 340, and 450  $\mu\text{g/ml}$  in a sister chromatid exchange assay, and at concentrations of 0, 0.9, 45, 112, and 225  $\mu\text{g/ml}$  in a chromosomal aberration assay.<sup>67</sup> A dose-dependent and statistically significant increase in sister chromatid exchanges per cell was observed; increases were observed with

concentrations of  $\geq 110 \mu\text{g/ml}$  ( $p < 0.05$ ) in the absence of S9 metabolic activation. Significant increases in the percentage of chromosomal aberrations were also observed with  $\geq 45 \mu\text{g/ml}$  ( $p < 0.05$ ) without metabolic activation.

#### Punica Granatum Pericarp Extract

The mutagenic potential of a tradename mixture containing 10% Punica Granatum Pericarp Extract, 10% *Lactobacillus* ferment lysate, 10% *Camellia sinensis* leaf extract, 2% *Lactobacillus* ferment, and 1% caffeine in water was studied in an Ames test using *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2uvrA, with and without metabolic activation.<sup>69</sup> Cells were incubated with the test material at doses of 1.5 to 5000  $\mu\text{g/plate}$  in sterile deionized water. No mutagenicity was observed at any dose level. Positive and negative controls yielded expected results.

A supplier reported that a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids) was negative in an Ames test when tested at 5000  $\mu\text{g/plate}$ .<sup>16</sup> No further details were provided.

### **In Vivo**

#### Punica Granatum Fruit Extract

In a mouse bone marrow micronucleus assay studying the genotoxic effects of a hydroalcoholic extract of pomegranate fruit, the extract was administered intraperitoneally at doses of 7, 70, 184, 369, or 700 mg/kg bw to 5 Balb/C mice/sex/group at intervals of 24 h (further details on dosing not reported).<sup>67</sup> A dose-dependent increase in the number of polychromatic erythrocytes with micronuclei was observed. The genotoxicity index increase was statistically significant at doses  $\geq 70$  mg/kg bw in both sexes. The cytotoxicity index was significantly increased at doses of  $\geq 70$  and 184 mg/kg bw in males and females, respectively.

### **ANTI-GENOTOXICITY**

#### Punica Granatum Leaf Extract

In a mouse bone marrow micronucleus assay studying anti-genotoxicity effects of an aqueous pomegranate leaf extract, groups of 6 male Swiss mice received 0, 400, 600, or 800 mg/kg bw of the extract in distilled water by gavage for 7 days before exposure to the genotoxicant cyclophosphamide (CPH).<sup>29</sup> Another two groups of 6 mice served as genotoxicant and test material (800 mg/kg extract) controls. Prior to the final treatment with the extract, the mice received 40 mg/kg CPH, and all mice were killed after 24 h. Anti-genotoxic effects were observed in a non-dose dependent manner at all 3 extract dose levels. The maximum reduction was observed in mice that received 800 mg/kg of the extract. There was no reduction in the percentage of polychromatic erythrocytes following treatment with the extract and CPH. No genotoxic effects were observed to the pomegranate leaf extract alone.

### **CARCINOGENICITY**

No relevant carcinogenicity studies were found in the published literature, and unpublished data were not submitted.

### **OTHER RELEVANT STUDIES**

#### **Skin Lightening**

#### **In Vitro**

#### Punica Granatum Fruit Extract

The potential for an ethanolic pomegranate fruit extract to inhibit melanin production has been studied in vitro using the Melan-a melanocyte cell culture model.<sup>70</sup> The Melan-a cells were treated with pomegranate fruit extract that was standardized to 20% punicalagins. The test material was produced from fruit (with peel) that was macerated and extracted with a 75% - 80% ethanol solution at a ratio of 1:4 (fruit:solvent) before filtration and vacuum processing. Melanin content was reduced by approximately 40% to 60% at test concentrations of 50  $\mu\text{g/ml}$  and 100  $\mu\text{g/ml}$ , respectively. Further testing with the purified punicalagins isolated from pomegranate fruit found that these constituents reduced melanin production by 60%, 70%, and 75% of control levels at test concentrations of 20  $\mu\text{g/ml}$ , 60  $\mu\text{g/ml}$ , and 100  $\mu\text{g/ml}$ , respectively.

#### Punica Granatum Peel Extract

An aqueous pomegranate extract of rind containing 90% ellagic acid showed inhibitory activity against mushroom tyrosinase ( $\text{IC}_{50}$  182.2  $\mu\text{g/ml}$ ) in vitro.<sup>71</sup> The inhibition effects were comparable to arbutin ( $\text{IC}_{50}$  162.2  $\mu\text{g/ml}$ ), but was about ten times weaker than L-ascorbic acid ( $\text{IC}_{50}$  18.4  $\mu\text{g/ml}$ ).

#### **Animal**

#### Punica Granatum Peel Extract

Mid-wavelength ultraviolet (UVB) light-induced skin pigmentation was inhibited in female brownish guinea pigs after the animals received aqueous pomegranate extract of rind orally for 35 days.<sup>71</sup> There were 6 animals per dose group that received either 100 mg/kg/day of the extract diluted in water at 100 mg/ml, 1000 mg/kg/day of the extract diluted in water at

100 mg/ml, water, or 600 mg/kg/day L-ascorbic acid diluted in water at 60 mg/ml. The animals were irradiated on days 7, 9, and 11. The number of L-3,4-dihydroxyphenylalanine (DOPA)-positive melanocytes in the epidermis of the UV-irradiated guinea pigs were reduced in the animals that received the pomegranate extract. The researchers of this in vivo study and the in vitro study above concluded that the skin-whitening effects were likely due to inhibition of the proliferation of melanocytes and melanin synthesis by tyrosinase in melanocytes.

## **Human**

### **Punica Granatum Juice**

In a study of a water/oil emulsion containing 4% concentrated pomegranate juice, the test material (amount not reported) was applied daily to the cheeks of 25 healthy volunteers for 60 days.<sup>72</sup> A Mexameter® was used to measure the melanin on the cheeks of the volunteers on the day prior to application and at weeks 1 - 4, 6, and 8. Significant decreases (details not provided) in skin melanin content were observed.

## **DERMAL IRRITATION AND SENSITIZATION STUDIES**

### **Irritation**

#### **In Vitro**

##### **Punica Granatum Pericarp Extract**

An undiluted tradename mixture containing 10% Punica Granatum Pericarp Extract, 10% *Lactobacillus* ferment lysate, 10% *Camellia sinensis* leaf extract, 2% *Lactobacillus* ferment, and 1% caffeine in water was predicted to be non-irritating in an EpiDerm™ reconstructed human epidermal model.<sup>73</sup> Negative and positive controls yielded expected results.

#### **Human**

##### **Punica Granatum Juice**

No dermal irritation was observed in a 60-day study of a water/oil emulsion containing 4% concentrated pomegranate juice in 25 healthy volunteers.<sup>72</sup> The test material (amount not reported) was applied daily to the cheeks, and the volunteers self-scored the patches on a scale of 0 to 3.0 for the presence of erythema.

##### **Punica Granatum Pericarp Extract**

A supplier reported that a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids) tested at 20% was negative in a human single patch test using 44 subjects.<sup>16</sup> No further details were provided.

### **Sensitization**

#### **In Vitro/In Chemico**

##### **Punica Granatum Pericarp Extract**

A tradename mixture containing 10% Punica Granatum Pericarp Extract, 10% *Lactobacillus* ferment lysate, 10% *Camellia sinensis* leaf extract, 2% *Lactobacillus* ferment, and 1% caffeine in water was not predicted to be a sensitizer in a direct peptide reactivity assay (DPRA) performed in accordance with OECD TG 442C.<sup>74</sup> The 100 mM product (in acetonitrile) was tested at 5 mM with the cysteine peptide and at 25 mM with the lysine peptide. The controls yielded expected results.

The same tradename mixture containing 10% Punica Granatum Pericarp Extract was not predicted to be a sensitizer in a KeratinoSens™ ARE-Nrf2 Luciferase test performed in accordance with OECD TG 422D.<sup>75</sup> The test material was prepared in dimethyl sulfoxide at 0.98 to 2000 µM. The controls yielded expected results.

#### **Animal**

##### **Punica Granatum Pericarp Extract**

A supplier reported that a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids) tested at 20% was negative in a guinea pig skin sensitization test using 5 animals.<sup>16</sup> No further details were provided.

#### **Human**

##### **Punica Granatum Flower Extract**

In a human repeat patch test (HRIPT), the sensitization potential of a product containing 0.4% Punica Granatum Flower Extract was tested in 105 subjects.<sup>76</sup> For both the induction and the challenge phases, 0.2 g of the test material was applied to a ¾ square inch pad and adhered to the upper backs of the subjects as an occlusive patch. The induction phase was followed by a 2-week rest period. One subject suffered an adverse medical event during the study, but this event was not treatment-related. No other adverse reactions were observed. The test material was not a dermal irritant or dermal sensitizer.

### Punica Granatum Fruit Extract

In a HRIPT, the sensitization potential of a leave-on product containing 0.1% Punica Granatum Fruit Extract was tested in 100 subjects.<sup>77</sup> For both the induction and the challenge phases, 0.2 g of the test material was applied directly on the backs of the subjects and allowed to air dry; the test patches were not occluded. No adverse reactions were observed. The test material was determined to be non-irritating and non-sensitizing. No further details were provided.

### Punica Granatum Pericarp Extract

A supplier reported that a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids), when tested at 30%, was negative in a HRIPT using 52 subjects.<sup>16</sup> No further details were provided.

## **Photosensitization**

### **Animal**

#### Punica Granatum Pericarp Extract

A supplier reported that a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids) tested at 20% was negative in a photosensitization test using 5 guinea pigs.<sup>16</sup> No further details were provided.

## **OCULAR IRRITATION STUDIES**

### **In Vitro**

#### Punica Granatum Pericarp Extract

An undiluted tradename mixture containing 10% Punica Granatum Pericarp Extract, 10% *Lactobacillus* ferment lysate, 10% *Camellia sinensis* leaf extract, 2% *Lactobacillus* ferment, and 1% caffeine in water was predicted to be non-irritating in an EpiOcular™ cornea epithelial model.<sup>73</sup> Negative and positive controls yielded expected results.

A supplier reported that a tradename mixture containing water, butylene glycol, and Punica Granatum Pericarp Extract (0.5% solids) tested at 100% was predicted to be non-irritating in a human corneal epithelium eye irritation test.<sup>16</sup> No further details were provided.

## **SUMMARY**

According to the *Dictionary*, most of the 18 *Punica granatum*-derived ingredients detailed in this safety assessment are reported to function in cosmetics as skin conditioning agents, while some are reported to have other functions, such as abrasives and antioxidants. It should be noted that Punica Granatum Extract, defined as an extract of the whole plant, is no longer listed in the *Dictionary*; trade names that were associated with this ingredient are now included for the monographs associated with Punica Granatum Fruit Extract or Punica Granatum Pericarp Extract. Punica Granatum Extract is still included in the list of ingredients named in this report, however, because it has the most uses in the US FDA Voluntary Cosmetic Registration Program VCRP database and because concentration of use data are also associated with this name.

Investigations into the antioxidant activity of various extracts derived from parts of *Punica granatum* are numerous; these studies are not detailed in this report. The available toxicity data that correspond to specific use of these ingredients in cosmetics are extremely limited. The focus of this safety assessment is on data relevant to the use of *Punica granatum*-derived ingredients in cosmetics, with specific focus on topical exposure when available.

According to 2020 VCRP survey data, Punica Granatum Extract has the most reported uses in cosmetic products, with a total of 334; the majority of the uses are in leave-on skin care products. Punica Granatum Fruit Extract has the second greatest number of reported uses in this safety assessment with 188 uses; the majority of these uses are also in leave-on skin care products. The results of the concentration of use survey conducted in 2017 by the Council indicated that Punica Granatum Seed Extract is used at up to 0.3% (in leave-on cuticle softeners). Punica Granatum Extract and Punica Granatum Fruit Extract are used at up to 0.13% (in moisturizing preparations) and 0.1% (in face and neck and night skin preparations), respectively.

In the US, the essential oils, solvent-free oleoresins, and natural extractives from *Punica granatum* L. (pomegranate) are GRAS for their use in food intended for human consumption and in animal drugs, feeds, and related products. Extensive research has been performed on the extracts of various parts of *Punica granatum* for use as alternative or therapeutic treatments for various conditions.

The oral LD<sub>50</sub> in mice and rats for a pomegranate fruit extract was greater than 5000 mg/kg bw. No mortalities were observed in mice that received an ethanolic extract of pomegranate seeds at up to 5000 mg/kg. The oral LD<sub>50</sub> for a tradename mixture containing Punica Granatum Pericarp Extract (0.5% solids) was greater than 2000 mg/kg in mice.

In repeated dose studies, no adverse effects were reported in a 15-day oral rat study of methanolic pomegranate peel extract at up to 500 mg/kg/day. In a 90-day study, the NOAEL for an oral study of a pomegranate fruit extract in rats was 600 mg/kg/day, the maximum dose tested. No adverse effects were noted in rats that received lyophilized ethanolic

pomegranate fruit extract at up to 7 mg/kg intranasally for 35 days. The only biochemical effect observed was an increase in creatinine values in the high dose group, but there was no kidney damage noted histopathologically.

Abnormal sperm were observed in male mice treated with a hydroalcoholic pomegranate fruit extract at doses  $\geq 70$  mg/kg bw. Route of exposure was not defined. No adverse effects were observed in an oral DART study in female mice that received pomegranate seed extract (1.0 g/kg suspended in 0.2 ml distilled water) or pomegranate juice extract (3.3 ml/kg suspended in 0.2 ml distilled water) separately or as a mixture on gestation days 8 - 18, and there was no effect on the fetuses. In a 7-week rat sperm study, increases in epididymal sperm concentration, sperm motility, spermatogenic cell density, diameter of seminiferous tubules, germinal cell layer thickness, and a decreased abnormal sperm rate were observed with daily pomegranate juice consumption (0.25 ml or 0.5 ml in distilled water or 1.0 ml neat) via gavage when compared to the controls.

Positive genotoxic effects to a hydroalcoholic extract of pomegranate fruit were observed in an Ames test (at  $\geq 2$  mg/plate), a reverse mutation study in *S. cerevisiae*, and in CHO cell assays (at  $\geq 45$   $\mu$ g/ml), with and without metabolic activation. The same extract was associated with a dose-dependent increase in the number of polychromatic erythrocytes in a mouse micronucleus assay, with statistical significance at  $\geq 70$  mg/kg bw. No genotoxic effects were observed to tradename mixtures containing Punica Granatum Pericarp Extract in Ames tests or to a pomegranate leaf extract in a mouse micronucleus assay.

In vitro and in vivo studies indicate that a pomegranate fruit extract, pomegranate juice, and a pomegranate peel extract may inhibit melanin production. Melanin content was reduced by approximately 40% to 60% at test concentrations of 50  $\mu$ g/ml and 100  $\mu$ g/ml pomegranate fruit extract, respectively, in an in vitro study; while in a 60-day human study, significant decreases in melanin content were observed to a water/oil emulsion containing 4% concentrated pomegranate juice.

In an in vitro human epidermal model, an undiluted tradename mixture containing 10% Punica Granatum Pericarp Extract was predicted to be non-irritating. In a 60-day self-scored study of an emulsion containing 4% concentrated pomegranate juice, no dermal irritation was observed following daily application to the cheeks of human volunteers. No irritation was observed in a human single patch test of a tradename mixture containing Punica Granatum Pericarp Extract (0.5% solids) tested at 20%. In in vitro and in chemico assays, a tradename mixture containing 10% Punica Granatum Pericarp Extract was not predicted to be a sensitizer. Results of a guinea pig sensitization test of Punica Granatum Pericarp Extract (0.5% solids), a photosensitization test in guinea pigs of Punica Granatum Pericarp Extract (0.5% solids), and sensitization tests in humans to a leave-on product containing Punica Granatum Fruit Extract (0.1%) and to a tradename mixture containing Punica Granatum Pericarp Extract (0.5% solids) were negative.

No ocular irritation was predicted in in vitro cornea epithelial models of tradename mixtures containing up to 10% Punica Granatum Pericarp Extract.

No relevant chronic toxicity or carcinogenicity studies on *Punica granatum*-derived ingredients were found in the published literature, and no unpublished data were provided. No relevant toxicokinetics studies were found in the published literature; however, in general, toxicokinetics data are not expected to be found on botanical ingredients because each botanical ingredient is a complex mixture of constituents.

## **DISCUSSION**

The Panel reviewed the botanical ingredients derived from the plant, *Punica granatum*. The Panel expressed concern about pesticide residues, heavy metals, and other plant species that may be present in botanical ingredients, and stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

Data included in this report indicate that extracts of parts of *Punica granatum* may have a skin lightening effect. The Panel noted that skin lightening is considered to be a drug effect, and should not occur during the use of cosmetic products. Because of that caveat, and based on the low concentrations of use of these extracts in cosmetic products, the Panel's knowledge of the mechanism of action (i.e., inhibition of tyrosinase activity by polyphenols), the results of the in vitro study of pomegranate fruit extract, and clinical experience, concern for this effect in cosmetics was mitigated. Nevertheless, cosmetic formulators should only use *Punica granatum* extracts in products in a manner that does not cause depigmentation.

Some *Punica granatum*-derived ingredients were reported to be used in spray and powder products that could possibly be inhaled. For example, Punica Granatum Extract is used in a face and neck spray at 0.001% and Punica Granatum Fruit Juice is used in a face powder at 0.01%. The Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns (e.g., data on an ethanolic pomegranate fruit extract did not produce adverse effects in rats treated via intranasal injection). Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and

summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at <https://www.cir-safety.org/cir-findings>.

Although the Panel found the data on the flower, fruit, juice, pericarp, and seed ingredients to be sufficient, the Panel determined that the data are insufficient to make a determination of safety for the following ingredients: Punica Granatum Extract, Punica Granatum Bark Extract, Punica Granatum Bark/Fruit Extract, Punica Granatum Callus Culture Extract, Punica Granatum Fruit/Root/Stem Powder, Punica Granatum Fruit/Sucrose Ferment Filtrate, Punica Granatum Leaf Cell Extract, Punica Granatum Peel Extract, and Punica Granatum Seed Cell Culture Lysate. The additional data needed to determine safety for these cosmetic ingredients are:

- Method of manufacturing with regard to solvent-type used for the extracts
- Composition and impurities data
- Systemic toxicity data
- Dermal irritation and sensitization data

The Panel noted that Punica Granatum Extract is no longer listed in the *Dictionary*. However, this ingredient has the highest number of uses reported in the US FDA VCRP database, and concentration of use data are still associated with this name, indicating that this ingredient, as it was originally defined, may still be in use.

### CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 9 *Punica granatum* (pomegranate)-derived ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

Punica Granatum Flower Extract  
Punica Granatum Fruit Extract  
Punica Granatum Fruit Juice  
Punica Granatum Fruit Water  
Punica Granatum Juice Extract

Punica Granatum Pericarp Extract  
Punica Granatum Seed  
Punica Granatum Seed Extract  
Punica Granatum Seed Powder

The Panel also concluded that the available data are insufficient to make a determination of safety under the intended conditions of use for the following 9 *Punica granatum* (pomegranate)-derived ingredients.

Punica Granatum Extract‡  
Punica Granatum Bark Extract  
Punica Granatum Bark/Fruit Extract\*  
Punica Granatum Callus Culture Extract\*  
Punica Granatum Fruit/Root/Stem Powder\*

Punica Granatum Fruit/Sucrose Ferment Filtrate\*  
Punica Granatum Leaf Cell Extract\*  
Punica Granatum Peel Extract\*  
Punica Granatum Seed Cell Culture Lysate\*

‡ *Ingredient has been deleted from the Dictionary, but uses are currently reported.*

\* *Uses not reported.*

## TABLES

**Table 1. Definitions and functions of the ingredients in this safety assessment.**<sup>1</sup>

Ingredient/CAS No.	Definition & Structure	Function
Punica Granatum Extract ‡ 84961-57-9 (generic)	Punica Granatum Extract is the extract of the whole plant, <i>Punica granatum</i> .	Fragrance Ingredient; Skin-Conditioning Agent – Misc.
Punica Granatum Bark Extract 84961-57-9 (generic)	Punica Granatum Bark Extract is the extract of the bark of <i>Punica granatum</i> .	Fragrance Ingredient; Skin-Conditioning Agent – Misc.
Punica Granatum Bark/Fruit Extract 84961-57-9 (generic)	Punica Granatum Bark/Fruit Extract is the extract of the bark and fruit of <i>Punica granatum</i> .	Antimicrobial Agent; Antioxidant; Cosmetic Astringent
Punica Granatum Callus Culture Extract 84961-57-9 (generic)	Punica Granatum Callus Culture Extract is the extract of a culture of the callus of <i>Punica granatum</i> .	Skin-Conditioning Agent – Misc.
Punica Granatum Flower Extract 84961-57-9 (generic)	Punica Granatum Flower Extract is the extract of the flowers of <i>Punica granatum</i> .	Skin-Conditioning Agent – Misc.
Punica Granatum Fruit Extract 84961-57-9 (generic)	Punica Granatum Fruit Extract is the extract of the fruit of <i>Punica granatum</i> .	Skin-Conditioning Agent – Misc.
Punica Granatum Fruit Juice 84961-57-9 (generic)	Punica Granatum Fruit Juice is the juice expressed from the fruit of the pomegranate, <i>Punica granatum</i> .	Flavoring Agent; Skin-Conditioning Agent – Misc.
Punica Granatum Fruit/Root/Stem Powder 84961-57-9 (generic)	Punica Granatum Fruit/Root/Stem Powder is the powder obtained from the finely ground fruit, roots, and stems of <i>Punica granatum</i> .	Antioxidants; Hair Conditioning Agent; Skin-Conditioning Agent – Misc.
Punica Granatum Fruit/Sucrose Ferment Filtrate	Punica Granatum Fruit/Sucrose Ferment Filtrate is a filtrate of the product obtained by the spontaneous fermentation of the fruit of <i>Punica granatum</i> and sucrose.	Antioxidants
Punica Granatum Fruit Water 84961-57-9 (generic)	Punica Granatum Fruit Water is an aqueous solution of the steam distillates obtained from the fruit of <i>Punica granatum</i> .	Flavoring Agent; Fragrance Ingredient; Skin-Conditioning Agent – Misc.
Punica Granatum Juice Extract 84961-57-9 (generic)	Punica Granatum Juice Extract is the extract of the juice of <i>Punica granatum</i> .	Skin-Conditioning Agent – Misc.
Punica Granatum Leaf Cell Extract 84961-57-9 (generic)	Punica Granatum Leaf Cell Extract is the extract of a culture of the leaf cells of <i>Punica granatum</i> .	Antioxidant; Skin Protectant
Punica Granatum Peel Extract 84961-57-9 (generic)	Punica Granatum Peel Extract is the extract of the peel of <i>Punica granatum</i> .	Antimicrobial Agent; Antioxidant; Cosmetic Astringent; Preservative; Skin-Conditioning Agent – Misc.
Punica Granatum Pericarp Extract 84961-57-9 (generic)	Punica Granatum Pericarp Extract is the extract of the pericarp of <i>Punica granatum</i> .	Skin-Conditioning Agent – Misc.
Punica Granatum Seed 84961-57-9 (generic)	Punica Granatum Seed is the seed of <i>Punica granatum</i> .	Abrasive; Bulking Agent; Skin-Conditioning Agent – Misc.
Punica Granatum Seed Cell Culture Lysate	Punica Granatum Seed Cell Culture Lysate is a lysate of a suspension of the cultured seed cells of <i>Punica granatum</i> .	Skin-Conditioning Agent – Misc.
Punica Granatum Seed Extract 84961-57-9 (generic)	Punica Granatum Seed Extract is the extract of the seeds of <i>Punica granatum</i> .	Skin-Conditioning Agent – Misc.
Punica Granatum Seed Powder 84961-57-9 (generic)	Punica Granatum Seed Powder is the powder obtained from the dried, ground seeds of <i>Punica granatum</i> .	Abrasive

‡ Ingredient has been deleted from the *Dictionary*, but uses are currently reported.

**Table 2. Generic plant part definitions as they apply to pomegranate-derived ingredients.<sup>1</sup>**

Plant Part	Definition
Bark	Tough protective covering of the woody stems and roots of trees and other woody perennial plants, consisting of cells produced by a cork cambium.
Callus Culture	An undifferentiated mass of cells produced through tissue culture
Flower	The reproductive shoot in flowering plants, usually with sepals, petals, stamens and pistil(s).
Fruit	Mature, ripened ovary of flowering plant, containing seeds
Juice	The liquid contained in the vegetative parts or fruits
Leaf	Flattened photosynthetic organs, attached to stems.
Pericarp	Fruit wall; ripened walls of a plant ovary/fruit, consists of exocarp (peel), mesocarp ("fruit") and endocarp (surrounds seed)
Root	Organ of a plant that absorbs and transports water and nutrients, lacks leaves and nodes, usually underground.
Seed	A propagating sexual structure resulting from the fertilization of an ovule, formed by embryo, endosperm, or seed coat.
Stem	A slender or elongated structure that supports a plant or a plant part or plant organ.

**Table 3. Phytochemical constituents of pomegranate extracts (mg/g of dry extract)<sup>3,6,26-29</sup>**

	Flower Extract	Peel Extract	Seed Extract	Juice Extract	Leaf Extract	Stem Extract
Total phenolic content	336.51 (M)	276-413 (E) 190.27-298 (M) 185 (A)	2.57-73 (E) 0.65 (M)	12.4-23.8 (E) 0.094 (A) 0.057 (B)	87.81 (M) 70.00 (A)	52.92 (M)
Total flavonoid content	213.54 (M)	36-54 (E) 49.8-80.10 (M) 23.05 (A)	7.55-38.0 (E) 0.33 (M)	1.8-8.7 (E) 0.46 (A) 0.22 (B)	63.89 (M) 50.43 (A)	41.36 (M)
Total flavonol content		25-45 (E) 0.39-0.44 (A)	3.4-22 (E)	1.5-2.0 (E)		
Total proanthocyanidin content	1.46 (M)	2.48-14.09 (M) 9.09 (A)	0.13 (M)		0.21 (M)	0.32 (M)

Solvents: M = methanol, E = ethanol, A = water/aqueous, B = *n*-butanol

**Table 4. Fatty acid composition (%) for pomegranate seed extract (ethanolic)<sup>3</sup>**

Palmitic Acid	4.7
Stearic Acid	2.2
Oleic Acid	5.3
Vaccenic Acid	0.8
$\alpha$ -Linoleic Acid	8.8
$\alpha$ -Linolenic Acid	0.5
Gondoic Acid	0.5
Punicic Acid	73.7
$\alpha$ -Eleostearic Acid	1.6
Catalpic Acid	1.2

**Table 5. Frequency (2020) and concentration of use (2017 and 2019) according to duration and type of exposure for *Punica granatum*-derived ingredients.<sup>39-41</sup>**

	<i># of Uses</i>	<i>Max Conc of Use (%)</i>	<i># of Uses</i>	<i>Max Conc of Use (%)</i>	<i># of Uses</i>	<i>Max Conc of Use (%)</i>	<i># of Uses</i>	<i>Max Conc of Use (%)</i>
	<b>Punica Granatum Extract*</b>		<b>Punica Granatum Bark Extract</b>		<b>Punica Granatum Flower Extract</b>		<b>Punica Granatum Fruit Extract</b>	
<b>Totals<sup>†</sup></b>	<b>334</b>	<b>0.00001-0.13</b>	<b>15</b>	<b>NR</b>	<b>5</b>	<b>0.0001</b>	<b>188</b>	<b>0.0000002-0.1</b>
<b><i>Duration of Use</i></b>								
Leave-On	235	0.00001-0.13	14	NR	4	NR	127	0.0000002-0.1
Rinse Off	98	0.0001-0.00085	1	NR	1	0.0001	59	0.000005-0.1
Diluted for (Bath) Use	1	NR	NR	NR	NR	NR	2	0.0005
<b><i>Exposure Type</i></b>								
Eye Area	18	0.001	1	NR	NR	NR	20	0.000005-0.018
Incidental Ingestion	13	NR	NR	NR	NR	NR	2	0.0005-0.02
Incidental Inhalation-Spray	2; 79 <sup>a</sup> ; 69 <sup>b</sup>	0.00001-0.001; 0.00001-0.003 <sup>a</sup>	3 <sup>a</sup> ; 9 <sup>b</sup>	NR	2 <sup>b</sup>	NR	38 <sup>a</sup> ; 52 <sup>b</sup>	0.00002-0.0005; 0.00002-0.02 <sup>a</sup>
Incidental Inhalation-Powder	7; 69 <sup>b</sup>	0.02-0.1 <sup>c</sup>	9 <sup>b</sup>	NR	2 <sup>b</sup>	NR	52 <sup>b</sup>	0.005; 0.0002-0.1 <sup>c</sup>
Dermal Contact	256	0.001-0.13	12	NR	4	NR	162	0.0000002-0.1
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	0.0005
Hair - Non-Coloring	55	0.00001-0.1	2	NR	1	0.0001	20	0.00002-0.1
Hair-Coloring	8	NR	NR	NR	NR	NR	NR	NR
Nail	2	NR	NR	NR	NR	NR	NR	0.00001-0.001
Mucous Membrane	26	NR	NR	NR	NR	NR	17	0.0005-0.02
Baby Products	2	NR	1	NR	NR	NR	NR	0.000005
<b><i>Duration of Use</i></b>								
	<b>Punica Granatum Fruit Juice</b>		<b>Punica Granatum Fruit Water</b>		<b>Punica Granatum Juice Extract</b>		<b>Punica Granatum Pericarp Extract</b>	
<b>Totals<sup>†</sup></b>	<b>86</b>	<b>0.0001-0.1</b>	<b>15</b>	<b>NR</b>	<b>6</b>	<b>0.005</b>	<b>5</b>	<b>0.0000002-0.1</b>
<b><i>Duration of Use</i></b>								
Leave-On	68	0.01-0.1	9	NR	3	NR	4	0.0000002-0.005
Rinse Off	18	0.0001	6	NR	2	0.005	1	0.01-0.1
Diluted for (Bath) Use	NR	NR	NR	NR	1	NR	NR	NR
<b><i>Exposure Type</i></b>								
Eye Area	9	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	3	NR	NR	NR	NR	NR	3	NR
Incidental Inhalation-Spray	27 <sup>a</sup> ; 23 <sup>b</sup>	NR	9 <sup>a</sup>	NR	1 <sup>a</sup> ; 1 <sup>b</sup>	NR	1 <sup>b</sup>	0.00002; 0.00002-0.005 <sup>a</sup>
Incidental Inhalation-Powder	23 <sup>b</sup>	0.01	NR	NR	1 <sup>b</sup>	NR	1 <sup>b</sup>	NR
Dermal Contact	75	0.01-0.1	15	NR	5	0.005	2	0.0000002-0.01
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	8	0.0001	NR	NR	NR	NR	NR	0.00002-0.1
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	8	NR	NR	NR	2	NR	3	NR
Baby Products	NR	NR	NR	NR	1	NR	NR	NR

**Table 5. Frequency (2020) and concentration of use (2017 and 2019) according to duration and type of exposure for *Punica granatum*-derived ingredients.<sup>39-41</sup>**

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Punica Granatum Seed		Punica Granatum Seed Extract		Punica Granatum Seed Powder			
<b>Totals†</b>	<b>5</b>	<b>NR</b>	<b>2</b>	<b>0.01-0.3</b>	<b>6</b>	<b>0.01</b>		
<b>Duration of Use</b>								
Leave-On	3	NR	2	0.01-0.3	4	NR		
Rinse Off	2	NR	NR	NR	1	0.01		
Diluted for (Bath) Use	NR	NR	NR	NR	1	0.01		
<b>Exposure Type</b>								
Eye Area	NR	NR	1	NR	NR	NR		
Incidental Ingestion	NR	NR	NR	0.11	NR	NR		
Incidental Inhalation-Spray	3 <sup>a</sup>	NR	1 <sup>a</sup>	NR	1 <sup>a</sup> ; 2 <sup>b</sup>	NR		
Incidental Inhalation-Powder	NR	NR	NR	NR	2 <sup>b</sup>	NR		
Dermal Contact	5	NR	2	0.01	6	0.01		
Deodorant (underarm)	NR	NR	NR	NR	NR	NR		
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR		
Hair-Coloring	NR	NR	NR	NR	NR	NR		
Nail	NR	NR	NR	0.3	NR	NR		
Mucous Membrane	2	NR	NR	0.11	1	0.01		
Baby Products	NR	NR	NR	NR	NR	NR		

NR = Not reported.

\* Uses are reported in the VCRP and concentration of use survey under this non-INCI name

† 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.

<sup>a</sup>. It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

<sup>b</sup>. Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

<sup>c</sup>. It is possible these products may be powders, but it is not specified whether the reported uses are powders.

**Table 6. Ingredients not reported in use.<sup>39-41</sup>**

Punica Granatum Bark/Fruit Extract  
Punica Granatum Callus Culture Extract  
Punica Granatum Fruit/Root/Stem Powder  
Punica Granatum Fruit/Sucrose Ferment Filtrate  
Punica Granatum Leaf Cell Extract  
Punica Granatum Peel Extract  
Punica Granatum Seed Cell Culture Lysate

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