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Safety Assessment of *Citrus* Plant- and Seed-Derived Ingredients as Used in Cosmetics

Christina L. Burnett*, Wilma F. Bergfeld, Donald V. Belsito**, Ronald A. Hill**, Curtis D. Klaassen**, Daniel C. Liebler**, James G. Marks, Jr**, Ronald C. Shank**, Thomas J. Slaga**, Paul W. Snyder**, Lillian J. Gill***, and Bart Heldreth†**

Abstract

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 30 *Citrus* plant- and seed-derived ingredients, which are most frequently reported to function in cosmetics as fragrances and/or skin conditioning agents. Because final product formulations may contain multiple botanicals, each containing similar constituents of concern, formulators are advised to be aware of these constituents and to avoid reaching levels that may be hazardous to consumers. With *Citrus* plant- and seed-derived ingredients, the Panel was concerned about the presence of the hydroperoxides of limonene and linalool in cosmetics. Industry should use good manufacturing practices to limit impurities. The Panel reviewed the available data presented and concluded that 18 of these ingredients are safe in the present practices of use and concentration when formulated to be non-irritating and non-sensitizing. The data for the remaining 12 ingredients are insufficient to determine safety.

Keywords

citrus plant, citrus seed, safety, cosmetics

Introduction

This report assesses the safety of the 30 *Citrus* plant- and seed-derived ingredients listed below, which are reported in the *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*) to mainly function as skin conditioning agents-miscellaneous in cosmetic products (Table 1).[1] Citrus Aurantium (Bitter Orange) Oil is not currently listed in the *Dictionary*, but has been included in this report because of its high reported number of uses in the US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) database and presumed similarities to the other ingredients in this report. Two ingredients (Citrus Sunki Seed Extract and Citrus Sunki Seed Oil) are reported to function as skin bleaching agents; use as a skin bleaching agent is classified as a drug use and, as such, does not fall under the purview of CIR.

Citrus Aurantifolia (Lime) Oil	Citrus Iyo Oil
Citrus Aurantium (Bitter Orange) Oil	Citrus Junos Extract
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Extract	Citrus Junos Seed Extract
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil	Citrus Junos Seed Oil
Citrus Aurantium Dulcis (Orange) Flower/Leaf/Stem Powder	Citrus Limon (Lemon) Flower/Leaf/Stem Extract
Citrus Aurantium Dulcis (Orange) Oil	Citrus Limon (Lemon) Flower/Leaf/Stem Oil
Citrus Aurantium Dulcis (Orange) Seed Extract	Citrus Limon (Lemon) Leaf/Peel/Stem Oil
Citrus Aurantium Sinensis Powder	Citrus Nobilis (Mandarin Orange)
Citrus Australasica Seed Oil	Citrus Nobilis (Mandarin Orange) Oil
Citrus Depressa Seed Oil	Citrus Nobilis (Mandarin Orange) Water
Citrus Glauca Seed Oil	Citrus Paradisi (Grapefruit) Seed Extract

*Cosmetic Ingredient Review Senior Scientific Analyst/Writer
**Expert Panel for Cosmetic Ingredient Safety Member
***Cosmetic Ingredient Review Former Director
†Cosmetic Ingredient Review Executive Director

Corresponding Author:
Bart Heldreth, Executive Director, Cosmetic Ingredient Review, 1620 L Street, NW, Suite 1200, Washington, DC 20036, USA.
Email: cirinfo@cir-safety.org

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Citrus Grandis (Grapefruit)	Citrus Sunki Seed Extract
Citrus Grandis (Grapefruit) Extract	Citrus Sunki Seed Oil
Citrus Grandis Peel/Seed Extract	Citrus Reticulata (Tangerine) Extract
Citrus Grandis (Grapefruit) Seed Extract	Citrus Unshiu Extract

The Panel previously reviewed the safety of *Citrus*-derived peel oils, *Citrus* peel-derived ingredients, and *Citrus* fruit-derived ingredients in separate assessments and concluded that 14 *Citrus*-derived peel oils, 47 *Citrus* peel-derived ingredients, and 80 *Citrus* fruit-derived ingredients are safe for use in both rinse-off and leave-on cosmetic products when formulated to be non-sensitizing and non-irritating, provided that leave-on products do not contain more than 0.0015% (15 ppm) 5-methoxypsoralen (5-MOP).[2-4] The Panel also determined that 33 *Citrus* flower- and leaf-derived ingredients are safe in the present practices of use and concentration when formulated to be non-irritating and non-sensitizing.[5] The Panel has also reviewed the safety of Citrus Aurantifolia (Lime) Seed Oil, Citrus Aurantifolia (Lime) Seed Oil Unsaponifiables, Citrus Aurantium Dulcis (Orange) Seed Oil, Citrus Aurantium Dulcis (Orange) Seed Oil Unsaponifiables, Citrus Grandis (Grapefruit) Seed Oil, Citrus Grandis (Grapefruit) Seed Oil Unsaponifiables, Citrus Limon (Lemon) Seed Oil, and Citrus Paradisi (Grapefruit) Seed Oil, and concluded that these ingredients are safe in the present practices of use and concentration as described in the safety assessment of plant-derived fatty acid oils.[6]

To avoid redundancy of effort, the Cosmetic Ingredient Review (CIR) generally excludes from review ingredients that are known to function exclusively as fragrance ingredients when the ingredient has been or will be evaluated by the Research Institute for Fragrance Materials (RIFM). According to the *Dictionary*, three of the *Citrus* plant- and seed-derived ingredients in this report are reported to function exclusively as fragrance ingredients (see Table 2).[1] However, personal communications with RIFM in March 2015 revealed that these ingredients have neither been assessed for safety by RIFM, nor are these ingredients on RIFM's prioritized agenda to be reviewed in the foreseeable future. Thus, the Panel is reviewing the safety of these ingredients as part of this current assessment.

Botanical ingredients are composed of numerous constituents, some of which have the potential to cause toxic effects. In this assessment, the Panel is reviewing the potential toxicity of each *Citrus* plant- or seed-derived ingredient as a whole, complex substance. Except for specific constituents of concern that have been identified, the Panel is not reviewing the potential toxicity of the individual constituents of the *Citrus* plants and seeds from which the ingredients in this report are derived.

Note: In many of the published studies included in this assessment, the information provided is not sufficient to determine how well the substance being tested represents the cosmetic ingredient. In this safety assessment, if a substance tested in a study is not clearly a cosmetic ingredient, because of lack of information on the genus and species from which the substance was derived and/or the method of extraction used, the test substance will be referred to by a common name (eg, lemon extract). If the substance is clearly a cosmetic ingredient, the International Nomenclature of Cosmetic Ingredients (INCI) name will be used (eg, "Citrus Limon (Lemon) Extract"). Additionally, some inconsistencies were noted in both taxonomic and INCI naming conventions. For example, this report includes the sweet orange ingredient described as Citrus Aurantium Dulcis (Orange) in the *Dictionary*.[1] In contrast, most of the published literature and the FDA VCRP refer to this ingredient as Citrus Sinensis (Sweet Orange). Another example of a naming inconsistency is Citrus Grandis (Grapefruit); *Citrus grandis* is generally considered a name for a pomelo, which may also be referred to as *Citrus maxima*. *Citrus paradisi* appears to be the more widely accepted nomenclature for grapefruit. Finally, Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil is also known as petitgrain bigarade oil. The INCI Committee of the Personal Care Products Council (Council) is working to correct some of these inconsistencies. The genus and species names associated with the ingredient names designated by the INCI Committee are listed in Table 3.[7]

Chemistry

Definition and General Characterization

The definitions and functions of the *Citrus* plant- and seed-derived ingredients included in this report are provided in Table 1. The definition indicates what part(s) of the plant from which an ingredient is obtained. In some cases, the definition provides insight on the method(s) of manufacture.

According to the *Dictionary*, essential oils and waters are prepared from leaves, stems, flowers, bark, roots, or other parts of a plant or the whole plant.[1] Essential oils are prepared by a number of processes including, but not limited to, steam or dry distillation, flash pasteurization and mechanical processes such as cold-pressing; however, the most widely used method for preparing essential oils from plants is steam distillation. The condensate from steam distillation produces 2 distinct fractions that contain the volatile ingredients from the plant. The water insoluble fraction contains the "oil." The water soluble fraction contains constituents of the plant that are dissolved in water. The name assigned to the water insoluble fraction from steam distilled plant materials includes the term "oil" in the INCI name. The water soluble fraction from the steam distilled plant material includes the term "water" in the INCI name.

Essential oils are the hydrophobic, liquid, volatile aromatic compounds in the insoluble condensate fraction, and typically are small molecules, but their chemical structures can vary

Table 1. Definitions and Functions of *Citrus* Plant- and Seed-Derived Ingredients.[1]

Ingredient	Definition*	Function
Citrus Aurantifolia (Lime) Oil CAS No. 8008-26-2	Citrus Aurantifolia (Lime) Oil is the volatile oil obtained from the whole plant, *Citrus aurantifolia*.	Fragrance Ingredients; Skin-Conditioning Agents—Miscellaneous
Citrus Aurantium (Bitter Orange) Oil	Not in *Dictionary*.	Not in *Dictionary*
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Extract CAS No. 72968-50-4; 8016-38-4	Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Extract is the extract of the leaves and twigs of *Citrus aurantium amara*.	Skin-Conditioning Agents—Miscellaneous
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil	Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil is the volatile oil obtained from the leaves and twigs of *Citrus aurantium amara*.	Flavoring Agents; Fragrance Ingredients
Citrus Aurantium Dulcis (Orange) Flower/Leaf/Stem Powder	Citrus Aurantium Dulcis (Orange) Flower/Leaf/Stem Powder is the powder obtained from the dried, ground flowers, leaves and stems of *Citrus aurantium dulcis*.	Exfoliants
Citrus Aurantium Dulcis (Orange) Oil	Citrus Aurantium Dulcis (Orange) Oil is the volatile oil obtained from the whole plant, *Citrus aurantium dulcis*.	Fragrance Ingredients
Citrus Aurantium Dulcis (Orange) Seed Extract	Citrus Aurantium Dulcis (Orange) Seed Extract is the extract of the seeds of *Citrus aurantium dulcis*.	Skin-Conditioning Agents—Miscellaneous
Citrus Aurantium Sinensis Powder	Citrus Aurantium Sinensis Powder is the powder obtained the dried ground plant, *Citrus aurantium sinensis*.	Exfoliants
Citrus Australasica Seed Oil CAS No. 1174331-57-7 (generic)	Citrus Australasica seed oil is the fixed oil expressed from the seeds of *Citrus australasica*.	Antioxidants; Hair Conditioning Agents; Humectants; Skin-Conditioning Agents—Miscellaneous
Citrus Depressa Seed Oil	Citrus Depressa Seed Oil is the oil expressed from the seeds of *Citrus depressa*.	Skin-Conditioning Agents—Emollient
Citrus Glauca Seed Oil	Citrus Glauca Seed Oil is the oil expressed from the seeds of *Citrus glauca*.	Antioxidants; Humectants; Skin Protectants; Skin-Conditioning Agents—Emollient; Skin-Conditioning Agents—Humectant
Citrus Grandis (Grapefruit)	Citrus Grandis (Grapefruit) is a plant material derived from the whole plant, *Citrus grandis*.	Not reported
Citrus Grandis (Grapefruit) Extract	Citrus Grandis (Grapefruit) Extract is the extract of the whole plant, *Citrus grandis*.	Skin-Conditioning aAgents—Miscellaneous
Citrus Grandis Peel/Seed Extract	Citrus Grandis Peel/Seed Extract is the extract of the peel and seeds of *Citrus grandis*.	Antifungal Agents; Antimicrobial Agents; Preservatives
Citrus Grandis (Grapefruit) Seed Extract	Citrus Grandis (Grapefruit) Seed Extract is the extract of the seeds of *Citrus grandis*.	Preservatives; Skin-Conditioning Agents—Miscellaneous
Citrus Iyo Oil	Citrus Iyo Oil is the oil expressed from the whole plant, *Citrus iyo*.	Skin-Conditioning Agents—Emollient
Citrus Junos Extract	Citrus Junos Extract is the extract of the whole plant, *Citrus junos*.	Antioxidants
Citrus Junos Seed Extract	Citrus Junos Seed Extract is the extract of the seeds of *Citrus junos*.	Antioxidants
Citrus Junos Seed Oil	Citrus Junos Seed Oil is the oil expressed from the seeds of *Citrus junos*.	Skin-Conditioning Agents—Emollient
Citrus Limon (Lemon) Flower/Leaf/Stem Extract CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Flower/Leaf/Stem Extract is the extract of the flowers, leaves and stems of *Citrus limon*.	Fragrance Ingredients; Skin-Conditioning Agents—Miscellaneous
Citrus Limon (Lemon) Flower/Leaf/Stem Oil CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Flower/Leaf/Stem Oil is the volatile oil obtained from the flowers, leaves and stems of *Citrus limon*.	Fragrance Ingredients

(continued)

Table 1. (continued)

Ingredient	Definition*	Function
Citrus Limon (Lemon) Leaf/Peel/Stem Oil CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Leaf/Peel/Stem Oil is the volatile oil obtained from the leaves, peels, and stems of *Citrus limon.*	Skin-Conditioning Agents—Miscellaneous
Citrus Nobilis (Mandarin Orange)	Citrus Nobilis (Mandarin Orange) is a plant material derived from the whole plant, *Citrus nobilis.*	Not reported
Citrus Nobilis (Mandarin Orange) Oil	Citrus Nobilis (Mandarin Orange) Oil is the volatile oil obtained from the whole plant, *Citrus nobilis.*	Fragrance Ingredients
Citrus Nobilis (Mandarin Orange) Water	Citrus Nobilis (Mandarin Orange) Water is an aqueous solution of the steam distillate obtained from *Citrus nobilis.*	Skin-Conditioning Agents—Miscellaneous
Citrus Paradisi (Grapefruit) Seed Extract CAS No. 90045-43-5 (generic)	Citrus Paradisi (Grapefruit) Seed Extract is the extract of the seeds of *Citrus paradisi.*	Skin-Conditioning Agents—Miscellaneous
Citrus Reticulata (Tangerine) Extract	Citrus Reticulata (Tangerine) Extract is the extract of the whole plant, *Citrus reticulata.*	Skin-Conditioning Agents—Miscellaneous
Citrus Sunki Seed Extract	Citrus Sunki Seed Extract is the extract of the seeds of *Citrus sunki.*	Antioxidants; Skin Bleaching Agents; Skin-Conditioning Agents—Miscellaneous
Citrus Sunki Seed Oil	Citrus Sunki Seed Oil is the oil expressed from the seeds of *Citrus sunki.*	Antioxidants; Skin Bleaching Agents; Skin-Conditioning Agents—Miscellaneous
Citrus Unshiu Extract CAS No. 98106-71-9	Citrus Unshiu Extract is the extract of the whole plant, *Citrus unshiu.*	Skin-Conditioning Agents—Miscellaneous

*Accepted or alternate scientific names for these *Citrus* ingredients are found in Table 3.

Table 2. *Citrus* Plant- and Seed-Derived Ingredients That Potentially Function Solely as Fragrance Ingredients.

Citrus Aurantium Dulcis (Orange) Oil
Citrus Limon (Lemon) Flower/Leaf/Stem Oil
Citrus Nobilis (Mandarin Orange) Oil

twidely. Fixed oils, on the other hand, are hydrophobic, nonvolatile, fatty compounds from plants (including *Citrus* seeds), animals or algae. These are primarily composed of glycerides and, to some extent, free fatty acids. Constituents of these *Citrus*-derived ingredients may include both oil types. The volatile nature of essential oils makes them more likely to be useful as fragrances, but use as fragrances is not their only reported function.

Physical and Chemical Properties

Citrus Australasica Seed Oil. Citrus Australasica Seed Oil is reported to be a straw/yellow colored liquid with a refractive index of 1.476 (specification range 1.450-1.490 at 20°C) and a specific gravity of 0.917 (specification range 0.900-0.940 at 20°C).[8]

Citrus Glauca Seed Oil. According to a supplier, Citrus Glauca Seed Oil is a light brown to dark brown liquid.[9] At 20°C, the refractive index is 1.472 (specification range 1.450-1.490) and the specific gravity is 0.921 (specification range 0.900-0.940).

Method of Manufacturing

Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil. According to the *Food Chemicals Codex*, "petitgrain oil, Paraguay type" is a volatile oil obtained by steam distillation from the leaves and small twigs of the bitter orange tree, *Citrus aurantium* L. subspecies *amara*.[10]

Citrus Junos Seed Extract. A supplier has reported that Citrus Junos Seed Extract is produced by extracting dried seeds with 90% ethanolic solution, which is then filtered.[11] The material then undergoes sedimentation, filtration, and adjustment before packaging.

Citrus Paradisi (Grapefruit) Seed Extract. A supplier reported that Citrus Paradisi (Grapefruit) Seed Extract is manufactured by first grinding grapefruit seeds and then extracting in a mix of water and glycerin.[12] The mixture is then clarified and decontaminated by heat.

Constituents/Composition

The *Citrus* ingredients are complex botanicals composed of numerous constituents. Table 4 lists the fatty acid profiles for *Citrus* seed-derived oils that were previously reviewed in the

Table 3. Review of *Citrus* Species Names.[7]

Species name used in INCI names (common name)	Accepted species name
Citrus aurantifolia (lime)	*Citrus x aurantifolia*
Citrus aurantium amara (bitter orange)	*Citrus x aurantium*
Citrus aurantium bergamia (bergamot)	*Citrus x limon*
Citrus aurantium dulcis (orange) ALSO *Citrus sinensis* (orange)	*Citrus x aurantium*
Citrus clementina (clementine)	*Citrus x aurantium*
Citrus depressa	*Citrus reticulata*
Citrus glauca	*Citrus glauca*
Citrus grandis (grapefruit or pomelo)	*Citrus maxima* or *Citrus x aurantium*
Citrus hassaku	*Citrus medica x Citrus x aurantium*
Citrus iyo	*Citrus x aurantium*
Citrus jabara	Not known
Citrus japonica (kumquat)	*Citrus japonica*
Citrus junos	*Citrus x junos*
Citrus limon (lemon)	*Citrus x limon*
Citrus madurensis	*Citrus x microcarpa*
Citrus medica vulgaris	*Citrus reticulata*
Citrus natsudaidai	*Citrus x aurantium*
Citrus nobilis (mandarin orange)	*Citrus reticulata*
Citrus paradisi (grapefruit)	*Citrus x aurantium*
Citrus reticulata (tangerine)	*Citrus reticulata*
Citrus shunkokan	Cultivated hybrid
Citrus sinensis (orange) ALSO *Citrus aurantium dulcis* (orange)	*Citrus x aurantium*
Citrus sphaerocarpa	Cultivated hybrid
Citrus sudachi	*Citrus reticulata*
Citrus tachibana	Not listed
Citrus tamurana	Cultivated hybrid
Citrus tangelo (tangelo)	*Citrus x aurantium*
Citrus tangerine (tangerine)	*Citrus reticulata*
Citrus tankan	*Citrus reticulata*
Citrus unshiu	*Citrus reticulata*

Table 4. Total Fatty Acid Composition of *Citrus* Seed Oils, as Previously Reported (%).[5]

Fatty Acids	Citrus Aurantifolia (Lime) Seed Oil	Citrus Aurantium Dulcis (Orange) Seed Oil	Citrus Grandis (Grapefruit) Seed Oil	Citrus Limon (Lemon) Seed Oil	Citrus Paradisi (Seed) Oil
Lauric (C12)	NR	NR	1.5	NR	2.95
Myristic (C14)	1	NR	1	NR	1.01
Palmitic (C16)	20-30	14-22	18-30	18.8	36.25
Heptadecanoic (C17:0)	NR	NR	NR	0.08	NR
Stearic (C18)	3-8	2-6	2-8	3.5	5.95
Oleic (C18:1)	20-38	26-35	20-38	30.1	18.34
Linoleic (C18:2)	30-45	35-45	30-48	33.4	29.26
Linolenic (C18:3)	5-15	2-6	2-6	13.5	3.58
Arachidic (C20)	2	0.5	NR	0.3	0.38
Eicosenoic (C20:1)	NR	NR	NR	0.03	0.84
Behenic (C22)	NR	NR	NR	0.08	NR
Lignoceric (C24)	NR	NR	NR	0.2	NR
Others	NR	NR	NR	C23:0 = <0.01; C26:0 = 0.01	C12:1=1.44

NR = not reported.

safety assessment of plant-derived fatty acid oils.[5] The major fatty acid components in *Citrus* seed-derived oils are palmitic acid, oleic acid, and linoleic acids.

The International Fragrance Association (IFRA) has issued standards for limonene and linalool in natural products, stating that these constituents "should only be used when the level of peroxides is kept to the lowest practical level, for instance by adding antioxidants at the time of production."[13,14]

Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil. According to the Food Chemicals Codex, "petitgrain oil, Paraguay type" contains not less than 45.0% and not more than 60% esters calculated as linalyl acetate.[10] A fragrance raw materials monograph lists the components of petitgrain bigarade oil as α-pinene, β-pinene, sabinene, myrcene, limonene, cis-β-ocimene, trans-β-ocimene, linalool, linalyl acetate, terpineol-4, β-caryophyllene, α-terpineol, neryl acetate, geranyl acetate, nerol, geraniol, and nerolidol.[15] A breakdown of the key constituents of Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil is detailed in Table 5.

Table 5. Key Constituents (%) of Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil.*,32

	Bigarade type	Paraguayan type
Linalyl acetate	51.0-71.0	47.4-58.0
Linalool	12.3-24.2	20.8-25.2
(+)-limonene	0.4-8.0	0.3-1.1
α-terpineol	2.1-5.2	4.4-6.8
Geranyl acetate	1.9-3.4	2.9-4.5
β-pinene	0.3-2.7	0.3-1.2
Neryl acetate	0-2.6	2.1-3.0
Geraniol	1.4-2.3	2.1-3.0
(E)-β-ocimene	0.2-2.2	0-2.0
β-myrcene	0-2.0	0-2.0
Nerol	0.4-1.1	NR

NR = Not reported.
*Composition reported down to the level of 1%, or lower for known toxic constituents.

Citrus Australasica Seed Oil and Citrus Glauca Seed Oil. The fatty acid profiles for Citrus Australasica Seed Oil and Citrus Glauca Seed Oil are listed in Table 6.

Citrus Junos Seed Extract. A supplier reports that Citrus Junos Seed Extract is composed of saponin and sugar.[11] The concentrations of heavy metal impurities are not more than 20 ppm and the concentration of arsenic is not more than 2 ppm.

The fatty acid profile for *Citrus junos* Sieb. ex Tanaka is also listed in Table 6.

Citrus Paradisi (Grapefruit) Seed Extract. A supplier reported that a trade name material contains 67.0% to 73.0% glycerin, 26.0% to 32.8% water, and 0.2% to 1.0% Citrus Paradisi (Grapefruit) Seed Extract.[12]

Citrus Sinensis. In gas chromatography and gas chromatography-mass spectroscopy analysis of the essential oils from the leaves and green branches of Egyptian navel orange trees (*Citrus sinensis* (L.) Osbeck var. Malesy), 33 and 24 compounds were identified for the leaves and branches, respectively.[16]

Table 6. Fatty Acid Profiles (%) by Gas Chromatography.[8,9,33]

Fatty Acid	Citrus australasica seed oil	Citrus glauca seed oil	*Citrus junos* sieb. ex takana seed oil*
Undecanoic acid	NR	NR	3.27
Myristic acid	0.07	NR	NR
Palmitic acid	10.50	8.07	19.16
Palmitoleic acid	0.24	0.17	0.62
Margaric acid	0.08	0.05	NR
Heptadecanconic acid	0.07	NR	NR
Stearic acid	3.36	2.52	3.76
Elaidic acid	0.11	NR	NR
Oleic acid	36.55	47.39	32.01
cis-vaccenic acid	1.67	2.00	NR
Linolelaidic acid	0.05	NR	NR
Linoleic acid	41.01	36.28	33.99
α-linolenic acid	4.70	1.28	2.05
Arachadic acid	0.40	0.31	0.26
11-eicosenoic acid	0.28	0.42	NR
Behenic acid	0.42	0.61	NR
Lignoceric acid	0.15	0.32	NR
Unknown	NR	NR	4.48

*Reported as acid methyl esters.

These compounds made up 96.0% and 97.9%, respectively, of the total detected constituents. The major constituents were sabinene (36.5% leaves, 33.0% branches), terpinen-4-ol (8.2% leaves, 6.2% branches), δ-3-carene (7.0% leaves, 9.4% branches), limonene (6.8% leaves, 18.7% branches), trans-ocimene (6.7% leaves, 6.1% branches), and β-myrcene (4.5% leaves, 9.4% branches).

The composition of samples of dehulled sweet orange (*Citrus sinensis*) seed flour (dry weight) was reported to be 54.2% fat, 28.5% carbohydrate, 5.5% crude fiber, 3.1% crude protein, and 2.5% ash.[17] Mineral analysis showed high levels of calcium and potassium.

Use

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated based on data received from the 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 FDA's VCRP database. Use concentration data are submitted by Industry in response to surveys, conducted by the Council, of maximum reported use concentrations by product category.

According to 2016 VCRP data, Citrus Aurantium (Bitter Orange) Oil has the most reported uses of the cosmetic ingredients in this report, with a total of 295; more than half are in leave-on skin care preparations (Table 7).[18] This ingredient is not currently in the *Dictionary*, but has been included in this report because of the number of uses and presumed similarities to the other ingredients in this report. The ingredients with the next highest frequency of use are Citrus Aurantifolia (Lime) Oil (169 total uses) and Citrus Grandis (Grapefruit) Seed Extract (144 total uses); a majority of the uses for these ingredients are in leave-on skin care preparations. The results of the concentration of use survey indicate Citrus Aurantium Dulcis (Orange) Oil has the highest reported maximum concentration of use; it is used at up to 1% in a body and hand formulation.[19] Citrus Aurantifolia (Lime) Oil had the second highest reported maximum concentration of use; it is used at up to 0.36% in a lipstick.

In some cases, reports of uses were received from the VCRP, but no concentration of use data was provided. For example, Citrus Limon (Lemon) Flower/Leaf/Stem Extract is reported to be used in 8 formulations, but no use concentration data were available. In other cases, no uses were reported to the VCRP, but a maximum use concentration was provided in the industry survey. For example, Citrus Junos Seed Oil was not reported in the VCRP database, but the industry survey indicated that it is used in face and neck and body and hand formulations at up to 0.1%. It is presumed that Citrus Junos Seed Oil is used in at least 1 cosmetic formulation.

Table 8 lists all *Citrus* plant- and seed-derived ingredients not currently in use based on the VCRP data or the results of the Council concentration of use survey.

Some of these ingredients may be used in products that can come into contact with the eye or mucous membranes. For example, Citrus Aurantifolia (Lime) Oil is used in a lipstick at up to 0.36%. Additionally, some of these ingredients were reported to be used in hair sprays, fragrance preparations, face powder and body powders, spray deodorants, and spray skin care preparations and could possibly be inhaled. For example, Citrus Aurantifolia (Lime) Oil was reported to be used in body and hand sprays at a maximum concentration of 0.12% and Citrus Junos Seed Oil was reported to be used in face powders at up to 0.1%. 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.[20-23] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount.[21,22] 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.[22] 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. 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.[24-26]

The *Citrus* ingredients described in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union (EU). However, furocoumarins are prohibited from use in cosmetics, except for normal content in natural essences and in sun protection and bronzing products where the content shall be below 1 mg/kg.[27]

Non-Cosmetic

Petitgrain bigarade oil (Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil) is generally recognized as safe (GRAS) for intended use in foods for human consumption (21CFR182.20) and in animal drugs, feeds, and related products (21CFR582.20).

Toxicokinetics

No relevant published toxicokinetics studies on *Citrus* plant- and seed-derived ingredients were identified in a literature search for these ingredients, and no unpublished data were submitted; toxicokinetics data are not expected to be found

Table 7. Frequency and Concentration of Use According to Duration and Type of Exposure for *Citrus* Plant- and Seed-Derived Ingredients.[18,19]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Citrus Aurantifolia (lime) Oil		Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil[d]		Citrus Aurantium (Bitter Orange) Oil[e]		Citrus Aurantium Dulcis (Orange) Oil[f]	
Totals[†]	169	0.00000051-0.36	43	0.0000000026-0.0032	295	NR	4	0.0000032-1
Duration of use								
Leave-on	90	0.00049-0.36	25	0.00000014-0.0032	178	NR	3	0.000094-1
Rinse off	69	0.00015-0.17	14	0.00000015-0.000013	96	NR	NR	0.000026-0.81
Diluted for (bath) use	10	0.00000051	4	0.0000000026	21	NR	1	0.0000032-0.94
Exposure type								
Eye area	NR	NR	NR	NR	NR	NR	NR	0.00078-0.034
Incidental ingestion	NR	0.0015-0.36	NR	NR	2	NR	NR	0.034-0.95
Incidental inhalation-spray	9; 34[a]; 29[b]	0.00049-0.12; 0.0015-0.1[a]; 0.00067[b]	11[a]; 11[b]	0.00000014-0.00000043; 0.0000025[a]	31; 37[a]; 49[b]	NR	1; 2[a]	0.0022-0.12; 0.0053-0.26[a]; 0.000094[b]
Incidental inhalation-powder	1[c]; 29[b]	0.022; 0.0075-0.023[c]; 0.00067	11[b]	0.000011[c]	1; 3[c]; 49[b]	NR	NR	0.0012-0.0014; 0.18-1[c]; 0.000094[b]
Dermal contact	147	0.00000051-0.17	40	0.0000000026-0.0032	250	NR	3	0.0000032-1
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	0.039[a]; 0.038-0.06[g]
Hair-non-coloring	22	0.00049-0.02	3	0.00000014-0.0000025	32	NR	1	0.0022-0.81
Hair-coloring	NR	0.00015	NR	NR	11	NR	NR	0.000026-0.042
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous membrane	35	0.00000051-0.36	11	0.0000000026-0.000013	53	NR	1	0.0000032-0.95
Baby products	3	NR	NR	NR	9	NR	NR	NR
	Citrus Aurantium Dulcis (Orange) Seed Extract[h]		Citrus Aurantium Sinensis Powder[i]		Citrus Grandis (Grapefruit) Extract		Citrus Grandis (Grapefruit) Seed Extract	
Totals[†]	2	NR	1	NR	NR	0.0017-0.0059	144	0.0004-0.15
Duration of use								
Leave-on	2	NR	1	NR	NR	0.0017-0.003	85	0.076-0.15
Rinse off	NR	NR	NR	NR	NR	0.0022-0.0059	51	0.0004-0.12
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	8	NR
Exposure type								
Eye area	NR	NR	NR	NR	NR	NR	5	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR	12	0.076
Incidental inhalation-spray	2[b]	NR	1[b]	NR	NR	0.0017-0.003	2; 28[a]; 17[b]	NR
Incidental inhalation-powder	2[b]	NR	1[b]	NR	NR	NR	17[b]; 2[c]	0.1[c]
Dermal contact	2	NR	1	NR	NR	0.0022-0.0059	106	0.02-0.15

(continued)

Table 7. (continued)

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
Deodorant (underarm)	NR	NR	NR	NR	NR	0.0024[g]	14[a]	NR
Hair-non-coloring	NR	NR	NR	NR	NR	0.0017-0.005	23	0.0004
Hair-coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	NR	NR	NR	NR	0.0022-0.0059	26	0.076
Baby products	NR	NR	NR	NR	NR	NR	7	NR
	Citrus Junos Extract		Citrus Junos Seed Extract[j]		Citrus Junos Seed Oil		Citrus Limon (Lemon) Flower/Leaf/Stem Extract	
Totals[†]	NR	0.0001	7	0.001-0.0045	NR	0.001-0.1	8	NR
Duration of use								
Leave-on	NR	NR	7	0.001-0.0045	NR	0.01-0.1	8	NR
Rinse off	NR	0.0001	NR	0.001	NR	0.001	NR	NR
Diluted for (bath) use	NR	NR	NR	0.001	NR	NR	NR	NR
Exposure type								
Eye area	NR	NR	1	0.001	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental inhalation-spray	NR	NR	4[a]; 2[b]	NR	NR	NR	6[a]; 1[b]	NR
Incidental inhalation-powder	NR	NR	2[b]	0.0045[c]	NR	0.1; 0.1[c]	1[b]	NR
Dermal contact	NR	NR	7	0.001-0.0045	NR	0.001-0.1	8	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-non-coloring	NR	NR	NR	NR	NR	0.01	NR	NR
Hair-coloring	NR	0.0001	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	NR	NR	0.001	NR	NR	NR	NR
Baby products	NR	NR	NR	NR	NR	NR	NR	NR
	Citrus Nobilis (Mandarin Orange)		Citrus Nobilis (Mandarin Orange) Oil		Citrus Paradisi (Grapefruit) Seed Extract		Citrus Reticulata (Tangerine) Extract	
Totals[†]	NR	0.0005	36	0.0009-0.035	52	NR	NR	0.0001-0.0051
Duration of use								
Leave-on	NR	NR	28	NR	39	NR	NR	0.0002-0.0051
Rinse off	NR	0.0005	4	0.0009-0.035	13	NR	NR	0.0001-0.005
Diluted for (bath) use	NR	NR	4	NR	NR	NR	NR	NR
Exposure type								
Eye area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental ingestion	NR	NR	1	0.035	1	NR	NR	NR
Incidental inhalation-spray	NR	NR	8; 2[a]; 4[b]	NR	16[a]; 17[b]	NR	NR	0.0051[a]
Incidental inhalation-powder	NR	NR	4[b]; 1[c]	NR	17[b]; 1[c]	NR	NR	0.0002[c]

(continued)

Table 7. (continued)

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
Dermal contact	NR	0.0005	35	0.0009-0.0017	50	NR	NR	0.0002
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-non-coloring	NR	0.0005	NR	NR	1	NR	NR	0.0001-0.0051
Hair-coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	0.0005	7	0.0009-0.035	8	NR	NR	NR
Baby products	NR	NR	2	NR	2	NR	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]Listed as Citrus Aurantium (Bitter Orange) Leaf/Twig Oil in the VCRP database.
[e]Only listed in the VCRP database, not in the INCI dictionary. Included because of assumed similarity.
[f]Listed as Citrus Sinensis (Sweet Orange) Plant Oil in the VCRP database.
[g]Not a spray deodorant.
[h]Listed as Citrus Sinensis (Sweet Orange) Seed Extract in the VCRP database.
[i]Listed as Citrus Sinensis (Orange) Powder in the VCRP database.
[j]Listed as Citrus Junos (Xiang Cheng) Seed Extract in the VCRP database.

Table 8. Ingredients That are Not Reported to be in use[18,19].

Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Extract	Citrus Iyo Oil
Citrus Aurantium Dulcis (Orange) Flower/Leaf/Stem Powder	Citrus Limon (Lemon) Flower/Leaf/Stem Oil
Citrus Australasica Seed Oil	Citrus Limon (Lemon) Leaf/Peel/Stem Oil
Citrus Depressa Seed Oil	Citrus Nobilis (Mandarin Orange) Water
Citrus Glauca Seed Oil	Citrus Sunki Seed Extract
Citrus Grandis (Grapefruit)	Citrus Sunki Seed Oil
Citrus Grandis Peel/Seed Extract	Citrus Unshiu Extract

because botanical ingredients are mixtures of hundreds of constituents.

Toxicological Studies

Acute Toxicity

Dermal—Animal

Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil. The dermal LD_{50} of Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as petitgrain bigarade oil) was reported to be greater than 2 g/kg in rabbits; however, only 2 rabbits were used in the study.[15] An occlusive patch of undiluted test material was applied for 24 h.

Repeated Dose Toxicity

No relevant published repeated dose toxicity studies on *Citrus* plant- and seed-derived ingredients were identified in a literature search for these ingredients, and no unpublished data were submitted.

Reproductive and Developmental Toxicity

No relevant published reproductive and developmental studies on *Citrus* plant- and seed-derived ingredients were identified in a literature search for these ingredients, and no unpublished data were submitted.

Genotoxicity

No relevant published genotoxicity studies on *Citrus* plant- and seed-derived ingredients were identified in a literature search for these ingredients, and no unpublished data were submitted.

Carcinogenicity

No relevant published carcinogenicity studies on *Citrus* plant- and seed-derived ingredients were identified in a literature search for these ingredients, and no unpublished data were submitted.

Irritation and Sensitization

Dermal Irritation

Dermal irritation studies are summarized in Table 9.[15,28,29] In rabbit studies, slight erythema was observed after exposure to 2g/kg Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as petitgrain bigarade oil). In human subjects, no irritation was observed after topical exposure to petitgrain bigarade oil (up to 8% in petrolatum) or Citrus Grandis (Grapefruit) Seed Extract (0.15% in formulation).[29]

Dermal Sensitization

Dermal sensitization studies are presented in Table 10.[15,30] Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as petitgrain bigarade oil) at up to 8% in petrolatum was not sensitizing in humans.

Photosensitization

Photosensitization studies are presented in Table 11.[31] Undiluted Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as petitgrain bigarade oil) was not photosensitizing in tests with hairless mice or miniature swine.

Clinical Studies

No relevant published clinical studies on *Citrus* plant- and seed-derived ingredients were identified in a literature search for these ingredients, and no unpublished data were submitted.

Table 9. Dermal Irritation Studies for *Citrus* Plant- and Seed-Derived Ingredients.

Test article	Concentration/ dose	Test population	Procedure	Results	Reference
Animal					
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as "petitgrain bigarade oil")	2g/kg; undiluted	2 rabbits	24-h occlusive, single dose study	Slight erythema	15
Human					
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as "petitgrain bigarade oil")	0.1%, 2% or 5%; multiple vehicles	48 subjects at 0.1%, 30 subjects at 2%, and 30 subjects at 5%	24-72 h occlusive patch tests	No irritation	28
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as "petitgrain bigarade oil")	8% in petrolatum	25 subjects	48 h occlusive patch applied to the forearm or back	No irritation	15
Citrus Grandis (Grapefruit) Seed Extract	0.15% in a foot gel	12 subjects with normal, lesion-free skin	48 h occlusive patch (Finn chambers) on external arm, single application of 0.02 mL	No irritation (mean irritation index = 0.13)	29

Table 10. Sensitization Studies for *Citrus* Plant- and Seed-Derived Ingredients.

Test article	Concentration/ dose	Test population	Procedure	Results	Reference
Human					
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as "petitgrain bigarade oil")	2% in paraffin	200 patients with dermatitis tested with 35 essential oils plus an additional 50 patients with balsam sensitivity	sensitization patch study, details not provided	3 positive reactions, details not provided	30
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as "petitgrain bigarade oil")	8% in petrolatum	25 subjects	maximization study, details not provided	Not sensitizing	15

Table 11. Photosensitization Studies.

Test article	Concentration/ dose	Test population	Procedure	Results	Reference
Non-human					
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as "petitgrain bigarade oil")	Undiluted	hairless mice (#/group not stated)	test material was applied, and the test sites were irradiated with UVA irradiation by blacklight or xenon lamp	Not photosensitizing	31
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as "petitgrain bigarade oil")	Undiluted	Miniature swine (#/group not stated)	Test material was applied, and the test sites were irradiated with UVA irradiation by blacklight or xenon lamp	Not photosensitizing	31

Summary

The 30 *Citrus* plant- and seed-derived ingredients described in this report function primarily as skin conditioning agents-miscellaneous. Botanical ingredients are composed of hundreds of constituents, some of which have the potential to cause toxic effects. Presently, the Panel reviewed the information available on the potential toxicity of each *Citrus* plant- and seed-derived ingredient as a whole, complex substance; the Panel does not review the potential toxicity information on the individual constituents of which the *Citrus* plant- and seed-derived ingredients are comprised.

Citrus seed oils are fixed oils that are composed primarily of glycerides and, to some extent, free fatty acids, while the other *Citrus* oils in this safety assessment are essential oils that primarily contain volatile compounds. No composition information was found for ingredients defined as being derived from the whole plant.

Citrus Aurantium (Bitter Orange) Oil has the most reported uses of the ingredients in this report in cosmetic products, with a total of 295; more than half of the uses are in leave-on skin care preparations. This ingredient is not currently in the *Dictionary* but has been included in this report because of its high reported number of uses and presumed similarities to the other ingredients in this report. The ingredients with the next highest frequency of use are Citrus Aurantifolia (Lime) Oil (169 total uses) and Citrus Grandis (Grapefruit) Seed Extract (144 total uses); a majority of the uses for these ingredients are in leave-on skin care preparations. The results of the concentration of use survey indicate Citrus Aurantium Dulcis (Orange) Oil has the highest reported maximum concentration of use; it is used at up to 1% in a body and hand formulation. Citrus Aurantifolia (Lime) Oil had the second highest reported maximum concentration of use; it is used at up to 0.36% in a lipstick.

The *Citrus* ingredients described in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union (EU); however, furocoumarins are prohibited from use in cosmetics except for normal content in natural essences and in sun protection and bronzing products where the content shall be < 1 mg/kg.

Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil is considered GRAS in foods for human consumption and in animal drugs, feed, and related products.

The dermal LD_{50} of Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as petitgrain bigarade oil) was reported as greater than 2 g/kg in rabbits.

In rabbit dermal irritation studies, slight erythema was observed after exposure to unreported concentrations of Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as petitgrain bigarade oil). In human subjects, no irritation was observed after topical exposure to petitgrain bigarade oil (up to 8%).

Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil (described as petitgrain bigarade oil) at up to 8% was not sensitizing in humans and undiluted petitgrain bigarade oil was not photosensitizing in tests with hairless mice or miniature swine.

No relevant published studies on the toxicokinetics, repeated dose toxicity, reproductive and development toxicity, carcinogenicity, genotoxicity, or clinical assessments of *Citrus* plant- and seed-derived ingredients were discovered and no unpublished data were submitted to address these topics.

Discussion

During its review of *Citrus* plant- and seed-derived ingredients, the Panel noted that, because botanical ingredients are complex mixtures, there is concern that multiple botanical ingredients may each contribute to the final concentration of a single constituent. Therefore, when formulating products, manufacturers should avoid reaching levels in final formulation of botanical constituents that may cause sensitization or other adverse effects. Specific examples of constituents that could induce adverse effects include the hydroperoxides of limonene and linalool.

The issue of incidental inhalation exposure from hair sprays, fragrance preparations, face powder and body powders, spray deodorants, and spray skin care preparations was discussed by the Panel. There were no inhalation toxicity data available. The Panel noted that droplets/particles from

cosmetic products would not be respirable to any appreciable amount. The potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. In principle, inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. However, 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 the Cosmetic Ingredient Review (CIR) website (http://www.cir-safety.org/cir-findings).

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

The Panel determined that the composition data on the *Citrus* seed-derived ingredients found in this report were sufficient and no individual component of the seeds yielded any toxicological concern. The Panel also considered the composition, GRAS status, and safety test data on Citrus Aurantium Amara (Bitter Orange) Twig/Leaf Oil to be sufficient to support the safety of the use of this ingredient and the extract in cosmetics. The Panel determined that the conclusion of safe with the listed qualifications could be extended to Citrus Grandis (Grapefruit) Extract, Citrus Junos Extract, Citrus Nobilis (Mandarin Orange), Citrus Nobilis (Mandarin Orange) Oil, and Citrus Reticualta (Tangerine) Extract because these ingredients are largely used in rinse-off formulations at very low concentrations. However, the Panel concluded that the data are insufficient to make a conclusion on the safety of 12 *Citrus* plant-derived ingredients found in this safety assessment. The data that are needed to properly evaluate the safety of these ingredients are:

- Method of manufacturing
- Chemical composition and impurities
- Irritation and sensitization data
- If the composition data for these *Citrus* plant-derived ingredients are substantially different from that of the *Citrus* peel-, flower-, leaf- and seed-derived ingredients, then studies of systemic endpoints such as a 28-day dermal toxicity, reproductive and developmental toxicity, and genotoxicity are needed, as well as UV absorption spectra.

Conclusion

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 18 ingredients are safe in the present practices of use and concentration when formulated to be non-irritating and non-sensitizing.

Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Extract*	Citrus Junos Extract
Citrus Aurantium Amara (Bitter Orange) Leaf/Twig Oil	Citrus Junos Seed Extract
Citrus Aurantium Dulcis (Orange) Seed Extract	Citrus Junos Seed Oil
Citrus Australasica Seed Oil*	Citrus Nobilis (Mandarin Orange)
Citrus Depressa Seed Oil*	Citrus Nobilis (Mandarin Orange) Oil
Citrus Glauca Seed Oil*	Citrus Paradisi (Grapefruit) Seed Extract
Citrus Grandis (Grapefruit) Extract	Citrus Reticulata (Tangerine) Extract
Citrus Grandis Peel/Seed Extract*	Citrus Sunki Seed Extract*
Citrus Grandis (Grapefruit) Seed Extract	Citrus Sunki Seed Oil*

The Panel concluded the data on the remaining 12 ingredients listed below are insufficient to determine safety.

Citrus Aurantifolia (Lime) Oil	Citrus Iyo Oil*
Citrus Aurantium (Bitter Orange) Oil	Citrus Limon (Lemon) Flower/Leaf/Stem Extract
Citrus Aurantium Dulcis (Orange) Flower/Leaf/Stem Powder*	Citrus Limon (Lemon) Flower/Leaf/Stem Oil*
Citrus Aurantium Dulcis (Orange) Oil	Citrus Limon (Lemon) Leaf/Peel/Stem Oil*
Citrus Aurantium Sinensis Powder	Citrus Nobilis (Mandarin Orange) Water*
Citrus Grandis (Grapefruit)*	Citrus Unshiu Extract*

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

Author's Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1620 L Street, NW, Suite 1200, Washington, DC 20036, USA.

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