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Safety Assessment of *Citrus* Flower- and Leaf-Derived Ingredients as Used in Cosmetics

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Abstract

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of 33 *Citrus* flower- and leaf-derived ingredients, which are most frequently reported to function in cosmetics as fragrances and/or skin-conditioning agents. The Panel reviewed the available data to determine the safety of these ingredients. 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* flower- and leaf-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 that could be present in botanical ingredients. The Panel concluded that these ingredients are safe in the present practices of use and concentration when formulated to be non-irritating and non-sensitizing.

Keywords

cosmetics, safety, citrus flower, citrus leaf

Introduction

According to the *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*), *Citrus* flower- and leaf-derived ingredients are most frequently reported to function in cosmetics as fragrances and/or skin-conditioning agents (Table 1).[1] This report assesses the safety of the following 33 ingredients:

(continued)

Citrus Aurantifolia (Lime) Flower Extract	Citrus Grandis (Grapefruit) Leaf Extract
Citrus Aurantifolia (Lime) Leaf Oil	Citrus Hystrix Leaf Extract
Citrus Aurantium Amara (Bitter Orange) Flower Extract	Citrus Hystrix Leaf Oil
Citrus Aurantium Amara (Bitter Orange) Flower Oil	Citrus Junos Flower Oil
Citrus Aurantium Amara (Bitter Orange) Flower Water	Citrus Limon (Lemon) Flower Water
Citrus Aurantium Amara (Bitter Orange) Flower Wax	Citrus Limon (Lemon) Leaf Extract
Citrus Aurantium Bergamia (Bergamot) Leaf Cell Extract	Citrus Limon (Lemon) Leaf Cell Extract
	Citrus Natsudaidai Flower Water
Citrus Aurantium Bergamia (Bergamot) Leaf Extract	Citrus Natsudaidai Flower Oil
Citrus Aurantium Bergamia (Bergamot) Leaf Oil	Citrus Reticulata (Tangerine) Leaf Oil

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Citrus Aurantium Dulcis (Orange) Flower Extract	Citrus Reticulata (Tangerine) Leaf Water
Citrus Aurantium Dulcis (Orange) Flower Oil	Citrus Sinensis (Orange) Flower Water
Citrus Aurantium Dulcis (Orange) Flower Wax	Citrus Tamurana Flower Extract
Citrus Aurantium Dulcis (Orange) Flower	Citrus Unshiu Flower Extract
Citrus Aurantium Dulcis (Orange) Leaf Extract	Citrus Unshiu Flower Powder
Citrus Clementina Leaf Cell Extract	Citrus Unshiu Flower Water
Citrus Depressa Flower Water	Citrus Unshiu Leaf Extract

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

Ingredient	Definition	Function
Citrus Aurantifolia (Lime) Flower Extract	Citrus Aurantifolia (Lime) Flower Extract is the extract of the flowers of *Citrus aurantifolia*.	Cosmetic Astringents; Skin-Conditioning Agents—Miscellaneous
Citrus Aurantifolia (Lime) Leaf Oil	Citrus Aurantifolia (Lime) Leaf Oil is the volatile oil obtained from the leaves of *Citrus aurantifolia*.	Fragrance Ingredients
Citrus Aurantium Amara (Bitter Orange) Flower Extract CAS No. 72968-50-4	Citrus Aurantium Amara (Bitter Orange) Flower Extract is the extract of the flowers of *Citrus aurantium amara*.	Skin-Conditioning Agents—Occlusive
Citrus Aurantium Amara (Bitter Orange) Flower Oil	Citrus Aurantium Amara (Bitter Orange) Flower Oil is the volatile oil obtained from the flowers of *Citrus aurantium amara*.	Fragrance Ingredients; Skin-Conditioning Agents—Miscellaneous
Citrus Aurantium Amara (Bitter Orange) Flower Water	Citrus Aurantium Amara (Bitter Orange) Flower Water is an aqueous solution of the steam distillate obtained from the flowers of *Citrus aurantium amara*.	Fragrance Ingredients; Skin-Conditioning Agents—Miscellaneous
Citrus Aurantium Amara (Bitter Orange) Flower Wax	Citrus Aurantium Amara (Bitter Orange) Flower Wax is a wax obtained from the flower of *Citrus aurantium amara*.	Not reported
Citrus Aurantium Bergamia (Bergamot) Leaf Cell Extract	Citrus Aurantium Bergamia (Bergamot) Leaf Cell Extract is the extract of a culture of the leaf cells of *Citrus aurantium bergamia*.	Antioxidants; Skin Protectants
Citrus Aurantium Bergamia (Bergamot) Leaf Extract	Citrus Aurantium Bergamia (Bergamot) Leaf Extract is the extract of the leaves of *Citrus aurantium bergamia*.	Cosmetic Astringents
Citrus Aurantium Bergamia (Bergamot) Leaf Oil	Citrus Aurantium Bergamia (Bergamot) Leaf Oil is the volatile oil obtained from the leaves of *Citrus aurantium bergamia*.	Cosmetic Astringents
Citrus Aurantium Dulcis (Orange) Flower	Citrus Aurantium Dulcis (Orange) Flower is the flower of *Citrus aurantium dulcis*.	Skin-Conditioning Agents—Miscellaneous
Citrus Aurantium Dulcis (Orange) Flower Extract	Citrus Aurantium Dulcis (Orange) Flower Extract is the extract of the flowers of *Citrus aurantium dulcis*.	Skin-Conditioning Agents—Miscellaneous
Citrus Aurantium Dulcis (Orange) Flower Oil CAS No. 8016-38-4	Citrus Aurantium Dulcis (Orange) Flower Oil is the volatile oil obtained from the flowers of *Citrus aurantium dulcis*.	Fragrance Ingredients; Skin-Conditioning Agents—Miscellaneous
Citrus Aurantium Dulcis (Orange) Flower Wax	Citrus Aurantium Dulcis (Orange) Flower Wax is a wax obtained from the flowers of *Citrus aurantium dulcis*.	Skin-Conditioning Agents—Occlusive
Citrus Aurantium Dulcis (Orange) Leaf Extract	Citrus Aurantium Dulcis (Orange) Leaf Extract is the extract of the leaves of *Citrus aurantium dulcis*.	Skin-Conditioning Agents—Miscellaneous
Citrus Clementina Leaf Cell Extract	Citrus Clementina Leaf Cell Extract is the extract of a culture of the leaf cells of *Citrus clementina*.	Antioxidants; Skin Protectants
Citrus Depressa Flower Water	Citrus Depressa Flower Water is the aqueous solution of the steam distillates obtained from the flowers of *Citrus depressa*.	Skin-Conditioning Agents—Humectant
Citrus Junos Flower Oil	Citrus Junos Flower Oil is the volatile oil obtained from the flowers of *Citrus junos*.	Flavoring Agents; Fragrance Ingredients
Citrus Limon (Lemon) Flower Water	Citrus Limon (Lemon) Flower Water is an aqueous solution of the steam distillates obtained from the flowers of *Citrus limon* (lemon).	Skin-Conditioning Agents—Humectant
Citrus Grandis (Grapefruit) Leaf Extract	Citrus Grandis (Grapefruit) Leaf Extract is the extract of the leaves of *Citrus grandis*.	Skin-Conditioning Agents—Miscellaneous
Citrus Hystrix Leaf Extract	Citrus Hystrix Leaf Extract is the extract of the leaves of *Citrus hystrix*.	Skin-Conditioning Agents—Miscellaneous
Citrus Hystrix Leaf Oil (or Kaffir Lime (Citrus Hystrix) Leaf Oil)	Not in *Dictionary*.	Not in *Dictionary*.
Citrus Limon (Lemon) Leaf Cell Extract CAS No. 84929-31-7	Citrus Limon (Lemon) Leaf Cell Extract is the extract of a culture of the leaf cells of *Citrus limon*.	Skin-Conditioning Agents—Miscellaneous
Citrus Limon (Lemon) Leaf Extract	Citrus Limon (Lemon) Leaf Extract is the extract of the leaves of *Citrus limon*.	Antioxidants
Citrus Natsudaidai Flower Oil	Citrus Natsudaidai Flower Oil is the volatile oil obtained from the flowers of *Citrus natsudaidai*.	Fragrance Ingredients

(continued)

Table 1. (continued)

Ingredient	Definition	Function
Citrus Natsudaidai Flower Water	Citrus Natsudaidai Flower Water is the aqueous solution of the steam distillates obtained from the flowers of *Citrus natsudaidai*.	Fragrance Ingredients
Citrus Reticulata (Tangerine) Leaf Oil CAS No. 8014-17-3	Citrus Reticulata (Tangerine) Leaf Oil is the volatile oil derived from the leaves of *Citrus reticulate*	Fragrance Ingredients; Skin-Conditioning Agents—Miscellaneous
Citrus Reticulata (Tangerine) Leaf Water	Citrus Reticulata (Tangerine) Leaf Water is an aqueous solution of the steam distillate obtained from the leaves of *Citrus reticulata*.	Skin-Conditioning Agents—Miscellaneous
Citrus Sinensis (Orange) Flower Water	Citrus Sinensis (Orange) Flower Water is an aqueous solution of the steam distillates obtained from the flowers of *Citrus sinensis*.	Skin-Conditioning Agents—Humectant
Citrus Tamurana Flower Extract	Citrus Tamurana Flower Extract is the extract of the flowers of *Citrus tamurana*.	Skin-Conditioning Agents—Miscellaneous
Citrus Unshiu Flower Extract	Citrus Unshiu Flower Extract is the extract of the flowers of *Citrus unshiu*.	Skin Protectants; Skin-Conditioning Agents—Humectant
Citrus Unshiu Flower Powder	Citrus Unshiu Flower Powder is the powder obtained from the dried, ground flowers of *Citrus unshiu*.	Exfoliants
Citrus Unshiu Flower Water	Citrus Unshiu Flower Water is an aqueous solution of the steam distillates obtained from the flowers of *Citrus unshiu*.	Fragrance Ingredients
Citrus Unshiu Leaf Extract	Citrus Unshiu Leaf Extract is the extract of the leaves of *Citrus unshiu*.	Skin Protectants; Skin-Conditioning Agents—Humectant

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

The Panel has 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 oil ingredients, 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 assessed the safety of 30 *Citrus* plant- and seed-derived ingredients 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, while the data for the remaining 12 ingredients are insufficient to determine safety.[5]

Some of the *Citrus* flowers and leaves that are used to derive the ingredients described in this safety assessment are food ingredients. The US Food and Drug Administration (FDA) determined that the use of some *Citrus* flowers and leaves as direct food additives is generally recognized as safe (GRAS). Additionally, essential oils, oleoresins (solvent-free), and natural extracts (including distillates) derived from bitter orange flowers, sweet orange flowers and leaves, lemon leaves, mandarin and/or tangerine leaves, and possibly other *Citrus* flowers and leaves are GRAS for their intended use in foods for human and animal consumption. Daily consumption of these GRAS foods would result in much larger systemic exposures than what is expected from use in cosmetic products, even if there was 100% absorption from cosmetics. Thus, the systemic toxicity potential of *Citrus* flower- and leaf-derived ingredients via oral exposure is not addressed further in this report. The primary focus of the safety assessment is the review of the safety of topical exposure to the ingredients used as foods.

To avoid redundancy of effort, CIR generally excludes from review ingredients that are known to exclusively function as fragrance ingredients when the ingredient has been or will be evaluated by the Research Institute for Fragrance Materials (RIFM). According to the *Dictionary*, four of the *Citrus* flower- and leaf-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 the RIFM Expert Panel, nor are these ingredients on RIFM's prioritized agenda to be reviewed in the foreseeable future. Thus CIR is reviewing the safety of these ingredients as part of this current assessment.

Botanicals such as *Citrus*-derived ingredients contain numerous constituents, some of which have the potential to be toxic. In this assessment, CIR is reviewing the potential toxicity of each *Citrus* flower- or leaf-derived ingredient as a whole, complex substance. Except for specific constituents of concern that the Panel has identified, CIR is not reviewing the potential toxicity of the individual constituents of the *Citrus* flowers and leaves 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 test substance in a study is not clearly a cosmetic ingredient, because of lack of information on the genus and species from which the

Table 2. Citrus Ingredients that Potentially Function Exclusively as Fragrance Ingredients.

Citrus Aurantifolia (Lime) Leaf Oil
Citrus Natsudaidai Flower Oil
Citrus Natsudaidai Flower Water
Citrus Unshiu Flower Water

substance was derived and/or the method of extraction used, the test substance will be referred to by a common name (e.g., bitter orange flower oil). If the substance is clearly a cosmetic ingredient, the International Nomenclature of Cosmetic Ingredients (INCI) name will be used (e.g., "Citrus Aurantium Amara (Bitter Orange) Flower Oil"). 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 Voluntary Cosmetic Registration Program (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 pummelo, which may also be referred to as *Citrus maxima*. *Citrus paradisi* appears to be the more widely accepted nomenclature for grapefruit. 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.[6]

Table 3. Review of *Citrus* Genus Species Names.[6]

Genus Species Name Used in INCI Names (common name)	Accepted Genus 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*

Chemistry

Definition and General Characterization

The definitions and functions of the *Citrus* flower- and leaf-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 derived. In some cases, the definition provides insight on the method(s) of manufacture. Essential oils are the hydrophobic, liquid, volatile aroma compounds in the insoluble condensate fraction. The essential oils are typically mixtures of small molecules, but their chemical structures can vary widely. Fixed oils, on the other hand, are hydrophobic, nonvolatile, fatty compounds from plants, 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 that does not mean that fragrance is their only function.

Physical and Chemical Properties

Citrus Aurantium Amara (Bitter Orange) Flower Extract. A supplier reported that Citrus Aurantium Amara (Bitter Orange) Flower Extract in sunflower seed oil has an ultraviolet (UV) absorption wavelength <250 nm, with the maximum absorption value at 220 nm.[7]

Citrus Aurantium Dulcis (Orange) Flower Extract. As reported by a supplier, Citrus Aurantium Dulcis (Orange) Flower Extract is a medium-to-dark amber liquid with a characteristic odor.[8] At 25°C, the pH range is 4.0 to 6.5 (actual 4.1). Specific gravity range is 0.99 to 1.01 (1.01 actual) at 25°C. Citrus Aurantium Dulcis (Orange) Flower Extract is soluble in any proportion of water, has less than 100 organisms/g, and has a refractive index range of 1.3250 to 1.3450 (1.3385 actual) at 25°C.

Citrus Aurantium Dulcis (Orange) Flower Wax. A supplier reported that Citrus Aurantium Dulcis (Orange) Flower Wax has

a melting point of 60.0°C and a UV absorption value of 1250 at 280 nm.[9] No further details provided.

Method of Manufacturing

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 two 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 water soluble. 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.

Citrus Aurantium Amara (Bitter Orange) Flower Extract. A supplier reported that Citrus Aurantium (Bitter Orange) Flower Extract is produced by macerating the flowers in hot water followed by clarification, addition of glycerin and preservative, and filtration.[10] This supplier also reported that the flowers may be extracted in sunflower seed oil before clarification and decontamination.[11]

Another supplier reported that Citrus Aurantium Amara (Bitter Orange) Flower Extract was extracted by hydrocarbons (not specified) from *Citrus aurantium amara* flowers grown in Morocco.[12] The resultant mixture was treated with ethanol, filtered, and then concentrated and purified by distillation.

Citrus Aurantium Amara (Bitter Orange) Flower Water. As reported by a supplier, Citrus Aurantium Amara (Bitter Orange) Flower Water is produced through distillation of the flowers followed by acidification, addition of preservative, and decontamination.[13]

Citrus Aurantium Amara (Bitter Orange) Flower Wax. Figure 1 is a generic representation of the method of manufacturing for Citrus Aurantium Amara (Bitter Orange) Flower Wax. In the preparation of this ingredient, *Citrus aurantium amara* flowers undergo extraction with an organic solvent to form a "concrete," which is then dissolved in alcohol. The insoluble portion is the floral wax, which is further refined.

Citrus Aurantium Dulcis (Orange) Flower Extract. According to a supplier, fresh or dried flowers of *Citrus aurantium dulcis* are extracted with specified eluent under appropriate temperatures to yield a concentrate.[8] The concentrate is then blended with the desired diluent and preservation systems to produce Citrus Aurantium Dulcis (Orange) Flower Extract.

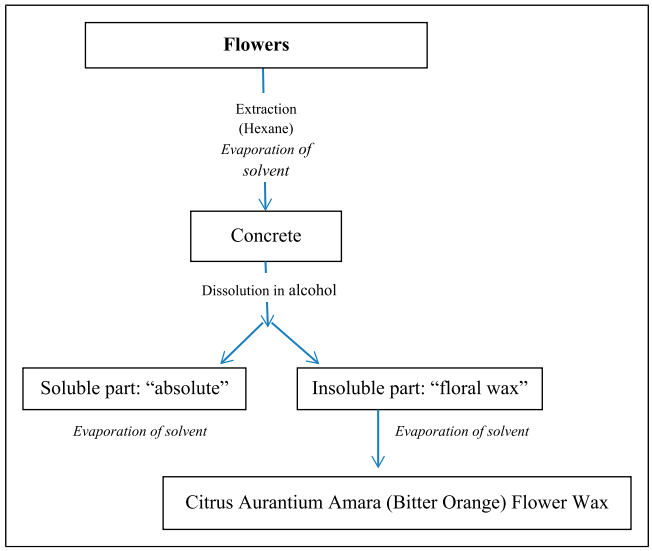

Figure 1. Manufacturing flow chart of Citrus Aurantium Amara (Bitter Orange) Flower Wax.[51]

Citrus Hystrix Leaf Extract. A supplier has reported that Citrus Hystrix Leaf Extract is produced by extracting dried leaves with 80% ethanolic solution, and the extract is filtered and concentrated before the addition of 70% 1,3-butylene glycolic solution.[14] The material then undergoes sedimentation, filtration, and adjustment before packaging.

Citrus Natsudaidai Flower Water and Oil. In the preparation of Citrus Natsudaidai Flower Water and Citrus Natsudaidai Flower Oil, *Citrus natsudaidai* flowers were handpicked and then refrigerated.[15] Approximately 4 to 8 kg of flowers were then distilled with 10 to 20 L of purified water. The water and oil were then separated and the resulting products were analyzed for heavy metals and bacteria content.

Citrus Reticulata (Tangerine) Leaf Oil. A supplier has reported that Citrus Reticulata (Tangerine) Leaf Oil is produced through the steam distillation of the dried leaves of *Citrus reticulata*.[16]

Constituents/Composition/Impurities

The *Citrus* ingredients are complex botanicals composed of numerous constituents. Table 4 presents the cosmetic allergens certificates of analysis for Citrus Aurantium Amara (Bitter Orange) Flower ingredients. Tables 5–10 list the composition (%) of several *Citrus* leaf and flower ingredients and volatiles.

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."[17,18]

International Fragrance Association has also issued a standard for methyl-N-methylanthranilate (or dimethyl

Table 4. Cosmetic Allergens Certificates from Manufacturer of Citrus Aurantium Amara (Bitter Orange) Flower Ingredients.[52-54]

Allergen	Citrus Aurantium Amara (Bitter Orange) Flower Wax	Citrus Aurantium Amara (Bitter Orange) Flower Water	Citrus Aurantium Amara (Bitter Orange) Flower Extract	Citrus Aurantium Amara (Bitter Orange) Flower Extract in sunflower seed oil‡
Amyl cinnamal	<5 ppm	ND	ND	ND
Benzyl alcohol	<20 ppm	ND	ND	ND
Cinnamyl alcohol	<1 ppm	ND	ND	ND
Citral	<10 ppm	ND	ND	ND
Eugenol	<5 ppm	ND	ND	ND
Hydroxycitronellal	<5 ppm	ND	ND	ND
Isoeugenol	<5 ppm	ND	ND	ND
Amylcinnamyl alcohol	<1 ppm	ND	ND	ND
Benzyl salicylate	<5 ppm	ND	ND	ND
Cinnamal	<5 ppm	ND	ND	ND
Coumarin	< 15 ppm	ND	ND	ND
Geraniol	<5 ppm	ND	ND	ND
Hydroxyisohexyl 3-cyclo hexane carboxaldehyde	<5 ppm	ND	ND	ND
Anise alcohol	<30 ppm	ND	ND	ND
Benzyl cinnamate	<15 ppm	ND	ND	ND
Farnesol	<50 ppm	ND	ND	ND
Butylphenyl methylpropional	<1 ppm	ND	ND	ND
Linalool	<50 ppm	ND	ND	ND
Benyl benzoate	<5 ppm	ND	ND	ND
Citronellol	<5 ppm	ND	ND	ND
Hexyl cinnamal	<1 ppm	ND	ND	ND
Limonene	< 200 ppm	ND	ND	ND
Methyl 2-octynoate	<1 ppm	ND	ND	ND
Alpha-isomethyl ionone	<1 ppm	ND	ND	ND
Evernia prunastri	ND	ND*	ND†	ND
Evernia furfuracea	ND	ND*	ND†	ND

Unless noted, detection limit was 2 ppm.
*Detection limit was 20 ppm.
†Detection limit was 5 ppm
‡Detection limit was 1 ppm for all allergens
ND = unable to be detected by GCSM.

anthranilate), stating that this substance should be restricted to 0.1% in leave-on products.[19] No restrictions were set for rinse-off or non-skin contact products.

The European Commission's Scientific Committee on Consumer Safety (SCCS) issued an opinion on the phototoxicity of methyl-N-methylanthranilate with the conclusion that this substance is phototoxic and may be safe for use at up to 0.1% in leave-on products, except for sunscreen/sun care products and products used on areas exposed to light.[20] There was no safety concern on the use of this substance at concentrations up to 0.2% in rinse-off products. The SCCS noted that this substance is a secondary amine and may be prone to *N*-nitrosation. The presence of methyl-*N*-methylantrhanilate in essential oils like petitgrain mandarin oil was considered in the SCCS opinion.

Citrus Aurantium Amara (Bitter Orange) Flower Extract. A supplier reported that their raw material contains 1.5%–2.5% Citrus Aurantium (Bitter Orange) Flower Extract, 73.05%–74.05% water, >23% glycerin, <1.0% citric acid, 0.3% sodium benzoate, and 0.15% potassium sorbate.[21] This product was certified to contain 27 ppm of acetaldehyde (detection limit was 10 ppm).[22] This product was certified to not contain the furocoumarins bergapten and 8-methoxypsoralen (detection limit was 10 ppm).[23]

Another raw material of this supplier was reported to contain 0.1%–0.5% Citrus Aurantium Amara (Bitter Orange) Flower Extract in 99.5%–99.9% sunflower seed oil.[24]

A raw material containing 0.15% Citrus Aurantium Amara (Bitter Orange) Flower Extract is reported to have 0.0016% (16 ppm) furanocoumarins with the following (calculated)

Table 5. Chemical Composition of *Citrus aurantium* (Bitter Orange) Flower Absolute.[55]

Constituent	Percent Range
Linalool	34.0-48.0
linalyl acetate	14.0-21.0
Farnesol	3.6-15.4
Nerolidol	4.9-8.9
Indole	2.6-9.9
methyl anthranilate	1.0-4.3
α-terpineol	1.5-3.7
Limonene	0-3.6
Geraniol	0-2.0
geranyl acetate	0-1.3
(E)-β-ocimene	0-2.2
2-phenethyl alcohol	0-2.1
β-pinene	0-2.7
benzyl cyanide	0-1.1
Nerol	0-1.1
neryl acetate	0-0.7
terpinen-4-ol + β-caryophyllene	0-0.8
Myrcene	0-0.5

break-out: 0.95 ppm psoralen, 0.3 ppm bergapten, 0.88 ppm oxypeudecanin, 0.08 ppm imperatorin, 0.18 ppm isoimperatorin, and 13.62 ppm epoxybergamottin.[12] This material also contains approximately 630 ppm linalool, 185 ppm linalyl acetate, 6 ppm β-pinene, and 2 ppm ocimene. Total polyphenolic content is approximately 29 ppm.

Citrus Aurantium Amara (Bitter Orange) Flower Water. A supplier reported that their raw material contains >98% Citrus Aurantium Amara Flower Water, <1% citric acid, 0.55% water, 0.3% sodium benzoate, and 0.15% potassium sorbate.[25] This product was certified to not contain furocoumarin, bergapten, bergaptol, bergamothine, citropten, coumarine, imperatorine, isoemperatorine, isopimpinelline, umbelliferone, or scopoletine (detection limit was 10 ppm).[26]

Citrus Aurantium Amara (Bitter Orange) Flower Wax. In data provided by a supplier, Citrus Aurantium Amara (Bitter Orange) Flower Wax had less than 0.1 mg/kg heavy metals (arsenic, cadmium, and lead) and no detectable pesticides (<0.005 mg/kg) or polycyclic aromatic hydrocarbons (<0.25 µg/kg).[27] Concentrations of aflatoxins (B1, B2, G1, G2) were less than 0.1 µg/kg, with the total aflatoxins concentration less than 0.4 µg/kg, and dioxins were less than 0.6 pg/g.

Citrus Aurantium Dulcis (Orange) Flower Extract. According to a supplier, impurities testing on Citrus Aurantium Dulcis (Orange) Flower Extract is performed on the concentrate in alcohol base.[8] No residual pesticides or heavy metals (including arsenic, lead, and mercury) were detected. In addition, none of the 26 cosmetic allergens listed in Table 4 were detected (detection limit <1 ppm).

Citrus Aurantium Dulcis (Orange) Flower Wax. A supplier reported that Citrus Aurantium Dulcis (Orange) Flower Wax contains 35%–50% hydrocarbons (C21–C35), 12%–20% polycosanols (C24–C36), 25%–40% esters (C40–C60), and 0.5%–5.0% essential oils and bioflavonids.[9]

Citrus Hystrix Leaf Extract. A supplier reports that Citrus Hystrix Leaf Extract is composed of tannin and sugar.[14] Impurities of heavy metals are not more than 20 ppm and arsenic is not more than 2 ppm.

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 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 Amara (Bitter Orange) Flower Oil has the most reported uses of the cosmetic ingredients in this report, with a total of 99; the majority of the uses are in leave-on skin care preparations (Table 11).[28] Citrus Aurantium Dulcis (Orange) Flower Extract has the second greatest number of overall uses reported, with a total of 70; a majority of the uses are in rinse-off and leave-on skin care preparations. The results of the concentration of use survey conducted by the Council indicate Citrus Aurantium Dulcis (Orange) Flower Oil has the highest reported maximum concentration of use; it is used at up to 0.66% in a depilatory.[29] Citrus Aurantium Dulcis (Orange) Flower Wax had the second highest reported maximum concentration of use; it is used at up to 0.12% in a lipstick.

Table 12 lists all *Citrus* flower- and leaf-derived ingredients not indicated to be 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 be incidentally ingested or come into contact with mucous membranes. For example, Citrus Aurantium Dulcis (Orange) Flower Wax is used at 0.12% in lipstick. Additionally, some of these ingredients were reported to be used in hair sprays, fragrance preparations, and face powders and could possibly be inhaled. For example, Citrus Aurantium Dulcis (Orange) Flower Oil was reported to be used in hair spray at a maximum concentration of 0.015%, and Citrus Aurantium Amara (Bitter Orange) Flower Oil was reported to be used in face powders at a maximum concentration of 0.01%. In practice, 95%–99% of

Table 6. Composition (%) of *Citrus* Flower and Leaves.[56-58]

	Citrus Natsudaidai Flower Oil	*Citrus reticulata* leaf oil (mandarin)	*Citrus aurantium* L. flower oil (bitter orange)	*Citrus aurantium* L. leaf oil (bitter orange)
β-pinene	4.49	4.71	19.08	1.90-3.58
Sabinene	0.65	0.57	2.01	0.22-0.37
β-myrcene	1.26	0.63	1.59	1.63-2.74
α-terpinene	0.35	NR	NR	NR
Limonene	23.48	3.63	12.04	0.53-0.77
Citronellol	NR	5.19	NR	NR
Eucalyptol	0.55	NR	NR	NR
α-phellandrene	NR	0.49	NR	NR
β-phellandrene or β-thujene	0.17	NR	NR	NR
α-pinene	NR	3.91	1.35	0.19
γ-terpinene or 3-carene	9.56	20.15	0.36/0.17	NR
β-cis-ocimene	4.69	NR	0.77	0.71-1.22
(E)-β-ocimene	NR	1.74	6.06	3.11-4.08
p-cymene	14.53	16.29	NR	NR
caryophyllene oxide	0.24	NR	NR	NR
dihydropseudoionone	0.34	NR	NR	NR
germacrene A	0.96	NR	0.13	NR
(E)-β-farnesene	0.06	NR	NR	00-0.13
β-bisabolene	0.93	NR	NR	NR
δ-elemene	NR	NR	0.12	NR
Elemene	2.90	NR	NR	NR
α-caryophyllene	0.47	NR	NR	NR
β-selinene	0.24	NR	NR	NR
α-selinene	0.83	NR	NR	NR
γ-cadinene	2.90	NR	NR	NR
α-farnesene	1.81	NR	NR	NR
β-cubebene	0.19	NR	NR	NR
α-humulene	NR	NR	NR	0-0.10
caryophyllene	1.40	NR	0.42	0.22-1.09
Linalool	7.57	9.55	29.14	36.03-58.21
linalool oxide	NR	NR	0.29	NR
Nerolidol	13.99	NR	1.76	0-0.10
Farnesol	0.40	NR	5.14	NR
α-terpineol	NR	0.85	4.56	7.11-12.89
(-)-4-terpineol	0.58	7.13	0.68	0.13-0.17
α-terpinolene	NR	NR	0.47	0.40-0.70
Carvacrol	0.80	NR	NR	NR
Nerol	NR	0.21	0.83	1.45-2.89
Neral	NR	0.36	NR	NR
Geranial	NR	0.83	NR	NR
Geraniol	0.26	NR	4.31	NR
geraniol or geranyl isopentanoate	0.25	NR	NR	NR
phenylethyl alcohol	NR	NR	NR	NR
Nonanal	NR	NR	NR	NR
linalyl acetate	NR	NR	3.88	12.42-23.00
linalyl propanoate	0.67	NR	NR	NR
methyl anthranylate	1.41	NR	0.19	NR
geranyl acetate	NR	2.13	2.59	4.49-8.70
bornyl acetate	NR	0.24	NR	NR
terpinyl acetate	NR	NR	0.20	0-0.11

(continued)

Table 6. (continued)

	Citrus Natsudaidai Flower Oil	*Citrus reticulata* leaf oil (mandarin)	*Citrus aurantium* L. flower oil (bitter orange)	*Citrus aurantium* L. leaf oil (bitter orange)
neryl acetate	NR	NR	1.30	2.18-4.46
Eicosane	0.35	NR	NR	NR
benzeneacetonitrile	NR	NR	NR	NR
bicyclogermacrene	NR	NR	NR	0.18-0.20

NR = not reported.

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.[30-33] 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.[31,32] 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.[34-36]

The *Citrus* flower- and leaf-derived ingredients in this safety assessment are not restricted from use under the rules governing cosmetic products in the European Union.[37]

Non-Cosmetic

The essential oils, oleoresins (solvent-free), and natural extractives (including distillates) derived from the following *Citrus* plant sources are GRAS for their intended use in foods for human consumption: *Citrus aurantifolia* (lime); *Citrus aurantium* (bergamot); *Citrus aurantium* (bitter orange: the flowers and peel); *Citrus limon* (lemon: the leaves); *Citrus paradisi* (grapefruit); *Citrus reticulata* (tangerine: the leaves); *Citrus reticulata blanco* (mandarin: the leaves); *Citrus sinensis* (orange: the leaf, flowers, and peel); and Citrus peels (species not specified) (21CFR182.20). These essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of these *Citrus* plant sources are GRAS for their intended use in animal drugs, feeds, and related products (21CFR582.20).

While not specifically listed as GRAS, *Citrus hystrix* (kaffir lime) leaves are recognized as a seasoning ingredient commonly used in Southeast Asian cuisine.[38]

Toxicokinetics

No relevant published toxicokinetics studies on *Citrus* flower- and leaf-derived ingredients were identified in a literature search for these ingredients and no unpublished data were submitted. Toxicokinetics data were not expected to be found because each botanical ingredient is a mixture of hundreds of constituents.

Toxicological Studies

Some of the *Citrus* ingredients in this assessment are found in foods, and daily exposures from food use would result in much greater systemic doses than those resulting from use in cosmetic products. Also, as noted earlier, essential oils, oleoresins (solvent-free), and natural extractives (including distillates) derived from bitter orange flowers, sweet orange flowers and leaves, lemon leaves, mandarin and/or tangerine leaves, and possibly other *Citrus* flowers and leaves are GRAS for their intended use in foods for human and animal consumption according to the FDA. Consequently, the systemic toxicity potential is not addressed further in this report. The safety assessment focuses on the potential for irritation and sensitization from topical exposure to these *Citrus* ingredients.

Acute and Repeated Dose Toxicity

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

Table 7. Key Constituents (%) of *Citrus* Flowers and Leaves.*[59]

	Citrus Limon (Lemon) Leaf Oil	Citrus Aurantium Amara (Bitter Orange) Flower Oil	Bitter Orange Flower Extract	Citrus Aurantium Amara (Bitter Orange) Flower Water	Bitter Orange Leaf Extract	Citrus Aurantium Amara (Bitter Orange) Leaf Oil	Citrus Reticulata (Mandarin) Leaf Oil	Citrus Hystrix Leaf Oil
β-pinene	3.5-13.6	3.5-13.0	NR	NR	NR	0.3-2.7	1.9-2.5	0.2-1.5
Sabinene	NR	0.4-2.8	NR	NR	NR	NR	NR	1.6-4.8
β-myrcene	0.4-1.5	1.4-3.1	NR	NR	2.5	0-2.0	NR	0.4-1.4
p-cymene	NR	NR	NR	NR	NR	NR	3.0-4.8	NR
(+)-limonene	8.1-30.7	6.0-17.9	NR	NR	NR	0.3-8.0	7.2-11.7	NR
Citronellal	1.5-2.9	NR	NR	NR	NR	NR	NR	58.9-81.5
α-pinene	0.1-2.2	0.8-1.1	NR	NR	NR	NR	1.8-2.3	NR
γ-terpinene	0.4-2.3	NR	NR	NR	NR	NR	23.9-28.5	0.1-1.1
(E)-β-ocimene	NR	4.6-7.0	NR	NR	1.2	0-2.2	NR	NR
(Z)-β-ocimene	NR	0.7-1.0	NR	NR	NR	NR	NR	NR
(+)-limonene + (Z)-β-ocimene	NR	NR	0-5.1	NR	NR	NR	NR	NR
β-caryophyllene	0.6-2.0	NR	NR	NR	NR	NR	1.2-1.4	NR
α-thujene	NR	NR	NR	NR	NR	NR	0.8-1.0	NR
Linalool	1.2-1.8	31.4-54.3	30.0-32.0	NR	42.5	12.3-25.2	NR	2.9-4.7
linalool + 2-phenylethanol	NR	NR	NR	67.5	NR	NR	NR	NR
2-phenylethanol	NR	NR	4.5-35.0	NR	NR	NR	NR	NR
(Z)-linalool oxide	NR	NR	NR	1.9	NR	NR	NR	NR
(E)-linalool oxide	NR	NR	NR	1.1	NR	NR	NR	NR
Nerolidol	NR	NR	0-7.6	NR	NR	NR	NR	NR
(E)-nerolidol	NR	1.3-4.0	NR	NR	NR	NR	NR	NR
Farnesol	NR	NR	trace-7.7	NR	NR	NR	NR	NR
(E,E)-farnesol	NR	1.6-3.2	NR	NR	NR	NR	NR	NR
(E,Z)-farnesol	NR	0.7-1.6	NR	NR	NR	NR	NR	NR
α-terpineol	0.4-1.1	1.1-5.8	2.0-2.4	20.0	NR	2.1-6.8	NR	NR
terpinen-4-ol	NR	0.3-1.3	NR	NR	NR	NR	NR	NR
Nerol	1.3-7.4	1.1-1.3	0.9-4.0	3.0	NR	0.4-1.1	NR	NR
Neral	6.5-25.3	NR	NR	NR	NR	NR	NR	NR
Geranial	10.9-39.0	NR	NR	NR	NR	NR	NR	NR
Geraniol	0.5-15.0	0.8-3.6	<1.5	NR	NR	1.4-3.0	NR	NR
isopulegol	NR	NR	NR	NR	NR	NR	NR	0.3-4.9
linalyl acetate	trace-6.5	0.6-10.0	7.0-16.8	NR	48.9	47.4-71.0	NR	NR
methyl anthranilate	NR	NR	3.0-15.0	3.0	NR	NR	NR	NR
dimethyl anthranilate	NR	NR	NR	NR	NR	NR	43.2-51.9	NR
geranyl acetate	trace-4.0	0.7-4.1	NR	NR	1.6	1.9-4.5	NR	NR
citronellyl acetate	NR	NR	NR	NR	NR	NR	NR	0.9-5.1
α-terpinyl acetate	trace-7.3	NR	NR	NR	NR	NR	NR	NR
neryl acetate	3.7-7.4	0.3-2.1	0.8-4.0	NR	1.0	0-3.0	NR	NR
Indole	NR	NR	0.1-1.0	NR	NR	NR	NR	NR
benzyl cyanide	NR	NR	1.0	NR	NR	NR	NR	NR

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

Table 8. Mandarin Leaf Oil Constituents (%) for 8 Different Cultivars.[60,61]

Constituent	Balady	Yussuf Effendy	Dancy	Maya	Clementine	Michal	Nectarine	Satsuma
methyl-*N*-methyl anthranilate	65.71	NR	NR	NR	NR	NR	NR	NR
Linalool	0.11	45.12	50.73	55.10	25.17	30.34	24.80	9.55
α-thujene	NR	0.78	0.65	NR	0.35	0.30	NR	NR
α-pinene	1.34	1.83	1.31	NR	1.70	1.28	0.98	3.91
Camphene	NR	NR	NR	NR	NR	trace	NR	NR
β-pinene	0.72	1.51	1.18	0.11	0.02	1.33	0.62	4.71
Sabinene	NR	NR	0.41	1.41	10.62	20.84	27.20	0.57
Myrcene	0.31	0.34	0.11	0.25	NR	0.54	2.00	0.63
α-phellandrene	0.05	trace	NR	NR	NR	NR	0.01	0.49
ethyl-2-butenoate	NR	NR	NR	0.01	NR	NR	NR	NR
α-terpinene	0.15	0.11	0.21	0.07	0.72	0.21	0.26	NR
Limonene	4.91	1.00	0.39	0.23	0.68	0.73	2.88	3.63
β-phellandrene	0.03	NR	NR	0.06	1.94	0.18	NR	NR
(*Z*)-β-ocimene	0.04	NR	0.10	2.31	NR	NR	4.16	NR
(*E*)-β-ocimene	NR	NR	NR	NR	NR	NR	NR	1.74
γ-terpinene	12.60	4.57	3.11	2.12	0.73	NR	NR	20.15
(*Z*)-3-hexenyl formate	0.11	NR	NR	NR	NR	NR	NR	NR
p-cymene	3.10	6.54	4.09	1.43	0.93	trace	0.32	16.29
bornyl acetate	NR	NR	NR	NR	NR	NR	NR	0.24
octenyl acetate	NR	NR	NR	NR	NR	NR	NR	0.36
terpinolene	0.53	0.34	NR	NR	NR	NR	0.32	1.62
Neral	NR	NR	NR	NR	NR	NR	NR	0.36
Nerol	NR	NR	NR	NR	NR	NR	NR	0.21
(*Z*)-2-pentenol	trace	NR	NR	NR	NR	NR	NR	NR
(*Z*)-3-hexenol	0.06	0.13	0.05	0.33	NR	trace	0.20	NR
ethyl octanoate	0.01	trace	NR	0.02	NR	0.02	0.04	NR
(*E*)-sabinene hydrate	0.01	NR	NR	2.79	NR	0.07	2.54	NR
ethyl nonanoate	0.01	NR	NR	NR	NR	NR	NR	NR
(*Z*)-linalool oxide	NR	0.06	0.44	NR	0.49	0.32	NR	NR
(*E*)-linalool oxide	NR	NR	0.21	NR	NR	0.29	NR	NR
α-copaene	NR	NR	NR	0.02	0.04	0.17	0.02	NR
Decanal	NR	NR	NR	0.03	NR	NR	NR	NR
benzaldehyde	NR	NR	NR	0.02	NR	NR	trace	NR
citronellal	NR	NR	NR	NR	NR	NR	0.25	NR
(*Z*)-sabinene hydrate	NR	NR	NR	NR	0.04	0.21	NR	NR
(*E*)-β-bergamotene	NR	NR	NR	0.02	NR	NR	0.03	NR
β-elemene	NR	NR	0.10	0.04	NR	NR	1.28	NR
terpinen-4-ol	1.63	NR	NR	NR	6.11	4.05	2.21	7.13
β-caryophyllene	0.14	5.44	0.24	2.00	0.16	0.09	0.30	NR
valencene	0.05	NR	NR	NR	NR	NR	NR	NR
methyl thymol	NR	NR	4.63	NR	NR	NR	NR	NR
terpinen-1-ol	0.01	trace	Trace	NR	0.02	0.02	trace	NR
citronellyl formate	NR	NR	NR	NR	2.56	0.65	trace	NR
ethyl decanoate	0.03	trace	NR	NR	0.10	0.14	trace	NR
(*E*)-β-farnesene	NR	NR	trace	trace	0.61	0.82	0.02	NR
α-humulene	0.08	0.51	0.25	0.11	0.16	0.55	trace	NR
Sabinol	NR	NR	trace	NR	trace	trace	NR	NR
α-terpineol	0.24	0.33	0.58	1.30	0.64	1.12	1.28	0.85
viridiflorene	trace	0.31	0.18	NR	trace	NR	NR	NR
α-muurolene	NR	trace	trace	0.02	trace	0.32	NR	NR
Bicyclogermacrene	NR	NR	NR	0.06	NR	0.54	0.03	NR
(*E*,*E*)-α-farnesene	NR	0.71	0.50	1.00	NR	trace	0.07	NR

(continued)

Table 8. (continued)

Constituent	Balady	Yussuf Effendy	Dancy	Maya	Clementine	Michal	Nectarine	Satsuma
citronellol	NR	NR	NR	trace	2.60	trace	0.06	5.19
γ-cadinene	NR	0.06	0.02	0.06	0.08	0.47	0.06	NR
methyl salicylate	1.00	NR	NR	NR	NR	NR	trace	NR
ethyl phenylacetate	0.06	NR	NR	0.02	NR	NR	0.06	NR
Anethole	NR	NR	0.02	0.01	0.02	trace	0.03	NR
Geranial	NR	NR	NR	NR	NR	NR	NR	0.83
Geraniol	NR	0.02	trace	0.03	0.04	0.05	0.10	0.35
geranyl acetate	NR	NR	NR	NR	NR	NR	NR	2.13
ethyl laurate	NR	0.02	trace	0.03	trace	trace	0.06	NR
p-cymen-8-ol	0.10	0.05	trace	trace	0.02	0.04	trace	NR
β-phenylethanol	NR	trace	0.02	0.03	NR	trace	0.03	NR
Myrtenol	NR	trace	trace	trace	trace	0.12	trace	NR
(*Z*)-carveol	0.04	NR	0.01	NR	0.03	0.06	NR	NR
humulene oxide	NR	0.03	trace	NR	NR	0.07	NR	NR
caryophyllene oxide	trace	0.31	0.33	NR	2.10	0.41	NR	0.42
Nerolidol	NR	0.04	trace	0.04	0.02	0.03	0.02	NR
ethyl myristate	0.18	0.11	0.14	0.05	0.88	0.41	0.06	NR
Thymol	0.12	14.43	11.70	8.21	NR	NR	NR	NR
(*E*)-carveol	0.04	NR	NR	NR	trace	trace	NR	NR
ethyl pentadecanoate	0.03	NR	NR	NR	NR	0.06	NR	NR
β-sinensal	NR	NR	0.41	2.98	2.11	1.52	1.60	NR
ethyl palmitate	1.83	2.31	2.79	6.08	7.22	4.84	3.36	NR
ethyl heptadecanoate	0.04	0.09	0.15	0.07	trace	0.31	0.08	NR
α-sinensal	NR	0.93	0.24	0.72	trace	0.17	0.48	NR
ethyl stearate	0.06	0.09	0.25	0.87	trace	0.53	0.16	NR
ethyl linoleate	0.74	0.78	0.39	1.06	0.83	1.78	0.60	NR
ethyl linolenate	2.64	2.84	0.68	6.88	3.63	4.89	3.33	NR
Phytol	0.14	0.19	0.12	1.29	0.09	0.88	0.74	NR

Trace is <0.01%; NR = not reported

Irritation and Sensitization

Dermal Irritation

Dermal irritation studies are summarized in Table 13.[14,39-42] In rabbit studies, moderate, reversible erythema was observed with undiluted Citrus Aurantium Amara (Bitter Orange) Flower Wax. Citrus Hystrix Leaf Extract was not irritating in rabbits at up to 10%. In human subjects, no irritation was observed after topical exposure to Citrus Natsudaidai Flower Oil (1% in jojoba seed oil) or Citrus Aurantium Amara (Bitter Orange) Flower Extract (up to 0.001% in leave-on formulations).

Ocular Irritation

Citrus Aurantium Amara (Bitter Orange) Flower Water. The irritancy potential of a raw material product containing >98% Citrus Aurantium Amara (Bitter Orange) Flower Water was tested in a hen's egg test-chorioallantoic membrane (HET-CAM) assay and a cytotoxicity in vitro (CFIO) method.[41] The test material was studied diluted at 10% in saline or in Hank's balanced salt solution. While the HET-CAM assay concluded the test material was practically not irritating, the CFIO method concluded that the test material must be considered slightly irritating to the eye.

Citrus Aurantium Amara (Bitter Orange) Flower Wax. The eye tolerance of Citrus Aurantium Amara (Bitter Orange) Flower Wax (>50%) was tested in vitro using the Statens Seruminstitut rabbit cornea (SIRC) cell model.[43] Tolerance was evaluated by measuring cytotoxicity. Negative control solutions were physiological serum or sample diluent and positive control solutions were 0.01% to 0.2% sodium dodecyl sulfate. Negligible cytotoxicity was observed.

Sensitization

Sensitization studies are presented in Table 14.[14,42,44-49] Citrus Hystrix Leaf Extract was not sensitizing in guinea pigs at up to 10%. In human repeated insult patch tests (HRIPT), Citrus Aurantium Amara (Bitter Orange) Flower Extract was considered not sensitizing in formulations at up to 0.0225%, Citrus Aurantium Amara (Bitter Orange) Flower Oil

Table 9. *Citrus* Flower Volatiles Composition (%), Identified by Headspace-Solid Phase Microextraction Gas Chromatography-Mass Spectrometry.[62]

	Citrus reticulata (mandarin orange)	*Citrus unshiu*	*Citrus sinensis* (sweet orange)	*Citrus limon* (lemon)	*Citrus grandis* (pomelo)
Hexanal	0.1-1	NR	0.1-1	0.1-1	0.1-1
2-hexanal	0.1-1	0.1-2.84	1.19-2.36	0.1-1.45	0.1-1.68
Benzaldehyde	trace-1	trace-1	trace-1	Trace	trace
benezene acetaldehyde	0.1-1.08	NR	0.1-1.31	0.1-1	1.34
lilac aldehyde B	NR	NR	Trace	NR	trace-1
Myrtenal	NR	0.1-1	Trace	NR	trace
Decanal	trace	trace	Trace	trace-1	trace-1
Undecanal	NR	NR	NR	trace-1	NR
α-thujene	0.1-1	0.1-1	0.1-1	trace-1	trace-2.18
α-pinene	0.1-1	0.1-2.80	0.1-1.42	0.1-1	0.1-1
Camphene	NR	NR	NR	NR	trace-4.48
Sabinene	NR	NR	6.07-11.15	NR	NR
β-pinene	6.59-9.20	2.92-6.51	3.53-11.88	0.1-2.07	1.67-7.49
β-myrcene	1.11-1.46	1.53-2.55	1.48-2.53	2.01-2.42	0.1-8.08
α-terpinene	0.1-1	0.1-1	0.1-1.62	NR	trace-1
p-cymene	0.1-1	6.538.56	0.1-1	NR	1.01
Limonene	1.07-1.48	1.69	1.54-4.64	44.95-52.53	2.19-4.92
(*Z*)-ocimene	trace	NR	0.1-1.71	0.1-1	0.1-1
(*E*)-ocimene	2.16-3.03	2.27-6.37	1.18-8.40	5.35-6.35	1.97-9.14
γ-terpinene	1.44-1.90	0.1-13.79	0.1-1	1.97-3.17	trace-11.06
Terpinolene	NR	NR	0.1-1	0.1-1	NR
2,4,6-octatriene,3,4-dimethyl	0.1-1	trace-1	trace-1	trace-1	trace-1
1,8-cineol	NR	3.15-6.05	NR	NR	NR
cis-β-terpineol	1.08-1.99	0.1-1	0.1-3.60	trace-1	trace-1
cis-linalol oxide	NR	NR	NR	NR	trace-1
Linalool	46.76-50.43	17.41-42.76	24.95-46.98	3.94-7.95	21.59-56.16
limonene oxide, *cis*	NR	NR	NR	NR	trace-1.15
limonene oxide, *trans*	NR	NR	NR	2.58-3.04	NR
Citronellal	0.1-1	0.1-1	0.1-1	0.1-1.05	trace-1
Umbellulone	trace	NR	NR	NR	NR
terpinen-4-ol	0.1-1	0.1-1	0.1-1	0.1-1	0.1-1
p-cymen-8-ol	trace-1	0.1-1	NR	NR	NR
α-terpineol	1.96-3.83	1.01-5.58	0.1-4.59	1.54	0.1-1
trans-dihydrocarvone	NR	NR	NR	0.1-1	NR
p-menth-1-en-9-al	trace-1	0.1-1	NR	0.1-1	0.1-1
cis-carveol	NR	0.1-1	Trace	0.1-1	trace
cis-geraniol	NR	0.1-1	0.1-1	trace-1	0.1-2.84
β-citronellol	trace-1	0.1-1	trace-1	Trace	0.1-1
methyl thymyl ether	1.07-1.93	NR	trace-5.74	Trace	NR
β-citral	trace-1	0.1-1	0.1-2.55	0.1-1	0.1-2.28
trans-geraniol	0.1-2.47	0.1-1	trace-6.80	NR	0.1-6.52
α-citral	trace-1	0.1-1	0.1-11.17	0.1-1.24	0.1-3.07
α-thujenal	NR	0.1-1.33	NR	NR	NR
Carvacrol	NR	NR	NR	0.1-1	NR
E,E-farnesal	NR	0.1-1	NR	trace-1	0.1-1
δ-elemene	0.1-1.36	NR	0.1-1	0.1-1	0.1-1.23
α-cubebene	trace	NR	NR	trace-1	NR
Copaene	NR	NR	NR	0.1-1	NR
β-elemene	trace-1	2.13-5.40	0.1-19.43	6.02-7.53	0.1-4.98
Zingiberene	0.1-1	NR	NR	NR	0.1-1

(continued)

Table 9. (continued)

	Citrus reticulata (mandarin orange)	*Citrus unshiu*	*Citrus sinensis* (sweet orange)	*Citrus limon* (lemon)	*Citrus grandis* (pomelo)
Bergamotene	NR	NR	trace-1	Trace	0.1-1
trans-α-bergamotene	trace-1	0.1-1	trace-1	Trace	NR
Caryophyllene	0.1-1	2.11-2.61	0.1-1.34	3.14-3.93	trace-2.18
α-santalene	NR	NR	NR	Trace	NR
β-cubebene	trace	0.1-1	0.56	Trace	0.06-1.64
γ-elemene	0.1-1.16	0.1-1	1.37	Trace	trace-1.77
Bicyclosesquiphellandrene	0.1-1	NR	0.1-1	NR	trace-1
β-farnesene	2.24-3.53	NR	2.03-3.89	1.64-2.26	trace-5.16
α-elemene	NR	NR	NR	Trace	0.1-1
germacrene D	trace-1	trace-1	1.36	0.1-1	0.1-1.17
β-eudesmene	NR	NR	Trace	0.1-1	NR
α-selinene	NR	trace-1	0.1-1	0.1-1	0.1-1
allo-aromadendrene	NR	NR	Trace	0.1-1	NR
Bicyclogermacrene	NR	trace-1	Trace	NR	trace-1
α-muurolene	0.1-1	NR	NR	NR	trace-1
α-bulnesene	trace-1	NR	Trace	0.1-1	trace
(Z,E)-α-farnesene	NR	NR	NR	0.1-1	trace-1
α-farnesene	0.1-1	NR	Trace	0.1-1	NR
β-bisabolene	NR	NR	NR	2.34-2.82	NR
δ-cadinene	1.30-2.17	NR	0.1-1.07	NR	0.1-1.13
β-sesquiphellandrene	0.1-1	4.31-6.41	0.1-1	Trace	0.1-1
eudesma-3,7(11)-diene	NR	NR	0.1-1	NR	NR
cis-α-bisabolene	NR	NR	NR	Trace	trace
Nerolidol	trace-1	0.1-1	0.1-3.64	trace-1	0.1-8.75
caryophyllene oxide	NR	0.1-1	NR	NR	NR
β-eudesmol	trace	NR	NR	NR	NR
Tetradecanal	NR	NR	0.1-1	NR	NR
Farnesol	0.1-1	0.1-1.07	0.1-1.54	0.1-1	0.1-2.38
α-sinensal	0.1-1	NR	0.1-1	NR	NR
Chrysanthenone	NR	0.1-1	0.1-1	NR	NR
cis-jasmone	0.1-1	0.1-1.44	0.1-1	trace-1	0.1-1
methyl geranate	NR	0.1-1	1.79-15.81	0.1-1	0.1-1
citronellyl acetate	NR	NR	NR	Trace	NR
nerol acetate	NR	trace	Trace	NR	0.1-1
geranyl acetate	NR	trace-1	NR	NR	NR
p-thymol	4.03-4.96	0.1-1	NR	0.1-1.05	trace
methyl jasmonate	NR	NR	Trace	NR	trace
1-octanol	NR	NR	NR	Trace	NR
phenylethyl alcohol	trace-1	0.1-1	trace-1	NR	0.1-1
Styrene	NR	NR	NR	Trace	NR
α,*p*-dimethylstyrene	0.1-1	1.33-2.17	NR	Trace	0.1-1
benzyl nitrile	0.1-4.61	1.20-3.43	0.1-2.49	Trace	0.1-1
Indole	2.28-4.99	3.69-5.00	4.45-10.41	0.1-1.01	4.79-8.84
methyl anthranilate	0.1-1	1.12-17.91	1.77	trace-2.47	2.79-8.21
pentadecane,3-methyl	NR	2.56	trace-1.14	Trace	NR
hexadecane,2-methyl	NR	trace	trace-1	NR	NR
8-heptadecene	1.70-2.23	0.1-1.26	trace-2.76	0.1-1.65	1.03
octadecane, 2-methyl	trace	NR	trace-1	NR	0.1-1

NR = not reported.

Table 10. Volatile Organic Compounds (%) in *Citrus* Leaves, Identified by Gas Chromatography-Mass Spectroscopy.[63]

	Citrus aurantium (bitter orange)	*Citrus sinensis* (sweet orange)	*Citrus grandis* (pomelo)	*Citrus paradisi* (grapefruit)	*Citrus depressa*	*Citrus reticulata* (mandarin orange)
Sabinene	NR	1.33	NR	1.38	NR	4.38
Myrcene	6.42	1.09	NR	0.00	0.96	4.06
Limonene	2.08	2.51	NR	2.68	11.18	2.52
Citronellol	NR	NR	11.68	NR	4.67	NR
α-pinene	NR	2.90	NR	NR	NR	1.01
β-pinene	NR	NR	NR	NR	1.03	NR
γ-terpinene	NR	0.40	NR	NR	NR	1.85
δ-3-carene	1.99	NR	NR	NR	NR	NR
2-carene	0.59	NR	NR	NR	NR	NR
(E)-β-ocimene	4.82	3.75	1.45	1.34	1.86	4.14
Ocimene	0.87	NR	NR	NR	NR	NR
o-Isopropenyltoluene	NR	NR	NR	NR	NR	NR
α-farnesene	NR	NR	NR	NR	1.59	NR
(E)-β-farnesene	NR	0.43	NR	2.28	NR	0.57
α-bisabolene	NR	NR	NR	NR	NR	NR
β-bisabolene	NR	NR	NR	NR	1.11	NR
β-elemene	NR	0.97	NR	1.99	NR	NR
γ-elemene	NR	NR	NR	NR	NR	0.43
α-selinene	NR	0.34	NR	1.26	NR	NR
δ-cadinene	NR	NR	0.40	NR	NR	0.29
Ledene	NR	NR	NR	NR	NR	0.47
α-humulene	NR	0.20	0.23	0.70	NR	NR
β-caryophyllene	1.07	0.52	2.16	0.91	2.16	0.31
Linalool	56.93	14.45	5.76	8.26	23.56	67.27
β-fenchyl alcohol	NR	NR	NR	NR	NR	NR
2-cyclohexen-1-ol	NR	0.36	NR	NR	NR	NR
α-terpineol	0.91	0.87	NR	NR	4.22	2.04
α-terpinolene	0.82	0.99	NR	NR	1.00	1.44
terpinen-4-ol	NR	NR	NR	NR	NR	1.49
Citronella	0.78	3.60	54.26	17.33	12.51	NR
Nerol	1.65	4.14	NR	6.27	NR	NR
Neral	2.31	16.14	NR	11.35	5.78	NR
Geranial	3.33	23.24	NR	16.25	8.26	NR
Geraniol	NR	2.07	NR	2.07	0.96	NR
Nonanal	NR	NR	NR	NR	NR	NR
linalyl acetate	5.12	NR	NR	NR	NR	NR
linalyl propanoate	NR	NR	NR	1.19	NR	NR
citronellyl propionate	NR	NR	NR	0.37	NR	NR
geranyl acetate	4.72	0.43	NR	NR	NR	NR
neryl acetate	2.08	0.19	NR	0.46	NR	NR
citronellyl acetate	NR	NR	1.22	NR	NR	NR
α-bergamotene	NR	NR	NR	NR	0.57	NR
aromadendrene	NR	NR	0.52	NR	NR	NR
propanoic acid	NR	0.40	0.31	NR	NR	0.38
1,3,8-p-menthatriene	NR	NR	NR	NR	NR	NR
2-octene	NR	2.29	NR	NR	NR	NR
1,5-hexadiene	NR	NR	NR	NR	NR	NR
1,5-heptadiene	NR	NR	NR	NR	NR	NR
Isopulegol	NR	NR	10.36	4.34	2.71	NR
neo-isopulegol	NR	NR	1.33	NR	NR	NR
Bicyclogermacrene	NR	NR	0.86	NR	NR	NR

(continued)

Table 10. (continued)

	Citrus aurantium (bitter orange)	*Citrus sinensis* (sweet orange)	*Citrus grandis* (pomelo)	*Citrus paradisi* (grapefruit)	*Citrus depressa*	*Citrus reticulata* (mandarin orange)
bicycloelemene	NR	NR	0.40	NR	NR	NR
spiro[2.5]octane	NR	NR	4.07	2.29	1.64	NR
Cyclooctane	NR	7.12	NR	NR	NR	NR
3-cyclohexene-carboxaldehyde	NR	4.18	NR	4.61	NR	NR
thymyl methyl ether	NR	NR	NR	NR	6.94	1.14

NR = not reported.

(described as neroli oil) was not sensitizing at 4% in petrolatum; Citrus Aurantium Dulcis (Orange) Flower Oil was not irritating or sensitizing at 0.4% in a face and neck product, and Citrus Reticulata (Tangerine) Leaf Oil was not irritating or sensitizing at 0.1% in a face and neck product.

Photosensitization

Photosensitization studies are presented in Table 15.[42,50] Undiluted Citrus Aurantium Amara (Bitter Orange) Flower Oil (described as neroli oil) was not photosensitizing in tests with hairless mice or miniature swine. Citrus Aurantium Amara (Bitter Orange) Flower Extract at up to 0.002% in a leave-on product was not phototoxic or photosensitizing.

Clinical Studies

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

Summary

The 33 *Citrus* flower- and leaf-derived ingredients described in this report function primarily as fragrances and/or skin-conditioning agents. Botanicals such as *Citrus* are composed of hundreds of constituents, some of which have the potential to be toxic. CIR reviewed the information available for each *Citrus* flower- and leaf-derived ingredient as a whole, complex substance; CIR did not review the potential toxicity information on the individual constituents of which the *Citrus* flower- and leaf-derived ingredients are composed.

Citrus Aurantium Amara (Bitter Orange) Flower Oil has the most reported uses of the cosmetic ingredients in this report, with a total of 99; the majority of the uses are in leave-on skin care preparations. Citrus Aurantium Dulcis (Orange) Flower Extract has the second greatest number of overall uses reported, with a total of 70; a majority of the uses are in rinse-off and leave-on skin care preparations. The results of the concentration of use survey conducted by the Council indicate that Citrus Aurantium Dulcis (Orange) Flower Oil has the highest reported maximum concentration of use; it is used at up to 0.66% in a depilatory. Citrus Aurantium Dulcis (Orange) Flower Wax had the second highest reported maximum concentration of use; it is used at up to 0.12% in a lipstick.

The *Citrus* flower- and leaf-derived ingredients in this safety assessment are not restricted from use under the rules governing cosmetic products in the European Union.

Some of the *Citrus* ingredients in this assessment are found in foods, and daily exposures from food use would result in much larger systemic exposures than those resulting from use in cosmetic products. Essential oils, oleoresins (solvent-free), and natural extractives (including distillates) derived from some *Citrus* sources (specifically *Citrus aurantium* (bitter orange; the flowers), *Citrus sinensis* (orange; the leaf and flowers), *Citrus limon* (lemon; leaves), and *Citrus reticulata* (mandarin or tangerine; leaves)) are GRAS for their intended use in foods for human and animal consumption according to the FDA. While not specifically listed as GRAS, *Citrus hystrix* (kaffir lime) leaves are commonly used in Southeast Asian cuisine.

In rabbit studies, moderate, reversible erythema reactions were observed with undiluted Citrus Aurantium Amara (Bitter Orange) Flower Wax. Citrus Hystrix Leaf Extract was not irritating in rabbits at up to 10%. In human subjects, no irritation was observed after topical exposure to Citrus Natsudaidai Flower Oil (1% in jojoba seed oil).

A raw material product containing >98% Citrus Aurantium Amara (Bitter Orange) Flower Water was considered practically not irritating in a HET-CAM assay but was considered slightly irritating to the eyes in a CFIO test. Essentially no cytotoxicity was observed in an in vitro eye tolerance study of Citrus Aurantium Amara (Bitter Orange) Flower Wax (>50%) using the SIRC cell strain.

Citrus Hystrix Leaf Extract was not sensitizing in guinea pigs at up to 10%. In human studies, Citrus Aurantium Amara (Bitter Orange) Flower Extract was considered not sensitizing in formulations at up to 0.0225%, and Citrus Aurantium Amara (Bitter Orange) Flower Oil was not sensitizing at 4% in petrolatum. Citrus Aurantium Dulcis (Orange) Flower Oil was not irritating or sensitizing at 0.4% in a face and neck product,

Table 11. Frequency and concentration of use according to duration and type of exposure for *Citrus* flower- and leaf-derived ingredients.[28,64]

	# 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) Flower Extract[d]		Citrus Aurantium Amara (Bitter Orange) Flower Extract[e]		Citrus Aurantium Amara (Bitter Orange) Flower Oil[e]		Citrus Aurantium Amara (Bitter Orange) Flower Water[e]	
Totals[†]	10	0.00001-0.005	45	0.000000072-0.032	99	0.00098-0.049	31	0.000033-0.05
Duration of Use								
Leave-On	5	0.00001-0.0005	36	0.000000072-0.032	83	0.00098-0.049	23	0.00016-0.0023
Rinse-Off	2	0.0005-0.005	9	0.00028-0.001	13	0.001-0.019	8	0.00005-0.05
Diluted for (Bath) Use	3	0.0005	NR	NR	3	NR	NR	0.000033
Exposure Type								
Eye Area	NR	NR	6	NR	4	NR	8	0.0017-0.0023
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1[a]	0.00001-0.0005; 0.00001[b]	1; 6[b]; 19[a]	0.000000072-0.001; 0.032[b]	2; 34[b]; 32[a]	0.0024; 0.049[b]	1; 10[b]; 3[a]	NR
Incidental Inhalation-Powder	1[a]	0.0005[c]	19[a]	0.001-0.023[c]	2[c]; 32[a]	0.01; 0.00098-0.005[c]	3[a]	0.00021[c]
Dermal Contact	9	0.0005	43	0.00001-0.023	95	0.00098-0.019	31	0.000033-0.05
Deodorant (underarm)	NR	NR	NR	0.00001-0.0099	NR	NR	NR	NR
Hair—Non-Coloring	1	0.00001-0.005	1	0.000000072-0.032	4	0.001-0.049	NR	0.00005-0.00014
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	1	NR	NR	NR	NR	NR
Mucous Membrane	4	0.0005	3	0.00028-0.001	8	0.019	1	0.000033-0.05
Baby Products	NR	NR	NR	NR	3	NR	NR	NR
	Citrus Aurantium Amara (Bitter Orange) Flower Wax[e]		Citrus Aurantium Bergamia (Bergamot) Leaf Extract		Citrus Aurantium Bergamia (Bergamot) Leaf Oil[f]		Citrus Aurantium Dulcis (Orange) Flower[g]	
Totals[†]	5	NR	NR	0.002	2	0.002	6	0.00008-0.005
Duration of Use								
Leave-On	5	NR	NR	0.002	2	0.002	5	NR
Rinse-Off	NR	NR	NR	0.002	NR	0.002	NR	0.00008-0.005
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	1	NR
Exposure Type								
Eye Area	1	NR	NR	NR	NR	NR	1	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1[b]; 2[a]	NR	NR	NR	2[a]	NR	3[b]; 1[a]	NR
Incidental Inhalation-Powder	2[a]	NR	NR	0.002[c]	2[a]	0.002[c]	1[a]	NR
Dermal Contact	4	NR	NR	0.002	2	0.002	6	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair—Non-Coloring	NR	NR	NR	0.002	NR	0.002	NR	0.00008-0.005
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	NR	1	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
	Citrus Aurantium Dulcis (Orange) Flower Extract[h]		Citrus Aurantium Dulcis (Orange) Flower Oil[i]		Citrus Aurantium Dulcis (Orange) Flower Water		Citrus Aurantium Dulcis (Orange) Flower Wax[j]	
Totals[†]	70	0.0000016-0.1	67	0.000011-0.66	16	NR	4	0.12
Duration of Use								
Leave-On	36	0.00003-0.056	44	0.000035-0.21	9	NR	2	0.12
Rinse-Off	33	0.0000016-0.04	19	0.000011-0.66	7	NR	2	NR

(continued)

Table 11. (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 (%)
	Citrus Aurantifolia (Lime) Flower Extract[d]		Citrus Aurantium Amara (Bitter Orange) Flower Extract[e]		Citrus Aurantium Amara (Bitter Orange) Flower Oil[e]		Citrus Aurantium Amara (Bitter Orange) Flower Water[e]	
Diluted for (Bath) Use	1	0.01-0.1	4	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	0.01	1	NR	2	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	0.12
Incidental Inhalation-Spray	2; 19[b]; 9[a]	0.01	8; 13[b]; 15[a]	0.015; 0.032[b]	1; 4[b]; 1[a]	NR	2[b]	NR
Incidental Inhalation-Powder	9[a]	0.002-0.056[c]	15[a]	0.04-0.21[c]	1[a]	NR	NR	NR
Dermal Contact	70	0.0000016-0.1	60	0.000011-0.66	14	NR	2	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair—Non-Coloring	NR	0.0002-0.005	6	0.015-0.069	2	NR	2	NR
Hair-Coloring	NR	0.0018	NR	NR	NR	NR	NR	NR
Nail	NR	NR	1	NR	NR	NR	NR	NR
Mucous Membrane	14	0.01-0.1	11	0.0099-0.12	NR	NR	NR	0.12
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Citrus Aurantium Dulcis (Orange) Leaf Extract		Citrus Reticulata (Tangerine) Leaf Oil[k]		Kaffir Lime (Citrus Hystrix) Leaf Oil[l]	
Totals[†]	1	0.1	35	0.02-0.1	26	NR
Duration of Use						
Leave-On	1	0.1	18	0.02-0.1	12	NR
Rinse-Off	NR	NR	12	0.066-0.069	12	NR
Diluted for (Bath) Use	NR	NR	5	NR	2	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	1	0.02	NR	NR
Incidental Inhalation-Spray	1[b]	NR	3; 4[b]; 6[a]	0.027[b]	2; 3[b]; 1[a]	NR
Incidental Inhalation-Powder	NR	NR	6[a]	0.1[c]	1[a]	NR
Dermal Contact	1	0.1	31	0.1	21	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—Non-Coloring	NR	NR	3	0.027-0.069	5	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	11	0.02	9	NR
Baby Products	NR	NR	1	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]Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.
[b]It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.
[c]It is possible these products may be powders, but it is not specified whether the reported uses are powders.
[d]Includes generic lime blossom extract in the VCRP database.
[e]Listed as Citrus Aurantium (Bitter Orange) in the VCRP database.
[f]Listed as Citrus Bergamia (Bergamot Orange) in the VCRP database.
[g]Includes uses listed under Orange Blossom in the VCRP database.
[h]Includes uses listed under Citrus Sinensis (Sweet Orange) Flower Extract in the VCRP database.
[i]Includes uses under Citrus Sinensis (Sweet Orange) Flower Oil; Oil of Orange Flowers; and Orange Flower Oil, Sweet in the VCRP database.
[j]Includes uses listed under Orange Blossom Wax in the VCRP database.
[k]Includes uses listed under Citrus Reticulata (Mandarin Orange) Leaf Oil in the VCRP database.
[l]Only listed in the VCRP database, not an INCI ingredient. Included because of similarity.

Table 12. Ingredients that are not Reported to be in Use.

Citrus Aurantifolia (Lime) Leaf Oil
Citrus Aurantium Bergamia (Bergamot) Leaf Cell Extract
Citrus Clementina Leaf Cell Extract
Citrus Depressa Flower Water
Citrus Grandis (Grapefruit) Leaf Extract
Citrus Hystrix Leaf Extract
Citrus Junos Flower Oil
Citrus Limon (Lemon) Flower Water
Citrus Limon (Lemon) Leaf Extract
Citrus Limon (Lemon) Leaf Cell Extract
Citrus Natsudaidai Flower Water
Citrus Natsudaidai Flower Oil
Citrus Reticulata (Tangerine) Leaf Water
Citrus Tamurana Flower Extract
Citrus Unshiu Flower Extract
Citrus Unshiu Flower Powder
Citrus Unshiu Flower Water
Citrus Unshiu Leaf Extract

and Citrus Reticulata (Tangerine) Leaf Oil was not irritating or sensitizing at 0.1% in a face and neck product.

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

Discussion

The *Citrus* ingredients in this assessment are found in foods, and daily exposures from the consumption of foods can be expected to yield much larger systemic exposures to these ingredients than those from use in cosmetic products. Essential oils, oleoresins (solvent-free), and natural extracts (including distillates) derived from some *Citrus* flowers and leaves are GRAS in foods and animal feeds. Consequently, the primary focus of this safety assessment is on the potential for irritation and sensitization from topical exposures to the *Citrus* ingredients.

Table 13. Dermal Irritation Studies for Citrus-Derived Ingredients.

Test Article	Concentration/ Dose	Test Population	Procedure	Results	Reference
NON-HUMAN					
Citrus Aurantium Amara (Bitter Orange) Flower Oil (described as "oil neroli Tunisian")	Neat	hairless mice and swine; details not provided	details not provided	no irritation	49
Citrus Aurantium Amara (Bitter Orange) Flower Oil (described as "oil neroli Tunisian")	Neat	rabbits; details not provided	24 h irritation test on intact and abraded skin; occluded; no further details provided	no irritation	49
Citrus Aurantium Amara (Bitter Orange) Flower Wax	Neat	6 New Zealand male rabbits	primary cutaneous tolerance test ; test material applied to scarified and intact shaved skin with 2.5 cm^2 occluded patches for 24 h	moderate irritation reactions (erythema) that were totally reversible by 72 h; reactions were accompanied by minor, isolated structural modifications	39
Citrus Hystrix Leaf Extract	10%	3 rabbits	primary skin irritation test, details not provided	no irritation	14
Citrus Hystrix Leaf Extract	10%	Details not provided	cumulative application test, details not provided	no irritation	14
HUMAN					
Citrus Aurantium Amara (Bitter Orange) Flower Extract	0.0001% in a leave-on product	26 subjects	Cumulative irritation patch; occluded; 100 µl applied on a total of 12 patches	not irritating	42
Citrus Aurantium Amara (Bitter Orange) Flower Extract	0.0005% to 0.001% in a leave-on product	140 subjects	Cumulative irritation patch; occluded; 20 µl applied on a total of 12 patches	not irritating	42
Citrus Aurantium Amara (Bitter Orange) Flower Oil (described as "oil neroli Tunisian")	4% in petrolatum	details not provided	48 h closed patch test; no further details provided	not irritating	49

(continued)

Table 13. (continued)

Test Article	Concentration/ Dose	Test Population	Procedure	Results	Reference
98% Citrus Aurantium Amara (Bitter Orange) Flower Water	10% diluted in distilled water	11 subjects	24 h occlusive cutaneous patch test; patch area 50 mm on upper back	No skin reaction in 9 subjects, very slight erythema in 2 subjects; irritation index = 0.04; not irritating	41
Citrus Natsudaidai Flower Oil	1% in jojoba seed oil	20 subjects	24 h human insult patch test using Finn chambers; control patches of white petrolatum, normal saline and distilled water	not irritating	40

Table 14. Sensitization Studies for Citrus-Derived Ingredients.

Test Article	Concentration/ Dose	Test Population	Procedure	Results	Reference
ANIMAL					
Citrus Hystrix Leaf Extract	10%	25 guinea pigs	dermal sensitization test, details not provided	not sensitizing	14
HUMAN					
Citrus Aurantium Amara (Bitter Orange) Flower Extract	0.0001% in a leave-on product	207 subjects	HRIPT; 50 μl; occlusive patch	not sensitizing	42
Citrus Aurantium Amara (Bitter Orange) Flower Extract	0.00001% in a rinse-off product	207 subjects	HRIPT; 50 μl; occlusive patch	not sensitizing	42
Citrus Aurantium Amara (Bitter Orange) Flower Extract	0.0225% in a cream	108 subjects	HRIPT; 0.2 g; occlusive patch	as many as 17 subjects had faint, minimal erythema reactions during induction (7^{th} patch); as many as7 subjects had a erythema reaction (4^{th} patch) during induction; as many as 3 subjects had a erythema with edema reactions (3^{rd} patch) during induction; during challenge as many as 14 subjects had faint, minimal erythema reactions (2^{nd} challenge reading) and as many as 6 subjects had erythema reactions (1^{st} challenge reading); study authors concluded test material was non-sensitizing	45
Citrus Aurantium Amara (Bitter Orange) Flower Extract	0.0225% in a body cream	106 subjects	HRIPT; 0.2 g; semi-occlusive patch	one subject had a faint, minimal erythema reaction on the 1^{st} challenge reading; study authors concluded test material was non-sensitizing	44
Citrus Aurantium Amara (Bitter Orange) Flower Oil	0.089%	108 healthy subjects	modified Marzulli and Maibach method with 0.02 ml over 50 mm^2; occlusive patch	not irritating; not sensitizing	46

(continued)

Table 14. (continued)

Test Article	Concentration/ Dose	Test Population	Procedure	Results	Reference
Citrus Aurantium Amara (Bitter Orange) Flower Oil (described as "oil neroli Tunisian")	4% in petrolatum	25 subjects	Kligman maximization test; details not provided	not sensitizing	49
Citrus Aurantium Dulcis (Orange) Flower Oil	0.4% in a face and neck product	104 subjects	modified HRIPT; semi-occlusive patch; 150 µl over 2 cm^2	not irritating, not sensitizing	47
Citrus Reticulata (Tangerine) Leaf Oil	0.1% in a face and neck product	52 subjects	HRIPT; 0.1-0.15 g; occlusive patch	not irritating; not sensitizing	48

Table 15. Photosensitization Studies.

Test Article	Concentration/ Dose	Test Population	Procedure	Results	Reference
NON-HUMAN					
Citrus Aurantium Amara (Bitter Orange) Flower Oil (described as "oil neroli bigarde petale")	Undiluted	hairless mutant mice (6/light source; 12 total) and miniature swine (1/light source; 2 total)	20 µl test material was applied to 2 cm^2 back skin, and the test sites were irradiated with UVA irradiation by blacklight or 6 kW long-arc xenon lamp; exposure was 40 min at a distance of 1 m	barely perceptible erythema; not photosensitizing	50
Citrus Aurantium Amara (Bitter Orange) Flower Oil (described as "oil neroli Tunisian")	Undiluted	hairless mutant mice (6/light source; 12 total) and miniature swine (1/light source; 2 total)	20 µl test material was applied to 2 cm^2 back skin, and the test sites were irradiated with UVA irradiation by blacklight or 6 kW long-arc xenon lamp; exposure was 40 min at a distance of 1 m	barely perceptible erythema; not photosensitizing	50
HUMAN					
Citrus Aurantium Amara (Bitter Orange) Flower Extract	0.0001% to 0.002% in a leave-on product	92 subjects	phototoxicity test; 20 µl test material; occluded; 17 min exposure to UVA	not phototoxic	42
Citrus Aurantium Amara (Bitter Orange) Flower Extract	0.0001% to 0.002% in a leave-on product	247 subjects	photoallergy test; 0.2 g test material; occluded; 17 min exposure to UVA	not photoallergenic	42

The Panel noted that, because botanical ingredients are complex mixtures, there is concern that multiple botanical ingredients in one formulation 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 Panel also noted that the compositions of the ingredients included in this report are highly variable, even when derived from plants within a single cultivar of a species. For example, leaf oil from some cultivars of *Citrus reticulata* may contain up to about 50% methyl-*N*-methylanthranilate (also known as dimethyl anthranilate), which is phototoxic. IFRA and the European Union SCCS have issued a 0.01% limit on this constituent in leave-on products. The maximum reported concentration of use for Citrus Reticulata (Tangerine) Leaf Oil in a leave-on product was 0.1%. Because the concentration of methyl-*N*-methylanthranilate in this ingredient would be below the limit established by IFRA and the SCCS, the Panel determined that there are no safety concerns about Citrus Reticulata (Tangerine) Leaf Oil as used in cosmetics.

The Panel recognized that constituents such as methyl-*N*-methylanthranilate may be prone to *N*-nitrosation. However, the use concentrations of these ingredients, of which such constituents are a small part, are so low that the Panel had no

safety concerns about the possibility of *N*-nitrosation of these *Citrus*-derived ingredients.

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

Conclusion

The CIR Expert Panel concluded that the following 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.

Citrus Aurantifolia (Lime) Flower Extract	Citrus Clementina Leaf Cell Extract*
Citrus Aurantifolia (Lime) Leaf Oil*	Citrus Depressa Flower Water*
Citrus Aurantium Amara (Bitter Orange) Flower Extract	Citrus Grandis (Grapefruit) Leaf Extract*
Citrus Aurantium Amara (Bitter Orange) Flower Oil	Citrus Hystrix Leaf Extract*
Citrus Aurantium Amara (Bitter Orange) Flower Water	Citrus Hystrix Leaf Oil
Citrus Aurantium Amara (Bitter Orange) Flower Wax	Citrus Junos Flower Oil*
Citrus Aurantium Bergamia (Bergamot) Leaf Cell Extract*	Citrus Limon (Lemon) Flower Water*
	Citrus Limon (Lemon) Leaf Extract*
Citrus Aurantium Bergamia (Bergamot) Leaf Extract	Citrus Limon (Lemon) Leaf Cell Extract*
Citrus Aurantium Bergamia (Bergamot) Leaf Oil	Citrus Natsudaidai Flower Water*
Citrus Aurantium Dulcis (Orange) Flower Extract	Citrus Natsudaidai Flower Oil*
Citrus Aurantium Dulcis (Orange) Flower Oil	Citrus Reticulata (Tangerine) Leaf Oil
Citrus Aurantium Dulcis (Orange) Flower Wax	Citrus Reticulata (Tangerine) Leaf Water*
Citrus Aurantium Dulcis (Orange) Flower	Citrus Sinensis (Orange) Flower Water
Citrus Aurantium Dulcis (Orange) Leaf Extract	Citrus Tamurana Flower Extract*
Citrus Unshiu Flower Extract*	Citrus Unshiu Flower Water*
Citrus Unshiu Flower Powder*	Citrus Unshiu Leaf 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.

Author Contributions

Christina L. Burnett contributed to conception and design, contributed to acquisition, analysis, and interpretation, drafted manuscript, and critically revised manuscript.Wilma F. Bergfeld, Donald V. Belsito, Ronald A. Hill, Curtis D. Klaassen, Daniel C. Liebler, James G. Marks, Ronald C. Shank, Thomas J. Slaga, Paul W. Snyder, and Lillian J. Gill contributed to conception and design, contributed to analysis and interpretation, and critically revised manuscript.Bart Heldreth contributed to design, contributed to analysis and interpretation, and critically revised manuscript.All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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