Safety Assessment of *Citrus* Peel-Derived Ingredients as Used in Cosmetics

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of 47 *Citrus* peel-derived ingredients, which are most frequently reported to function in cosmetics as skin conditioning agents. The Panel reviewed the available data to determine the safety of these ingredients. Because final product formulations may contain multiple botanical ingredients, 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. Industry should use good manufacturing practices to limit impurities that could be present in botanical ingredients. The Panel concluded that Citrus peel-derived ingredients are safe in the present practices of use and concentration 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).

INTRODUCTION

Citrus peel-derived ingredients are most frequently reported to function in cosmetics as skin conditioning agents, according to the *International Cosmetic Ingredient Dictionary and Handbook (Dictionary)* (Table 1).[1] This report assesses the safety of the following 47 ingredients:

Citrus Aurantifolia (Lime) Peel
Citrus Aurantifolia (Lime) Peel Extract
Citrus Aurantifolia (Lime) Peel Powder
Citrus Aurantifolia (Lime) Peel Water
Citrus Aurantium Amara (Bitter Orange) Peel
Citrus Aurantium Amara (Bitter Orange) Peel Extract
Citrus Aurantium Amara (Bitter Orange) Peel Powder
Citrus Aurantium Bergamia (Bergamot) Peel Water
Citrus Aurantium Dulcis (Orange) Peel Extract
Citrus Aurantium Dulcis (Orange) Peel Powder
Citrus Aurantium Dulcis (Orange) Peel Wax
Citrus Aurantium Sinensis Peel Extract
Citrus Aurantium Tachibana Peel Extract
Citrus Depressa Peel Extract
Citrus Depressa Peel Powder
Citrus Grandis (Grapefruit) Peel
Citrus Grandis (Grapefruit) Peel Extract
Citrus Grandis (Grapefruit) Peel Powder
Citrus Hassaku/Natsudaidai Peel Powder
Citrus Iyo Peel Extract
Citrus Iyo Peel Water
Citrus Jabara Peel Extract
Citrus Jabara Peel Powder
Citrus Jabara Peel Water
Citrus Junos Peel Extract
Citrus Junos Peel Powder
Citrus Junos Peel Water
Citrus Limon (Lemon) Peel
Citrus Limon (Lemon) Peel Extract
Citrus Limon (Lemon) Peel Powder
Citrus Limon (Lemon) Peel Water
Citrus Limon (Lemon) Peel Wax
Citrus Natsudaidai Peel Extract
Citrus Nobilis (Mandarin Orange) Peel Extract
Citrus Nobilis (Mandarin Orange) Peel Powder
Citrus Paradisi (Grapefruit) Peel Extract
Citrus Reticulata (Tangerine) Peel Extract
Citrus Reticulata (Tangerine) Peel Powder
Citrus Shunkokan Peel Extract
Citrus Sunki Peel Extract
Citrus Tachibana/Reticulata Peel Powder
Citrus Tangelo Peel Powder
Citrus Tangerina (Tangerine) Peel
Citrus Tangerina (Tangerine) Peel Extract
Citrus Unshiu Peel Extract
Citrus Unshiu Peel Powder
Citrus Unshiu Peel Water

The Panel has previously reviewed the safety of *Citrus*-derived peel oils and *Citrus* fruit-derived ingredients in separate assessments and concluded that 14 *Citrus*-derived peel oil 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).[2,3] The safety of *Citrus* flower- and leaf-derived ingredients and *Citrus* plant- and seed-derived ingredients are published in separate reports.

Some of the *Citrus* peels that are used to derive the ingredients described in this safety assessment are consumed as food. The U.S. Food and Drug Administration (FDA) determined that the use of some *Citrus* peels as direct food substances are generally recognized as safe (GRAS). Additionally, essential oils, oleoresins (solvent-free), and natural extracts (including distillates) derived from some *Citrus* peels 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* peel-derived ingredients via oral exposure is not addressed further in this report. The primary focus of this safety assessment is the review of the safety of topical exposure.

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* peel-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.

Botanical ingredients are complex mixtures of many constituents, some of which have the potential to cause toxic effects; for example, bergapten (aka 5-methoxysporalen or 5-MOP) is a naturally-occurring phototoxic furanocoumarin (psoralen) in some *Citrus* ingredients. In this assessment, CIR is reviewing the potential toxicity of each *Citrus* peel-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* peels 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 (e.g. sweet orange peel extract). If the substance is clearly a cosmetic ingredient, the International Nomenclature of Cosmetic Ingredients (INCI) name will be used (e.g. "Citrus Aurantium Dulcis (Orange) Peel 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 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.[4]

CHEMISTRY

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

Physical and Chemical Properties

Physical and chemical properties of Citrus Aurantium Dulcis (Orange) Peel Wax are provided in Table 4.

Method of Manufacturing

According to the *Dictionary*, waters are prepared from leaves, stems, flowers, bark, roots, or other parts of a plant or the whole plant.[5] Waters, and essential oils, are prepared by a number of processes, but the most widely used method 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 includes the term "water" in the INCI name.

Citrus Aurantium Amara (Bitter Orange) Peel Extract

A supplier reported that its Citrus Aurantium Amara (Bitter Orange) Peel Extract products are produced by extracting dried raw peels from *Citrus aurantium amara* with an ethanol solution.[6] The resultant materials then undergo filtration, concentration, sedimentation, and adjustment before packaging. One product (a powdered form) has anhydrous sodium sulfate added as a vehicle prior to packaging.

Another supplier reported that its products are produced by extracting ripe pericarp from *Citrus aurantium* Linne (Rutaceae) with either an ethanol or a 1,3-butylene glycol solution and then filtering the extract.[7]

Citrus Aurantium Dulcis (Orange) Peel Wax

According to data provided by a supplier, Citrus Aurantium Dulcis (Orange) Peel Wax is a by-product from orange essential oil and orange juice production.[8] Citrus Aurantium Dulcis (Orange) Peel Wax is obtained by distillation of citrus terpenes and orange essential oil from orange fruit peels. The crude wax is processed by physical methods only, and is further refined with various absorbents and filtration. The deodorization process removes all terpenes and most of the essential oil components.

Citrus Reticulata (Tangerine) Peel Extract

A supplier reported that Citrus Reticulata (Tangerine) Peel Extract is produced through the hydroalcoholic extraction of tangerine peel, which is then concentrated until it contains at least 98% of the flavonoid luteolin.[9] The resultant product is a powder.

Another supplier reported that its products are produced by extracting ripe peels of *Citrus reticulata* Blanco (Rutaceae) with either an ethanol solution or 1,3-butylene glycol solution and then filtering.[7]

Citrus Unshiu Peel Extract

According to a supplier, Citrus Unshiu Peel Extract is obtained by maceration of fine-cut *Citrus unshiu* peel in water and ethanol.[10] The resultant product is filtered and dried. Another supplier reports that its Citrus Unshiu Peel Extract products are produced by extracting dried raw peels with either an ethanol solution or a 1,3-butylene glycolic solution.[6] The resultant materials undergo various forms of filtration, concentration, sedimentation, and adjustment before packaging. One product (a powdered form) has anhydrous sodium sulfate added as a vehicle prior to packaging, while another has squalene added.

Constituents/Composition

The *Citrus* ingredients are complex botanicals made of numerous constituents.

Citrus Aurantifolia (Lime) Peel Extract

The volatile constituents of the hexane extract of *Citrus aurantifolia* are listed in Table 5.

Citrus Aurantium Amara (Bitter Orange) Peel Extract

A supplier reported that their Citrus Aurantium Amara (Bitter Orange) Peel Extract products contain flavonoids, sugar, and/or hesperidin.[6]

A supplier of a product containing 1.55% Citrus Aurantium Amara (Bitter Orange) Peel Extract, 25.81% alcohol, and 72.64% water stated that the product contained 2.8 ppm 5-MOP.[7] No other analysis was performed on this product. The same supplier has a product containing 2.0% Citrus Aurantium Amara (Bitter Orange) Peel Extract, 29.4% butylene glycol, and 68.6% water.

Citrus Aurantium Dulcis (Orange) Peel Wax

Based on data provided by a supplier, Citrus Aurantium Dulcis (Orange) Peel Wax is a water-free substance unlikely to be contaminated by microorganisms (bacteria, yeast, or fungi) because of the high temperature, filtration, and absorbents used during processing.[8]

The provided data indicate that Citrus Aurantium Dulcis (Orange) Peel Wax consists of approximately 60% esters (C42-C60), 18% phytosterols (beta-sitosterol, stigmasterol), 3% sterol esters, 8% free fatty acids, 5% hydrocarbons, and 4% free fatty alcohols.[8] Approximately 50% of Citrus Aurantium Dulcis (Orange) Peel Wax consists of unsaturated monoesters of unsaturated fatty acids and long-chain alcohols, with the fatty acids consisting mostly of linoleic, oleic, linolenic, arachidic, and erucic acids.[12] The fatty alcohol portion of the ester is mostly dotriacontanol (C32) and tetratricontanol (C34).

Table 6 and Table 7 present additional chemical composition data on Citrus Aurantium Dulcis (Orange) Peel Wax.

Citrus Reticulata (Tangerine) Peel Extract

A supplier of a product containing 3.06% Citrus Reticulata (Tangerine) Peel Extract, 25.41% alcohol, and 71.53% water reported that its product did not contain furanocoumarins.[7] Another product of this supplier contained 3.0% Citrus Reticulata (Tangerine) Peel Extract, 29.1% water, 67.9% butylene glycol, and no furanocoumarins. No further composition data were provided on these products.

Citrus Unshiu Peel Extract

According to a supplier, Citrus Unshiu Peel Extract is composed of pectin, peptides and amino acids, essential oils, phenolic acids, flavonoids (flavonols, flavones, flavonones), carotenoid pigment, and tocopherol analogues.[10] Another supplier reports that its Citrus Unshiu Peel Extract products contain flavonoids, sugar, and/or hesperidin.[6] One product was reported to contain essential oil component (no further details provided).

Impurities

Citrus Aurantium Amara (Bitter Orange) Peel Extract

A supplier reports that its Citrus Aurantium Amara (Bitter Orange) Peel Extract products contain no more than 20 ppm heavy metals (one product not more than 10 ppm) and no more than 2 ppm arsenic.[6]

Citrus Aurantium Dulcis (Orange) Peel Wax

According to data provided by a supplier of Citrus Aurantium Dulcis (Orange) Peel Wax, 1,4-dioxane, ethylene oxide, solvents (e.g., benzol), nitrosamines and free amines were not present in this product.[8] Heavy metals, pesticides, and polycyclic aromatic hydrocarbons were absent or present at very low concentrations (detail not provided). Low concentrations of fragrance allergens were present (detail not provided).

Citrus Unshiu Peel Extract

According to a supplier, a commercial product containing 0.5% Citrus Unshiu Peel Extract (dry) contains < 2.5 ppm (detection limit) allergens, < 1 ppm heavy metals, < 5 ppm (detection limit) formaldehyde, < 0.04 ppm (detection limit) pesticides, and < 10 ppm (detection limit) ethanol.[10] An analysis of just the ingredient Citrus Unshiu Peel Extract found allergens and ethanol to be less than detection limits. The allergens under analysis were not specified.

Another supplier reports that its Citrus Unshiu Peel Extract products contain no more than 20 ppm heavy metals (a few products were no more than 10 ppm) and no more than 2 ppm arsenic (one products was no more than 1 ppm).[6]

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated based on data received from the U.S. 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 Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2016 VCRP data, Citrus Limon (Lemon) Peel Extract has the most reported uses with a total of 150; more than half are in rinse-off preparations (e.g. non-coloring hair conditioners, hair shampoos, and skin cleansing preparations; Table 8).[13] Citrus Paradisi (Grapefruit) Peel Extract has the second greatest number of overall uses with a total of 61; more than half are in skin care preparations. The results of the concentration of use survey conducted in 2016 by the Council indicate that Citrus Aurantium Dulcis (Orange) Peel Powder has the highest reported maximum concentration of use; it is used at up to 2% in skin cleansing preparations.[14] The highest reported maximum concentration of use in a leave-on product is 1.9% Citrus Aurantium Dulcis (Orange) Peel Wax in a lipstick.

Table 9 lists all *Citrus* peel-derived ingredients not reported to be in use based on the VCRP data or the results of the Council concentration of use survey.

In some cases, reports of uses were received from the VCRP, but no concentration of use data were provided in the survey. For example, Citrus Paradisi (Grapefruit) Peel Extract is reported to be used in 61 formulations, but no use concentration data were provided. In other cases, no uses were reported to the VCRP, but a maximum use concentration was provided. For example, Citrus Aurantium Amara (Bitter Orange) Peel was not reported in the VCRP database to be in use, but the industry survey indicated that it is used at concentrations up to 0.2%. It should be presumed that Citrus Aurantium Amara (Bitter Orange) Peel is used in at least one cosmetic formulation.

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) Peel Wax is used at 1.9% in a lipstick and Citrus Aurantium Amara (Bitter Orange) Peel is used at 0.2% in personal cleanliness products. Additionally, some of these ingredients were reported to be used in fragrance preparations, hair sprays, skin care preparation sprays, and face powders and could possibly be inhaled. For example, Citrus Aurantium Dulcis (Orange) Peel Extract was reported to be used in a moisturizing product at a maximum concentration of 0.15% and Citrus Grandis (Grapefruit) Peel Extract 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.[15-18] 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.[16,17] 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.[19-21]

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.[22]

The International Fragrance Association (IFRA) has issued standards for *Citrus* oils and other furocoumarin-containing essential oils.[23] Finished products that are applied to the skin, excluding rinse-off products like bath preparations and soaps, must not contain more than 0.0015% or 15 ppm 5-MOP. This equates to a concentration of 0.0075% or 75 ppm in a fragrance compound when used at 20% in a consumer product that is applied to the skin. If the level of 5-MOP has not been determined, limits specified for individual oils should be observed, and when such oils are used in combination with other phototoxic-constituent containing ingredients, the potential for an additive effect should be considered and use concentrations should be reduced accordingly.

An IFRA standard also has been issued for 7-methoxycoumarin, which is prohibited for use in fragrance compounds.[24] Based on established maximum levels of this substance from commercially-available natural sources (like essential oils, extracts and absolutes), IFRA has determined that exposure to 7-methoxycoumarin from the use of these oils and extracts is acceptable if the level of 7-methoxycoumarin in the finished product does not exceed 100 ppm.

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); *Citrus paradisi* (grapefruit); *Citrus reticulata* (tangerine); *Citrus reticulata blanco* (mandarin); *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).

Citrus aurantium amara (bitter orange) and extracts of its dried fruit and peel have been used in traditional Western medicines and in Chinese and Japanese herbal medicines.[25]

TOXICOKINETICS

No relevant published toxicokinetic studies on *Citrus* peel-derived ingredients were identified in a literature search for these ingredients and no unpublished data were submitted; these types of data were not expected to be found because botanical ingredients are mixtures of many constituents.

TOXICOLOGICAL STUDIES

Acute Toxicity

Some of the *Citrus* ingredients in this assessment are foods, and daily exposure from consumption would result in much larger systemic exposures than those resulting from use in cosmetic products. Also, as noted earlier, essential oils, oleoresins (solvent-free), and natural extractives (including distillates) derived from some *Citrus* peels are GRAS for their intended use in foods for human and animal consumption according to the FDA. Thus, the systemic toxicity potential of *Citrus* peel-derived ingredients via oral exposure is not addressed further in this report. The safety assessment is focused on the potential for irritation and sensitization from topical exposure to the *Citrus* ingredients used in cosmetic products.

Repeated Dose Toxicity

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

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

No relevant published reproductive and developmental studies on C*itrus* peel-derived ingredients were identified in a literature search, and no unpublished data were submitted.

GENOTOXICITY

Citrus Reticulata (Tangerine) Peel Extract

A formulation containing 3% Citrus Reticulata (Tangerine) Peel Extract was not genotoxic in a reverse mutation assay (no further details provided).[26]

CARCINOGENICITY

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

IRRITATION AND SENSITIZATION

Dermal Irritation

Dermal irritation studies are summarized in Table 10.[6,8,12,26-31] No irritation potential was observed for Citrus Aurantium Dulcis (Orange) Peel Wax (100%) or Citrus Reticulata (Tangerine) Peel Extract (3.0% in formulation) in in vitro tests. Citrus Aurantium Amara (Bitter Orange) Peel Extract was not irritating when tested at up to 2.0% in formulation in guinea pigs and 100% in rabbits. In human subjects, no irritation was observed after topical exposure to Citrus Aurantium Dulcis (Orange) Peel Wax (100%), Citrus Limon (Lemon) Peel Extract (0.1% in a moisturizer), and Citrus Unshiu Peel Extract (0.5% in formulation). Any irritation observed in tests with Citrus Aurantium Amara (Bitter Orange) Peel Extract (1.55% in formulation; 20% water solution) and Citrus Reticulata (Tangerine) Peel Extract (3.06% in formulation) was resolved within 24-h of exposure.

Ocular Irritation

Citrus Aurantium Amara (Bitter Orange) Peel Extract

The ocular irritation potential of an undiluted formulation containing 2.0% Citrus Aurantium Amara (Bitter Orange) Peel Extract was studied in 3 albino rabbits.[29] The test material was instilled into the conjunctival sac of one eye and the other eye served as a control. Eyes were observed for irritation at 0, 1, 24, 48, and 72 h post-instillation. Redness was observed in the conjunctiva immediately after instillation, but not at later time points. No inflammatory signs were observed in the iris or cornea. The test material was considered almost non-irritating.

Citrus Limon (Lemon) Peel Extract

In an Epiocular™ tissue equivalent in vitro assay, a moisturizer containing 0.1% Citrus Limon (Lemon) Peel Extract tested neat at pH 5.5 was not predicted to be an ocular irritant.[32]

Citrus Reticulata (Tangerine) Peel Extract

In an in vitro assay using the neutral red release method on SIRC cell lines, 3.0% Citrus Reticulata (Tangerine) Peel Extract in formulation was classified as having relatively low cytotoxicity.[26] This suggests that this ingredient is likely not an ocular irritant.

Sensitization

Dermal sensitization studies are summarized in Table 11.[6,9,26,29,33-38] No sensitization was observed in guinea pigs exposed to Citrus Aurantium Amara (Bitter Orange) Peel Extract (2.0% in formulation). Citrus Aurantifolia (Lime) Peel Extract (2.14% in a face and neck product), Citrus Aurantium Dulcis (Orange) Peel Wax (1.9% in a lipstick), Citrus Grandis (Grapefruit) Peel Extract (up to 0.5% in formulation), Citrus Reticulata (Tangerine) Peel Extract (up to 3.0% in formulation), and Citrus Unshiu Peel Extract (up to 100%) were not dermal irritants or sensitizers in human repeated insult patch tests (HRIPTs).

Phototoxicity and Photosensitization

Phototoxicity and photosensitization studies are presented in Table 12.[26,29,39-43] No photo irritation was observed in an in vitro study of Citrus Reticulata (Tangerine) Peel Extract (3.0% in formulation). Citrus Auratnium Amara (Bitter Orange) Peel Extract (2.0% in formulation) did not induce photo irritation or photosensitization in guinea pigs. Undiluted lemon peel juice produced phototoxic reactions in several rat studies. In humans, Citrus Aurantium Dulcis (Orange) Peel wax (100%) was not phototoxic, but phototoxic reactions were observed in 3 subjects (out of 4) with type I skin exposed to undiluted sweet orange peel.

Occupational Exposure

In a retrospective study (2001-2010) of professional food handlers in Denmark, 8.5% (16/188) of the patients had positive skin prick test reactions to orange peel and 7.9% (15/191) of the patients had positive skin prick test reactions to lemon peel.[44]

SUMMARY

The 47 *Citrus* peel-derived ingredients described in this report are reported to function in cosmetics primarily as skin conditioning agents. Botanical ingredients such as those derived from the genus *Citrus* are composed of hundreds of constituents, some of which have the potential to cause toxic effects; for example, bergapten (aka 5-methoxypsoralen or 5-MOP) is a naturally-occurring, phototoxic furanocoumarin (psoralen) in *Citrus*. CIR reviewed the information available on the potential toxicity of each *Citrus* peel-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* peels from which the ingredients in this report are derived.

Citrus Limon (Lemon) Peel Extract has the most reported uses of the cosmetic ingredients in this report, with a total of 150; more than half of the uses are in rinse-off preparations (e.g., non-coloring hair conditioners, hair shampoos, and skin cleansing preparations). Citrus Paradisi (Grapefruit) Peel Extract has the second greatest number of overall uses reported, with a total of 61; more than half of the uses are in skin care preparations. The results of the concentration of use survey conducted in 2016 by the Council indicate Citrus Aurantium Dulcis (Orange) Peel Powder has the highest reported maximum concentration of use; it is used at up to 2% in skin cleansing preparations. The highest reported maximum concentration of use in a leave-on product is 1.9% in a lipstick for Citrus Aurantium Dulcis (Orange) Peel Wax.

The Citrus ingredients described in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the 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. IFRA also has issued standards for *Citrus* oils and other furocoumarin-containing essential oils. Finished products that are applied to

the skin, excluding rinse-off products like bath preparations and soaps, must not contain more than 0.0015% or 15 ppm 5-MOP. If the level of 5-MOP has not been determined, limits specified for individual oils should be observed, and when these oils are used in combination with other phototoxic ingredients, the potential additive effect should be taken into consideration and use levels in the final formulation should be carefully monitored.

Some of the *Citrus* ingredients in this assessment are found in foods, and daily exposure from food use would result in much greater systemic exposures than those from cosmetic products. Essential oils, oleoresins (solvent-free), and natural extractives (including distillates) derived from some *Citrus* peels are GRAS for their intended use in foods for human and animal consumption, according to the FDA.

A formulation containing 3% Citrus Reticulata (Tangerine) Peel Extract was not genotoxic in a reverse mutation assay (no further details provided).

No irritation potential was observed for Citrus Aurantium Dulcis (Orange) Peel Wax (100%) or Citrus Reticulata (Tangerine) Peel Extract (3.0% in formulation) in in vitro tests. Citrus Aurantium Amara (Bitter Orange) Peel Extract was not irritating when tested up to 2.0% in formulation in rodents and 100% in rabbits. In human subjects, no irritation was observed after topical exposure to Citrus Aurantium Dulcis (Orange) Peel Wax (100%), Citrus Limon (Lemon) Peel Extract (0.1% in a moisturizer), and Citrus Unshiu Peel Extract (0.5% in formulation). Any irritation observed in tests with Citrus Aurantium Amara (Bitter Orange) Peel Extract (1.55% in formulation; 20% water solution) and Citrus Reticulata (Tangerine) Peel Extract (3.06% in formulation) was resolved within 24-h of exposure.

In in vitro assays, Citrus Limon (Lemon) Peel Extract (0.1% in a moisturizer) and Citrus Reticulata (Tangerine) Peel Extract (3.0% in formulation) did not predict ocular irritation. An undiluted formulation containing 2.0% Citrus Aurantium Amara (Bitter Orange) Peel Extract was almost non-irritating to the eyes of 3 albino rabbits.

No sensitization was observed in guinea pigs exposed to Citrus Aurantium Amara (Bitter Orange) Peel Extract (2.0% in formulation). Citrus Aurantifolia (Lime) Peel Extract (2.14% in a face and neck product), Citrus Aurantium Dulcis (Orange) Peel Wax (1.9% in a lipstick), Citrus Grandis (Grapefruit) Peel Extract (up to 0.5% in formulation), Citrus Reticulata (Tangerine) Peel Extract (up to 3.0% in formulation), and Citrus Unshiu Peel Extract (up to 100%) were not dermal irritants or sensitizers in HRIPTs.

No photo irritation was observed in an in vitro study of Citrus Reticulata (Tangerine) Peel Extract (3.0% in formulation). Citrus Auratnium Amara (Bitter Orange) Peel Extract (2.0% in formulation) did not induce photo irritation or photosensitization in guinea pigs. Undiluted lemon peel juice produced phototoxic reactions in several rat studies. In humans, Citrus Aurantium Dulcis (Orange) Peel Wax (100%) was not phototoxic, but phototoxic reactions were observed in 3 subjects (out of 4) with type I skin exposed to undiluted sweet orange peel.

In a retrospective study of professional food handlers in Denmark, 8.5% (16/188) of the patients had positive skin prick test reactions to orange peel and 7.9% (15/191) of the patients had positive skin prick test reactions to lemon peel.

No relevant published studies on the toxicokinetics, repeated dose toxicity, reproductive and development toxicity, or carcinogenicity of *Citrus* peel-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 the use of cosmetic products. Essential oils, oleoresins (solvent-free), and natural extracts (including distillates) derived from some *Citrus* peels are GRAS in foods and animal feeds. Additionally, volatile oils of limes, lemons, grapefruits, bitter oranges, oranges, and tangerines are used as flavoring agents. Consequently, the primary focus of this safety assessment is on the potential for irritation and sensitization from dermal exposures to the *Citrus* ingredients.

Although there are many differences among *Citrus* peel-derived ingredients derived from different species, cultivars, growth conditions, extraction methods, and preparation techniques, the weight of the evidence indicates a consistent lack of irritation and sensitization across multiple test methods and ingredients, including testing at maximum use concentrations. However, the Panel expressed concern about the potential for constituents in *Citrus* peel-derived ingredients, including the furocoumarin 5-MOP, to cause phototoxicity. IFRA has issued standards for *Citrus* oils and other furocoumarin-containing essential oils, and the Panel agreed that adherence to the IFRA standards for such constituents will prevent phototoxicity. According to these standards, finished products that are applied to the skin, excluding rinse-off products, must not contain more than 0.0015%, or 15 ppm, 5-MOP. An IFRA standard also has been issued for 7-methoxycoumarin; based on established maximum levels of this substance from commercially-available natural sources (like essential oils, extracts and absolutes), exposure to 7-methoxycoumarin from the use of these oils and extracts is regarded to be acceptable if the level of 7-methoxycoumarin in the finished product does not exceed 100 ppm.

Additionally, during the assessment of safety for the *Citrus*-derived peel oils, the Panel was concerned with findings of a rodent carcinogenicity study in which tumor promotion may have been caused by repeated skin irritation and resultant proliferation of 9,10-dimethyl-1,2-benzanthracene (DMBA)-treated basal cells. The Panel concluded that *Citrus*-derived peel oils could potentially promote tumors if the formulation produces irritation. While no significant skin irritation was reported following the use of *Citrus* peel-derived ingredients, the Panel felt that these botanical ingredients must be formulated to be non-irritating.

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 plant constituents that may cause sensitization or other adverse effects. Specific examples of constituents that could induce adverse effects are limonene, citral, and furocoumarins (such as 5- MOP and 7-methoxycoumarin).

The Panel discussed the issue of incidental inhalation exposure in fragrance preparations, hair sprays, skin care preparation sprays, and face powders. There were no inhalation toxicity data available. The Panel considered other pertinent data indicating that incidental inhalation exposures to *Citrus* peel-derived ingredients in such cosmetic products would not cause adverse health effects, including data characterizing the potential for these ingredients to cause ocular or dermal irritation or sensitization, and other effects. These ingredients are reportedly used at concentrations up to 0.15% in cosmetic products that may be aerosolized. 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.

Finally, the Panel expressed concern about pesticide residues and heavy metals 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 the following 47 *Citrus* peel-derived ingredients are safe in the present practices of use and concentration 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-MOP.

Citrus Aurantifolia (Lime) Peel*
Citrus Aurantifolia (Lime) Peel Extract
Citrus Aurantifolia (Lime) Peel Powder
Citrus Aurantifolia (Lime) Peel Water*
Citrus Aurantium Amara (Bitter Orange) Peel
Citrus Aurantium Amara (Bitter Orange) Peel Extract
Citrus Aurantium Amara (Bitter Orange) Peel Powder
Citrus Aurantium Bergamia (Bergamot) Peel Water
Citrus Aurantium Dulcis (Orange) Peel Extract
Citrus Aurantium Dulcis (Orange) Peel Powder
Citrus Aurantium Dulcis (Orange) Peel Wax
Citrus Aurantium Sinensis Peel Extract*
Citrus Aurantium Tachibana Peel Extract
Citrus Depressa Peel Extract
Citrus Depressa Peel Powder*
Citrus Grandis (Grapefruit) Peel*
Citrus Grandis (Grapefruit) Peel Extract
Citrus Grandis (Grapefruit) Peel Powder*
Citrus Hassaku/Natsudaidai Peel Powder*
Citrus Iyo Peel Extract*
Citrus Iyo Peel Water*
Citrus Jabara Peel Extract
Citrus Jabara Peel Powder*
Citrus Jabara Peel Water*
Citrus Junos Peel Extract
Citrus Junos Peel Powder
Citrus Junos Peel Water*
Citrus Limon (Lemon) Peel
Citrus Limon (Lemon) Peel Extract
Citrus Limon (Lemon) Peel Powder
Citrus Limon (Lemon) Peel Water*
Citrus Limon (Lemon) Peel Wax
Citrus Natsudaidai Peel Extract*
Citrus Nobilis (Mandarin Orange) Peel Extract
Citrus Nobilis (Mandarin Orange) Peel Powder*
Citrus Paradisi (Grapefruit) Peel Extract
Citrus Reticulata (Tangerine) Peel Extract
Citrus Reticulata (Tangerine) Peel Powder*
Citrus Shunkokan Peel Extract*
Citrus Sunki Peel Extract*
Citrus Tachibana/Reticulata Peel Powder*
Citrus Tangelo Peel Powder*
Citrus Tangerina (Tangerine) Peel*
Citrus Tangerina (Tangerine) Peel Extract
Citrus Unshiu Peel Extract
Citrus Unshiu Peel Powder
Citrus Unshiu Peel Water*

*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.

TABLES

Table 1. Definitions and functions of *Citrus* peel-derived ingredients.[1]

Ingredient	Definition	Function
Citrus Aurantifolia (Lime) Peel	Citrus Aurantifolia (Lime) Peel is the peel obtained from *Citrus aurantifolia.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantifolia (Lime) Peel Extract CAS No. 90063-52-8	Citrus Aurantifolia (Lime) Peel Extract is the extract of the peel of *Citrus aurantifolia.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantifolia (Lime) Peel Powder	Citrus Aurantifolia (Lime) Peel Powder is the powder obtained from the dried, ground peel of *Citrus aurantifolia.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantifolia (Lime) Peel Water	Citrus Aurantifolia (Lime) Peel Water is the aqueous solution of the steam distillates obtained from the peel of *Citrus aurantifolia.*	Fragrance Ingredients
Citrus Aurantium Amara (Bitter Orange) Peel	Citrus Aurantium Amara (Bitter Orange) Peel is the peel of *Citrus aurantium amara.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Amara (Bitter Orange) Peel Extract CAS No. 72968-50-4	Citrus Aurantium Amara (Bitter Orange) Peel Extract is the extract of the peel of *Citrus aurantium amara.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Amara (Bitter Orange) Peel Powder	Citrus Aurantium Amara (Bitter Orange) Peel Powder is the powder obtained from the dried, ground peel of *Citrus aurantium amara.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Bergamia (Bergamot) Peel Water	Citrus Aurantium Bergamia (Bergamot) Peel Water is an aqueous solution of the steam distillate obtained from the peel of *Citrus aurantium bergamia.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Dulcis (Orange) Peel Extract	Citrus Aurantium Dulcis (Orange) Peel Extract is the extract of the peel of *Citrus aurantium dulcis.*	Binders; Emulsion Stabilizers; Skin-Conditioning Agents - Miscellaneous; Viscosity Increasing Agents - Aqueous
Citrus Aurantium Dulcis (Orange) Peel Powder	Citrus Aurantium Dulcis (Orange) Peel Powder is the powder obtained from the dried, ground peel of *Citrus aurantium dulcis.*	Absorbents
Citrus Aurantium Dulcis (Orange) Peel Wax	Citrus Aurantium Dulcis (Orange) Peel Wax is a wax obtained from the peel of the orange, *Citrus aurantium dulcis.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Sinensis Peel Extract	Citrus Aurantium Sinensis Peel Extract is the extract of the peel of *Citrus aurantium sinenesis.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Tachibana Peel Extract	Citrus Aurantium Tachibana Peel Extract is the extract of the peel of *Citrus aurantium tachibana.*	Skin-Conditioning Agents - Humectant
Citrus Depressa Peel Extract	Citrus Depressa Peel Extract is the extract of the peel of *Citrus depressa.*	Skin-Conditioning Agents - Humectant
Citrus Depressa Peel Powder	Citrus Depressa Peel Powder is the powder obtained from the dried, ground peel of *Citrus depressa.*	Skin-Conditioning Agents - Miscellaneous
Citrus Grandis (Grapefruit) Peel	Citrus Grandis (Grapefruit) Peel is the peel of *Citrus grandis.*	Skin-Conditioning Agents - Miscellaneous
Citrus Grandis (Grapefruit) Peel Extract	Citrus Grandis (Grapefruit) Peel Extract is the extract of the peel of *Citrus grandis.*	Skin-Conditioning Agents - Miscellaneous
Citrus Grandis (Grapefruit) Peel Powder	Citrus Grandis (Grapefruit) Peel Powder is the powder obtained from the dried, ground peel of *Citrus grandis.*	Absorbents
Citrus Hassaku/Natsudaidai Peel Powder	Citrus Hassaku/Natsudaidai Peel Powder is the powder obtained from the dried, ground peel of a hybrid of *Citrus hassaku* and *Citrus natsudaidai.*	Flavoring Agents
Citrus Iyo Peel Extract	Citrus Iyo Peel Extract is the extract of the peel of *Citrus iyo.*	Skin-Conditioning Agents - Humectant
Citrus Iyo Peel Water	Citrus Iyo Peel Water is an aqueous solution of the steam distillate obtained from the peel of *Citrus iyo.*	Skin-Conditioning Agents - Humectant
Citrus Jabara Peel Extract	Citrus Jabara Peel Extract is the extract of the peel of *Citrus jabara.*	Skin-Conditioning Agents - Miscellaneous
Citrus Jabara Peel Powder	Citrus Jabara Peel Powder is the powder obtained from the dried, ground peels of *Citrus jabara.*	Fragrance Ingredients
Citrus Jabara Peel Water	Citrus Jabara Peel Water is an aqueous solution of the steam distillate obtained from the peel of *Citrus jabara*.	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Junos Peel Extract	Citrus Junos Peel Extract is the extract of the peel of *Citrus junos.*	Skin-Conditioning Agents - Miscellaneous
Citrus Junos Peel Powder	Citrus Junos Peel Powder is the dried, ground powder obtained from the peels of *Citrus junos.*	Fragrance Ingredients
Citrus Junos Peel Water	Citrus Junos Peel Water is an aqueous solution of the steam distillate obtained from the peel of *Citrus junos.*	Skin-Conditioning Agents - Miscellaneous
Citrus Limon (Lemon) Peel CAS No. 84929-31-7; 85085-28-5; 92346-89-9	Citrus Limon (Lemon) Peel is the peel of *Citrus limon.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Limon (Lemon) Peel Extract CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Peel Extract is the extract of the peel of *Citrus limon.*	Skin Protectants; Skin-Conditioning Agents - Emollient
Citrus Limon (Lemon) Peel Powder CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Peel Powder is the powder obtained from the dried, ground peel of *Citrus limon.*	Absorbents

Table 1. Definitions and functions of *Citrus* peel-derived ingredients.[1]

Ingredient	Definition	Function
Citrus Limon (Lemon) Peel Water CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Peel Water is an aqueous solution of the steam distillate obtained from the peel of *Citrus limon.*	Skin-Conditioning Agents - Miscellaneous
Citrus Limon (Lemon) Peel Wax CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Peel Wax is the wax obtained from the peel of *Citrus limon.*	Skin-Conditioning Agents - Occlusive
Citrus Natsudaidai Peel Extract	Citrus Natsudaidai Peel Extract is the extract of the peel of *Citrus natsudaidai*.	Skin-Conditioning Agents - Humectant
Citrus Nobilis (Mandarin Orange) Peel Extract CAS No. 90063-83-5	Citrus Nobilis (Mandarin Orange) Peel Extract is the extract of the peel of *Citrus nobilis.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Nobilis (Mandarin Orange) Peel Powder	Citrus Nobilis (Mandarin Orange) Peel Powder is the powder obtained from the dried, ground peel of *Citrus nobilis.*	Abrasives
Citrus Paradisi (Grapefruit) Peel Extract CAS No. 90045-43-5 (generic)	Citrus Paradisi (Grapefruit) Peel Extract is the extract obtained from the peel of *Citrus paradisi*.	Skin-Conditioning Agents - Miscellaneous
Citrus Reticulata (Tangerine) Peel Extract	Citrus Reticulata (Tangerine) Peel Extract is the extract of the peel of *Citrus reticulata.*	Skin-Conditioning Agents - Miscellaneous
Citrus Reticulata (Tangerine) Peel Powder	Citrus Reticulata (Tangerine) Peel Powder is the powder obtained from the dried, ground peel of *Citrus reticulata.*	Skin-Conditioning Agents - Miscellaneous
Citrus Shunkokan Peel Extract	Citrus Shunkokan Peel Extract is the extract of the peel of *Citrus shunkokan.*	Antioxidants
Citrus Sunki Peel Extract	Citrus Sunki Peel Extract is the extract of the peel of *Citrus sunki.*	Humectants; Skin Protectants; Skin-Conditioning Agents - Humectant
Citrus Tachibana/Reticulata Peel Powder	Citrus Tachibana/Reticulata Peel Powder is the powder obtained from the finely ground peel of a hybrid of *Citrus tachibana* and *Citrus reticulata.*	Skin-Conditioning Agents - Miscellaneous
Citrus Tangelo Peel Powder	Citrus Tangelo Peel Powder is the powder obtained from the dried, ground peel of *Citrus tangelo.*	Flavoring Agents
Citrus Tangerina (Tangerine) Peel	Citrus Tangerina (Tangerine) Peel is the peel of the tangerine, *Citrus tangerina.*	Abrasives
Citrus Tangerina (Tangerine) Peel Extract	Citrus Tangerina (Tangerine) Peel Extract is the extract of the peel of *Citrus tangerina.*	Cosmetic Astringents
Citrus Unshiu Peel Extract	Citrus Unshiu Peel Extract is the extract of the peel of *Citrus unshiu.*	Skin-Conditioning Agents - Miscellaneous
Citrus Unshiu Peel Powder	Citrus Unshiu Peel Powder is the powder of the dried, ground peel of *Citrus unshiu.*	Fragrance Ingredients
Citrus Unshiu Peel Water	Citrus Unshiu Peel Water is the aqueous solution of the steam distillates obtained from the peel of *Citrus unshiu.*	Skin Protectants

Table 2. Citrus-ingredients that potentially function solely as fragrance ingredients.

Citrus Aurantifolia (Lime) Peel Water
Citrus Jabara Peel Powder

Citrus Junos Peel Powder
Citrus Unshiu Peel Powder

Table 3. Review of *Citrus* genus species names.[4]

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)	*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)	*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. Physical and chemical properties of Citrus Aurantium Dulcis (Orange) Peel Wax.

Property	Description	Reference
	Citrus Aurantium Dulcis (Orange) Peel Wax	
Color	light reddish-brown to orange	12
Odor	mild to very low characteristic	12
Appearance	semi-solid	12
molecular weight	> 400	8
melting point	45-57 ºC refined; 35-50 ºC deodorized	12
congealing point	45-55 ºC refined; 30-45 ºC deodorized	12
acid value	8-20 refined; 10-20 deodorized	12
saponification value	70-110 refined and deodorized	12
hydroxyl value	20-50 refined; 10-40 deodorized	12
log P	> 3.5	8
UV absorbance	210-240 nm	12

Table 5. Volatile constituents from *Citrus aurantifolia* peel extract as analyzed by gas chromatography-mass spectrometry.[45]

Constituent	%
tetrahydro-2-methyl-2*H*-pyran	0.72
4-hexen-3-one	0.51
3-methyl-3-penten-2-one	0.33
3-hexen-2-one	0.48
2,3-dimethyl-2,3-butanediol	1.67
Resorcinol	3.65
p-cymene	0.36
1-methoxycyclohexene	8.00
linalool oxide	1.18
crysantenile acetate	0.40
Corylone	6.93
terpinen-4-ol	1.66
α-terpineol	5.97
3-nethyl-1,2-cyclopentanedione	8.27
3,7-dimethyl-(*Z*)-2,6-octadienal	1.09
Carvone	0.88
Geraniol	1.15
Citral	2.21
1,8-dimethyl-4-(1-methylethyl)-spiro[4.5]dec-8-en-7-one	0.56
geranyl formate	0.70
oleic acid	0.69
7-methyl-(*Z*)-8-tetradecen-1-ol acetate	2.83
geranyl acetone	1.84
Bergamotene	1.00
(*Z*)-8-methyl-9-tetradecenoic acid	1.24
trans-α-bisabolene	1.02
caryophyllene oxide	3.02
Spathulenol	1.95
Umbelliferone	4.36
(*Z*)-11(13,14-epoxy)tetradecen-1-ol acetate	0.59
trans-phytol	0.22
1-heptatriacontanol	0.42
Versalide	0.51
methyl palmitate	0.29
palmitic acid	6.89
5,7-dimethoxycoumarin	15.80
5-methoxypsoralen	1.14
linoleic acid	0.96
Tricosane	0.31
5,8-dimethoxypsoralen	6.08
Pentacosane	0.46
Tetracosanal	0.70
Octacosane	0.39
Nonacosane	0.50

Table 6. Primary chemical composition of Citrus Aurantium Dulcis (Orange) Peel Wax by percent.[12]

unsaturated monoesters, hydroxyl-monoesters, and monoesters	50-65
free fatty acids C12-C26	6-15
hydrocarbons C21- C33	8-15
sterol esters	5-18
free sterols	4-8
free alcohols	2-7
Carotenoids	0.5-2
Glycolipids	0.5-2
Phospholipids	0.5-2
Flavonoids	0.2-1
fragrance compounds, natural	0.2-0.8

Table 7. Constituents of Citrus Aurantium Dulcis (Orange) Peel Wax with color or aroma characteristics.

color compounds (carotenoids)	**aroma compounds (alcohols, aldehydes, ketones, esters, and hydrocarbons)**
Phytoene	octan-1-ol
Phytolluene	nonanal
α-carotene	linalool
β-carotene	*p*-mentha-2,8-dien-1-ol
γ-carotene	sabinol
δ-carotene	isopulegol
Lycopene	4-methylacetophenone
Cryptoxanthin	α-terpineol
hydroxy-α-carotene	ethyl ocatanoate
Cyroflevin	decanal
Rubiflavin	carveol
Rubixanthin	neral
Lutein	carvone
Canthaxanthin	pipertone
Zeaxanthin	geranial
Antheraxanthin	perillyl alcohol
Violaxanthin	α-cubebene
Luteoxanthin	hexyl hexanoate
Auroxanthin	β-elemene
β-citraurin	β-famesene
Liavoxanthin	caryophyllene
Sintaxanthin	γ-selinene
Xanthophylls	β-copaene
	δ-cadinene
	bisabolene
	valencene

Table 8. Frequency and concentration of use according to duration and type of exposure for *Citrus* peel-derived ingredients.[13,14]

	# 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) Peel Extract		**Citrus Aurantifolia (Lime) Peel Powder**		**Citrus Aurantium Amara (Bitter Orange) Peel**		**Citrus Aurantium Amara (Bitter Orange) Peel Extract[d]**	
Totals[†]	**15**	**0.0000013-1.1**	**3**	**0.06**	**NR**	**0.002-0.2**	**49**	**0.0000016-0.05**
Duration of Use								
Leave-On	13	0.0000013-1.1	2	0.06	NR	0.002-0.16	32	0.00002-0.018
Rinse Off	2	0.0001-0.006	1	NR	NR	0.002-0.2	16	0.0000016-0.05
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	1	0.002
Exposure Type								
Eye Area	NR	0.00005	NR	NR	NR	NR	2	0.00006-0.018
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	0.0002
Incidental Inhalation-Spray	6[a]; 2[b]	0.0005-0.05[a]	NR	NR	NR	NR	1; 13[a]; 10[b]	0.001-0.002; 0.002[a]
Incidental Inhalation-Powder	2[b]	NR	NR	0.06[c]	NR	0.002-0.16[c]	10[b]	0.001; 0.0001-0.005[c]
Dermal Contact	15	0.00005-1.1	3	0.06	NR	0.002-0.2	39	0.0000016-0.05
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.0000013-0.006	NR	NR	NR	0.002	10	0.00001-0.0063
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	0.00002-0.0001
Mucous Membrane	NR	0.0021	NR	NR	NR	0.2	2	0.0000016-0.0032
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Citrus Aurantium Amara (Bitter Orange) Peel Powder[d]		**Citrus Aurantium Amara (Bitter Orange) Peel Wax[d]**		**Citrus Aurantium Bergamia (Bergamot) Peel Water**		**Citrus Aurantium Dulcis (Orange) Peel Extract[e]**	
Totals[†]	**2**	**1.6**	**5**	**NR**	**NR**	**0.0001**	**56**	**0.000002-0.25**
Duration of Use								
Leave-On	NR	NR	3	NR	NR	NR	28	0.000002-0.25
Rinse Off	2	1.6	2	NR	NR	0.0001	27	0.0000025-0.14
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	1	0.0025
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	1	0.0005
Incidental Ingestion	NR	NR	3	NR	NR	NR	2	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR	14[a]; 4[b]	0.0005-0.15; 0.00001-0.0005[a]
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	4[b]	0.028; 0.000002-0.02[c]
Dermal Contact	2	1.6	1	NR	NR	NR	35	0.000002-0.25
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	1	NR	NR	0.0001	19	0.00001-0.03
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	4	NR	NR	NR	15	0.0000025-0.14
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 8. Frequency and concentration of use according to duration and type of exposure for *Citrus* peel-derived ingredients.[13,14]

	# 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 Aurantium Dulcis (Orange) Peel Powder		**Citrus Aurantium Dulcis (Orange) Peel Wax[f]**		**Citrus Aurantium Tachibana Peel Extract[g]**		**Citrus Depressa Peel Extract**	
Totals[†]	**11**	**0.4-2**	**9**	**0.5-1.9**	**8**	**0.00016-0.0032**	**NR**	**0.0014**
Duration of Use								
Leave-On	5	NR	9	0.5-1.9	7	0.0016-0.0032	NR	0.0014
Rinse Off	6	0.4-2	NR	NR	1	0.00016-0.0032	NR	0.0014
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	1	0.5-1.9	NR	NR	NR	NR
Incidental Inhalation-Spray	3[b]	NR	4[a]	NR	1[a]; 3[b]	0.0016	NR	NR
Incidental Inhalation-Powder	1; 3[b]	NR	NR	1[c]	3[b]	0.0016-0.0032[c]	NR	0.0014[c]
Dermal Contact	11	0.4-2	5	1	8	0.00016-0.0032	NR	0.0014
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	3	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	2	0.4-0.5	1	0.5-1.9	NR	0.00016	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Citrus Grandis (Grapefruit) Peel Extract[h]		**Citrus Jabara Peel Extract**		**Citrus Junos Peel Extract[i]**		**Citrus Junos Peel Powder**	
Totals[†]	**49**	**0.0000013-0.5**	**NR**	**0.0037-0.037**	**1**	**0.0012-0.036**	**NR**	**0.002**
Duration of Use								
Leave-On	38	0.0000013-0.5	NR	0.0037-0.037	1	0.036	NR	0.002
Rinse Off	11	0.0001-0.023	NR	NR	NR	0.0012	NR	0.002
Diluted for (Bath) Use	NR	0.0005	NR	NR	NR	0.0012	NR	NR
Exposure Type								
Eye Area	3	0.01-0.5	NR	NR	1	0.036	NR	NR
Incidental Ingestion	1	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	14[a]; 9[b]	0.0095-0.01; 0.0009[b]	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	9[b]	0.1; 0.0009[b]; 0.0009-0.05[c]	NR	0.037; 0.0037[c]	NR	NR	NR	0.002[c]
Dermal Contact	45	0.0002-0.5	NR	0.0037-0.037	1	0.0012-0.036	NR	0.002
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	0.0000013-0.0002	NR	NR	NR	0.0012	NR	0.002
Hair-Coloring	2	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	2	0.0005-0.015	NR	NR	NR	0.0012	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 8. Frequency and concentration of use according to duration and type of exposure for *Citrus* peel-derived ingredients.[13,14]

	# 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 Limon (Lemon) Peel[j]		**Citrus Limon (Lemon) Peel Extract**		**Citrus Limon (Lemon) Peel Powder**		**Citrus Limon (Lemon) Peel Wax**	
Totals[†]	**4**	**0.4**	**150**	**0.000005-0.14**	**6**	**0.5**	**1**	**NR**
Duration of Use								
Leave-On	3	NR	62	0.000005-0.14	4	NR	NR	NR
Rinse Off	1	0.4	87	0.000008-0.057	2	0.5	1	NR
Diluted for (Bath) Use	NR	NR	1	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	2	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	3	0.000008-0.0025	NR	NR	NR	NR
Incidental Inhalation-Spray	1[a]; 1[b]	NR	2; 22[a]; 20[b]	0.000033-0.0005; 0.000008-0.0006 [a]	1[b]	NR	NR	NR
Incidental Inhalation-Powder	1[b]	NR	20[b]	0.0001-0.14[c]	1[b]	NR	NR	NR
Dermal Contact	4	0.4	89	0.000005-0.14	5	0.5	1	NR
Deodorant (underarm)	NR	NR	1[a]	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	55	0.000033-0.0031	NR	NR	NR	NR
Hair-Coloring	NR	NR	2	NR	NR	NR	NR	NR
Nail	NR	NR	1	NR	1	NR	NR	NR
Mucous Membrane	NR	0.4	17	0.000008-0.0051	1	0.5	1	NR
Baby Products	NR	NR	1	NR	NR	NR	NR	NR

	Citrus Nobilis (Mandarin Orange) Peel Extract		**Citrus Paradisi (Grapefruit) Peel Extract**		**Citrus Reticulata (Tangerine) Peel Extract[k]**		**Citrus Tangerina (Tangerine) Peel Extract**	
Totals[†]	**19**	**0.0000005-0.05**	**61**	**NR**	**36**	**0.00029-0.01**	**2**	**0.0000048**
Duration of Use								
Leave-On	8	0.0000005-0.025	39	NR	28	0.00048-0.01	1	NR
Rinse Off	11	0.000025-0.05	21	NR	8	0.00029-0.0012	1	0.0000048
Diluted for (Bath) Use	NR	0.0005-0.0025	1	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	1	NR	5	0.002	NR	NR
Incidental Ingestion	NR	NR	3	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	4[a]; 2[b]	0.0001-0.0005	23[a]; 8[b]	NR	17[a]; 4[b]	0.00048[a]	1[a]	NR
Incidental Inhalation-Powder	2[b]	0.0025[c]	8[b]; 2[c]	NR	4[b]	0.0012-0.01[c]	NR	NR
Dermal Contact	16	0.0000005-0.025	51	NR	36	0.00029-0.01	1	NR
Deodorant (underarm)	NR	0.0005	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	3	0.0001-0.05	7	NR	NR	NR	1	0.0000048
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	7	0.0001-0.0025	12	NR	6	0.00029	NR	NR
Baby Products	NR	NR	3	NR	NR	NR	NR	NR

Table 8. Frequency and concentration of use according to duration and type of exposure for *Citrus* peel-derived ingredients.[13,14]

	# 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 Unshiu Peel Extract[l]		**Citrus Unshiu Peel Powder**		**Orange Peel[m]**			
Totals[†]	**46**	**0.000002-0.094**	**NR**	**0.5**	**13**	**NS**		
Duration of Use								
Leave-On	31	0.00005-0.094	NR	NR	5	NS		
Rinse Off	14	0.000002-0.094	NR	NR	5	NS		
Diluted for (Bath) Use	1	0.03	NR	0.5	3	NS		
Exposure Type								
Eye Area	4	0.000002-0.002	NR	NR	NR	NS		
Incidental Ingestion	NR	0.00036	NR	NR	NR	NS		
Incidental Inhalation-Spray	9[a]; 15[b]	0.002	NR	NR	1[b]	NS		
Incidental Inhalation-Powder	15[b]	0.01; 0.0005-0.094[c]	NR	NR	1[b]	NS		
Dermal Contact	40	0.000002-0.094	NR	0.5	13	NS		
Deodorant (underarm)	NR	NR	NR	NR	NR	NS		
Hair - Non-Coloring	6	NR	NR	NR	NR	NS		
Hair-Coloring	NR	NR	NR	NR	NR	NS		
Nail	NR	NR	NR	NR	NR	NS		
Mucous Membrane	2	0.00036-0.03	NR	0.5	6	NS		
Baby Products	NR	NR	NR	NR	NR	NS		

NR = Not reported. NS = Not surveyed.

† 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) in the VCRP database.

[e.] Includes uses listed under Citrus Sinensis (Sweet Orange) Peel Extract in the VCRP database.

[f.] Listed as Citrus Sinensis (Sweet Orange) Peel Wax and Orange Peel Wax in the VCRP database.

[g.] Listed as Citrus Tachibana (Tachibana Orange) Peel Extract and Citrus Tachibana Peel Extract in the VCRP database.

[h.] Listed as Citrus Grandis (Pomelo) Peel Extract in the VCRP database.

[i.] Listed as Citrus Junos (Xiaang Cheng) Peel Extract in the VCRP database.

[j.] Listed as Lemon Peel in the VCRP database.

[k] Listed as Citrus Reticulata (Mandarin Orange) Peel Extract in the VCRP database.

[l.] Listed as Citrus Unshiu (Satsuma Orange) Peel Extract in the VCRP database.

[m.] Not in the INCI dictionary; included because of similarity.

Table 9. Ingredients that are not reported to be in use.

Citrus Aurantifolia (Lime) Peel
Citrus Aurantifolia (Lime) Peel Water
Citrus Aurantium Sinensis Peel Extract
Citrus Depressa Peel Powder
Citrus Grandis (Grapefruit) Peel
Citrus Grandis (Grapefruit) Peel Powder
Citrus Hassaku/Natsudaidai Peel Powder
Citrus Iyo Peel Extract
Citrus Iyo Peel Water
Citrus Jabara Peel Powder
Citrus Jabara Peel Water
Citrus Junos Peel Water
Citrus Limon (Lemon) Peel Water
Citrus Natsudaidai Peel Extract
Citrus Nobilis (Mandarin Orange) Peel Powder
Citrus Reticulata (Tangerine) Peel Powder
Citrus Shunkokan Peel Extract
Citrus Sunki Peel Extract
Citrus Tachibana/Reticulata Peel Powder
Citrus Tangelo Peel Powder
Citrus Tangerina (Tangerine) Peel
Citrus Unshiu Peel Water

Table 10. Dermal irritation studies for *Citrus* peel-derived ingredients.

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
In Vitro					
Citrus Aurantium Dulcis (Orange) Peel Wax	100%	details not provided	MATEX in vitro toxicity testing system; details not provided	no irritation	[8,12]
Citrus Reticulata (Tangerine) Peel Extract	3.0% in formulation	human reconstructed epidermis	SkinEthic model according to OECD 439; no further details provided	no irritation	[26]
Animal					
Citrus Aurantium Amara (Bitter Orange) Peel Extract	10% and 100% undiluted solutions	3 rabbits; details not provided	primary skin irritation test; details not provided	no irritation	[6]
Citrus Aurantium Amara (Bitter Orange) Peel Extract	2.0% in formulation, undiluted	3 guinea pigs; details not provided	primary skin irritation test on clipped skin; no further details provided	no irritation observed at 24, 48, or 72 h post-dosing	[29]
Citrus Aurantium Amara (Bitter Orange) Peel Extract	2.0% in formulation, in 50% water solution	3 guinea pigs; details not provided	cumulative skin irritation test on clipped skin; animals dosed once a day for 2 weeks; animals observed daily	no irritation	[29]
Human					
Citrus Aurantium Amara (Bitter Orange) Peel Extract	1.55% in formulation, in 20% water solution	30 subjects	48 h patch test; occluded	slight erythema in 1 subject 1 h post-patch removal, no irritation observed 24 h post-patch removal	[28]
Citrus Aurantium Dulcis (Orange) Peel Wax	100%	details not provided	48 h patch test; details not provided	no irritation	[8,12]
Citrus Limon (Lemon) Peel Extract	0.1% in a moisturizer	30 subjects	14 day cumulative irritation patch test; 14 applications of ~23 h over 15 days; control materials distilled water and sodium lauryl sulfate; test area was 2 cm^2 and semi-occluded; 0.2 ml test material applied to each patch	no irritation	[30]
Citrus Reticulata (Tangerine) Peel Extract	3.06% in formulation	30 subjects	48 h patch test; occluded	slight erythema observed in 2 subjects and well-defined erythema observed in 1 subject 1 h post-patch removal; no irritation observed 24 h post-patch removal	[27]
Citrus Unshiu Peel Extract	0.5% in formulation	10 subjects	24 h single patch test; details not provided	no irritation	[31]

Table 11. Dermal sensitization studies for *Citrus* peel-derived ingredients.

Test Article	Concentration/Dose	Test Population	Procedure	Results	References
			Animal		
Citrus Aurantium Amara (Bitter Orange) Peel Extract	2.0% in formulation; undiluted	12 guinea pigs; no further details	sensitization study with adjuvant on clipped skin; occluded; no further details	no dermal sensitization	[29]
			Human		
Citrus Aurantifolia (Lime) Peel Extract	2.14% in a face and neck product	109 subjects	modified HRIPT; test area was 2 cm^2 and semi-occluded; 150µl test material applied to each patch	no dermal irritation or sensitization	[34]
Citrus Aurantium Dulcis (Orange) Peel Wax	1.9% in a lipstick	33 sensitive skin subjects	4-week use test	no dermal irritation or sensitization	[36]
Citrus Aurantium Dulcis (Orange) Peel Wax	1.9% in a lipstick; undiluted	105 subjects	HRIPT; details not provided	no dermal irritation or sensitization	[37]
Citrus Grandis (Grapefruit) Peel Extract	0.1% in a face and neck product	209 subjects	modified HRIPT; test area was 2 cm^2 and semi-occluded; 200µl test material applied to each patch	no dermal irritation or sensitization	[33]
Citrus Grandis (Grapefruit) Peel Extract	0.5% in an eye product	55 subjects	HRIPT; details not provided	no dermal irritation or sensitization	[35]
Citrus Reticulata (Tangerine) Peel Extract	no provided	54 subjects	HRIPT; details not provided	no dermal irritation or sensitization	[9]
Citrus Reticulata (Tangerine) Peel Extract	3.0% in formulation; undiluted	56 subjects	HRIPT; semi-occluded; no further details	hypoallergenic	[26]
Citrus Unshiu Peel Extract	0.5%	50 subjects	HRIPT (Marzulli and Maibach method); occlusive patch; no further details	no dermal irritation or sensitization	[38]
Citrus Unshiu Peel Extract	10%	49 subjects	HRIPT; details not provided	no dermal irritation or sensitization	[6]
Citrus Unshiu Peel Extract	100% undiluted	54 subjects	HRIPT; details not provided	no dermal irritation or sensitization	[6]

Table 12. Photosensitization and phototoxicity studies.

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			In-Vitro		
Citrus Reticulata (Tangerine) Peel Extract	3.0% in formulation	mouse fibroblasts	in vitro 3T3 NRU phototoxicity test according to OECD 432	no photo irritation	26
			Animal		
Citrus Aurantium Amara (Bitter Orange) Peel Extract	2.0% in formulation; undiluted	5 guinea pigs; no further details	phototoxicity study on clipped skin; no further details	no photo irritation	29
Citrus Aurantium Amara (Bitter Orange) Peel Extract	2.0% in formulation; undiluted	10 guinea pigs; no further details	photosensitization study with adjuvant on clipped skin; no further details	no photo sensitization	29
lemon fruit juice and lemon peel juice (Tahitian and Sicilian varieties)	undiluted; liberally applied	3 adult rats (strain not specified) per group	-rats were painted with fresh lemon fruit juice or lemon peel juice from 2 lemon varieties on depilated skin on the right back; left side was negative control with only sunlight exposure -rats were placed in plastic tubes with eight orifices to allow natural sunlight through - exposure to sunlight was 2.5, 5 , 7.5, or 10 min -experiment repeated with Tahitian variety lemon peel juice with sun block SPF 45, UVA and UVB -biopsies performed for each time period for histopathological studies and photodocumentation	-phytophotodermatitis observed after 48 h after exposure to both types of peel juice -no reactions observed to peel juice without sun exposure or to sun exposure alone -minimum exposure time of 2.5 min sufficient to induce phototoxic reaction, with longer exposures causes more intense reactions -histopathological studies showed epithelial time-dependent vacuolar degeneration -sunblock diminished reaction intensity, but did not prevent it	39
lemon peel juice (Tahitian variety)	undiluted; liberally applied	4 albino rats	-epilated right half of back of rats was sprayed with peel juice -one quadrant exposed to natural sunlight for 5 min and the other for 8 min; -left back served as control -biopsies taken after 1, 2, 3, 4, 5, 6, 24, 48, and 72 h from both sides	-normal epidermis observed for first 6 time intervals on both sides -after 24 h, treated area showed keratinocyte necrosis, cytoplasmic vacuolization and spongiosis in all rats, independent of exposure time -after 48 h, erythema evident, strong vacuolization observed that progressed to sub- or intraepidermal blisters -erythema persisted after 72 h at a lesser intensity -control side has isolated keratinocyte necrosis with only 8 min of exposure after 24 h, but after 48 h only slight spongiosis was observed which resolved by 72 h	40
lemon peel juice (Tahitian variety)	undiluted	4 adult rats (strain not specified)	-test material was applied to depilated skin on the right side of the animal's back, left side served as a control -animals exposed for 8 min to mid-day sunlight -biopsies performed immediately after induction and after 1 and 2 h and evaluated by transmission electron microscopy -at 24 and 48 h after induction, light microscopy performed on tissues to evaluate changes	-no histological changes observed on control sites -immediately after induction, keratinocyte cytoplasmatic vacuolization and membrane ruptures near vacuolization sties were observed -at 1 h after, desmosomal changes observed in addition to vacuolization, keratin filaments were not attached to desmosomal plaques, and free desmosomes and membrane ruptures were observed -at 2 h after, similar changes were observed in addition to granular degeneration of keratin	41

Table 12. Photosensitization and phototoxicity studies.

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			Human		
Citrus Aurantium Dulcis (Orange) Peel wax	100% undiluted	11 subjects, fair skinned with skin types I-III	- 2 sites treated with 0.2 ml of the test material and 1 site was untreated; patches were occluded and applied to the back - 24 h after dosing, subjects were exposed to sunlight for 5-10 min, a Solar UV Simulator® with a 150 watt xenon arc lamp (UVA and UVB 290-400 nm) with a Schott WG 345 to filter out UVB (290-320 nm) so that only UVA was delivered (320-400 nm). - test sites were examined 15 min, 24 h, and 48 h after irradiation	no phototoxic response was observed	43
sweet orange peel, mesocarp, and fruit; alcohol extractions of all 3	undiluted	3 subjects with type I skin and 1 subject with type II skin	-in duplicate Finn Chambers, peel, mesocarp, or fruit were applied directly to skin or as alcohol extract solutions (0.2 g/0.2 ml) at 20 µl on paper discs -closed patches were 1 h in duration - 48 h after dosing, subjects were exposed to sunlight for 30 min, a Phillips blacklight TL 20W/09 (320-440 nm) that delivered a total dose of 2.5 J/cm^2 - test sites were examined 8, 24, 48, 72, and 96 h after irradiation	-strong erythema (++) observed in 2 subjects with type 1 skin and strong erythema and infiltration (+++) observed in 1 subject with type I skin after48 h after irradiation and exposure to pure peel and peel extract -slight erythema observed in all 3 type I subjects after exposure to pure peel and peel extract with no sun exposure after 48 h -no reactions observed to mesocarp or fruit, either pure or extract -no reactions induced in the type II skin subject	42

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