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

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date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a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

The 2015 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Christina Burnett, Senior Scientific Analyst/Writer.

Cosmetic Ingredient Review
1620 L Street NW, Suite 1200 ◇ Washington, DC 20036-4702 ◇ ph 202.331.0651 ◇ fax 202.331.0088 ◇
cirinfo@cir-safety.org

ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of 80 *Citrus* fruit-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. Industry should use good manufacturing practices to limit impurities that could be present in botanical ingredients. The Panel concluded that these 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).

INTRODUCTION

Citrus fruit-derived ingredients are widely used in cosmetics, and are most frequently reported to function in cosmetics as fragrances and/or skin conditioning agents (Table 1). This report assesses the safety of the following 80 *Citrus* fruit-derived ingredients:

citrus aurantifolia (lime)/citrus limon (lemon) fruit water
citrus aurantifolia (lime) fruit
citrus aurantifolia (lime) fruit extract
citrus aurantifolia (lime) fruit water
citrus aurantifolia (lime) juice
citrus aurantium amara (bitter orange) fruit extract
citrus aurantium amara (bitter orange) fruit juice extract
citrus aurantium bergamia (bergamot) fruit extract
citrus aurantium bergamia (bergamot) fruit water
citrus aurantium dulcis (orange) fruit extract
citrus aurantium dulcis (orange) fruit powder
citrus aurantium dulcis (orange) fruit water
citrus aurantium dulcis (orange) juice
citrus aurantium sinensis (orange) fiber
citrus clementina fruit extract
citrus clementina juice
citrus depressa fruit extract
citrus depressa fruit water
citrus glauca fruit extract
citrus grandis (grapefruit) fruit extract
citrus grandis (grapefruit) fruit/peel water
citrus grandis (grapefruit) fruit water
citrus grandis (grapefruit) juice
citrus grandis/paradisi fruit water
citrus hassaku fruit extract
citrus hassaku/natsudaidai fruit juice
citrus hassaku/natsudaidai fruit powder
citrus iyo fruit extract
citrus iyo fruit water
citrus jabara juice
citrus japonica fruit extract
citrus junos fruit extract
citrus junos fruit juice
citrus junos fruit oil
citrus junos fruit powder
citrus junos fruit water
citrus limon (lemon) fruit extract
citrus limon (lemon) fruit oil
citrus limon (lemon) fruit powder
citrus limon (lemon) fruit water
citrus limon (lemon) juice
citrus limon (lemon) juice extract
citrus limon (lemon) juice powder
citrus madurensis fruit extract
citrus madurensis fruit juice
citrus medica vulgaris fruit extract
citrus nobilis (mandarin orange) fruit extract
citrus nobilis (mandarin orange) fruit juice
citrus paradisi (grapefruit) fruit extract
citrus paradisi (grapefruit) fruit water
citrus paradisi (grapefruit) juice
citrus reticulata (tangerine) fruit
citrus reticulata (tangerine) fruit extract
citrus reticulata (tangerine) fruit water
citrus shunkokan fruit extract
citrus sinensis (orange) fruit extract
citrus sinensis (orange) fruit water
citrus sphaerocarpa fruit juice
citrus sudachi fruit extract
citrus sudachi fruit juice
citrus tachibana/reticulata fruit juice
citrus tamurana fruit extract
citrus tangelo fruit juice
citrus tangelo fruit powder
citrus tangerina (tangerine) fruit
citrus tangerina (tangerine) fruit water
citrus tankan fruit extract
citrus tankan fruit water
citrus unshiu/citrus reticulata/citrus iyo fruit water

citrus unshiu fruit extract
citrus unshiu fruit juice
citrus unshiu fruit juice ferment extract filtrate
citrus unshiu fruit oil
citrus unshiu fruit powder
citrus unshiu fruit water
citrus unshiu/sinensis/reticulata fruit extract
defatted citrus unshiu fruit
hydrolyzed citrus aurantium dulcis fruit extract
microcitrus australasica fruit extract
microcitrus australis fruit extract

The genus species names associated with the ingredient names designated by the International Nomenclature of Cosmetic Ingredients (INCI) Committee are listed in Table 2. For example, cosmetic ingredients with "citrus nobilis" (commonly known as mandarin orange) in the name are derived from the plant with the genus species name *Citrus reticulata*.[1]

The Panel has reviewed previously the safety of *Citrus*-derived peel oils and concluded that 14 *Citrus*-derived peel oil 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]

The *Citrus* fruits that are used to derive the ingredients described in this safety assessment are used as food and are considered generally recognized as safe (GRAS). Additionally, essential oils, oleoresins (solvent-free), and natural extracts (including distillates) derived from some *Citrus* fruits 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. Thus, the systemic toxicity potential of *Citrus* fruit-derived ingredients via oral exposure is not addressed further in this report. The primary focus of the safety assessment is the review of safety based on topical exposure.

The CIR does not review ingredients that function only as fragrance ingredients because, as fragrances, the safety of these ingredients falls under the purview of the Research Institute for Fragrance Materials (RIFM). Four of the *Citrus*-derived fruit ingredients in this report function only as fragrance ingredients, according to the *International Cosmetic Ingredient Dictionary and Handbook* (see Table 3).[4] However, according to personal communications with RIFM in March 2015, these ingredients were not included in their review process, thus CIR is reviewing the safety of these ingredients.

Botanicals, such as *Citrus* ingredients, contain 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* fruits. In this assessment, CIR is reviewing the potential toxicity of each *Citrus* fruit-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* fruits 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. lemon juice). If the substance is clearly a cosmetic ingredient, the INCI name will be used (e.g. "citrus limon (lemon) juice"). 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 *International Cosmetic Ingredient Dictionary and Handbook.*[4] In contrast, most of the published literature and Food and Drug Administration's 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.

CHEMISTRY

The definitions and functions of the *Citrus* fruit-derived ingredients included in this report are provided in Table 1. In some cases, the definition provides insight on the method(s) of manufacture. It should be noted that the term "water" in *Citrus* waters refers to the water soluble fraction of the condensate from steam distillation of the plant parts of interest. Essential oils are the hydrophobic, liquid, volatile aroma compounds in the insoluble condensate fraction. The essential oils are typically small molecules, but their chemical structures can vary rather 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 necessitate that fragrance is their only function.

Chemical and Physical Properties

The available chemical and physical properties of some *Citrus* fruit extracts sold to the cosmetics industry are found in Table 4.

Method of Manufacturing

Figure 1 is a generic representation of the method of manufacturing for *Citrus* fruit waters. Figures 2 and 3 are the manufacturing flow charts provided by suppliers of citrus nobilis (mandarin orange) fruit extract and citrus grandis (grapefruit) fruit extract.

A supplier reports that hydrolyzed citrus aurantium dulcis (orange) fruit is produced by solubilization of *Citrus aurantium dulcis* fruit in water, followed by enzymatic hydrolysis, separation of soluble and insoluble phases, filtration, and sterilizing filtration.[5] Another supplier reports that citrus junos fruit extract is produced by extracting the dried raw fruit with 50% vol. ethanolic solution, filtering, allowing sedimentation before adjusting the product and packaging.[6]

Constituents/Composition

The *Citrus* fruit-derived ingredients are complex botanicals composed of numerous constituents; there is great variation among *Citrus* species and cultivars because of frequent bud mutations, interspecific and intergeneric hybridization, and apoximis (i.e., one or more of several types of asexual reproduction).[7] The composition of *Citrus* fruits will vary based on the location where the plant is grown, the maturity of the plant, and storage conditions.[8] The method of extraction will also affect the compositions of the ingredients. Table 5 lists *Citrus* constituents that are established contact allergens, according to the European Commission's Scientific Committee on Consumer Safety (SCCS). Table 6 describes the cosmetics allergens certificates for some *Citrus* fruit waters and fruit extracts. Table 7 presents the constituents, composition, and impurities of some *Citrus* fruit extract products. Table 8 describes general constituent data on *Citrus* fruit (non-cosmetic grade).

USE

Cosmetic

The safety of these cosmetic ingredients is evaluated on the basis of the expected use in cosmetics. The Panel utilizes data received from the FDA and the cosmetics industry in determining the expected cosmetic use. The data received from the FDA are those it collects from manufacturers on the use of individual ingredients in cosmetics by cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP), and those from the cosmetic industry are submitted in response to a survey of the maximum reported use concentrations by category conducted by the Personal Care Products Council (Council).

According to the 2015 VCRP data, citrus limon (lemon) fruit extract has the most reported uses of the ingredients in this report in cosmetic products, with a total of 571; more than half of the uses are in leave-on skin care preparations (Table 9).[9] Citrus aurantium amara (bitter orange) fruit extract has the second greatest number of overall uses reported, with a total of 295; more than half of those uses also are in leave-on skin care preparations. The results of the concentration of use survey conducted in 2013 by the Council indicate citrus aurantium dulcis (orange) fruit water has the highest reported maximum concentration of use; it is used at up to 19% in paste masks and mud packs.[10] Citrus grandis (grapefruit) fruit extract had the second highest reported maximum concentration of uses; it is used at up to 15% in face and neck products. Most of the use concentrations that were reported for the other *Citrus* fruit ingredients were much lower than these two ingredients.

In some cases, reports of uses were received from the VCRP, but no concentration of use data were provided. For example, citrus medica vulgaris fruit extract is reported to be used in 11 formulations, but no use concentration data were available. In other cases, no reported uses were reported to the VCRP, but a maximum use concentration was provided in the industry survey. For example, citrus japonica fruit extract was not reported in the VCRP database to be in use, but the industry survey indicated that it is used in non-coloring hair conditioners at up to 0.0038%. It should be presumed that citrus japonica fruit extract is used in at least one cosmetic formulation.

Table 10 lists all *Citrus* fruit-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 limon (lemon) fruit extract is used at 0.03% in lipstick and citrus aurantifolia (lime) fruit extract is used at 0.2% in personal cleanliness products. Additionally, some of these ingredients were reported to be used in hair sprays and body and hand sprays and could possibly be inhaled. For example, citrus nobilis (mandarin orange) fruit extract was reported to be used in body and hand sprays at a maximum concentration of 0.0075%. 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.[11-14] 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.[12,13]

Under the rules governing cosmetic products in the European Union, *Citrus*-derived ingredients must have a furocoumarin content below 1 mg/kg in sun-protection products and in bronzing products.[15] The International Fragrance Association (IFRA) has issued standards for *Citrus* oils and other furocoumarin-containing essential oils.[16] 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 level 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 levels should be reduced accordingly.

An IFRA standard also has been issued for 7-methoxycoumarin, which is prohibited for use in fragrance compounds.[17] 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 Citrus fruits that are used to derive the ingredients described in this safety assessment are used as food. Per 21CFR§170.30(c)(1) and (2) and §170.30(c):

> "… food ingredients of natural biological origin that has been widely consumed for its nutrient properties in the United States prior to January 1, 1958, without known detrimental effects, which is subject only to conventional processing as practiced prior to January 1, 1958, and for which no known safety hazard exists, will ordinarily be regarded as generally recognized as safe (GRAS) without specific inclusion in 21CFR§182, §184, or §186.1."
>
> Further…"A substance used in food prior to January 1, 1958, may be GRAS through experience based on its common use in food when that use occurred exclusively or primarily outside of the United States if the information about the experience establishes that the use of the substance is safe within the meaning of the act (see §170.3(i)). Common use in food prior to January 1, 1958, that occurred outside of the United States shall be documented by published or other information and shall be corroborated by information from a second, independent source that confirms the history and circumstances of use of the substance. The information used to document and to corroborate the history and circumstances of use of the substance must be generally available; that is, it must be widely available in the country in which the history of use has occurred and readily available to interested qualified experts in this country. Persons claiming GRAS status for a substance based on its common use in food outside of the United States should obtain U.S. Food and Drug Administration concurrence that the use of the substance is GRAS."

The essential oils, oleoresins (solvent-free), and natural extractives (including distillates) derived from the following *Citrus* fruits 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) (21CFR§182.20). These essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of these *Citrus* fruits are GRAS for their intended use in animal drugs, feeds, and related products (21CFR§582.20).

Essential (or volatile) oils of limes, lemons, grapefruits, bitter oranges, oranges, and tangerines are described as flavoring agents in the *Food Chemicals Codex*, a compendium of internationally recognized standards published by the United States Pharmacopeia (USP) for the purity and identity of food ingredients.[3]

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.[18]

TOXICOLOGICAL STUDIES

As noted earlier, the *Citrus* ingredients in this assessment are found in foods, and daily exposures from food use would result in a much larger systemic exposure than those from use in cosmetic products. Essential oils, oleoresins (solvent-free), and natural extracts (including distillates) derived from some *Citrus* fruits are GRAS for their intended use in foods for human and animal consumption according to the FDA. Volatile oils of limes, lemons, grapefruits, bitter oranges, oranges, and tangerines are described as flavoring agents in the USP *Food Chemicals Codex*. Because the safety of these ingredients has been established for foods, and the systemic exposure from foods would be much greater than exposure from use of these ingredients in cosmetics, the systemic toxicity potential of these ingredients is not addressed further in this report. The primary focus of this safety assessment is on the potential for irritation and sensitization from topical exposure to these *Citrus* ingredients as used in cosmetic products.

GENOTOXICITY

In Vitro

Citrus nobilis (mandarin orange) fruit extract in dimethyl sulfoxide was analyzed for mutagenic potential in an Ames assay using *Salmonella typhimurium* strains TA97a, TA98, TA100, TA102, and TA1535, with and without S9

metabolic activation.[19] Concentrations tested were 0.05, 0.1, 0.5, 1.0, and 5.0 mg/plate. Positive and negative controls yielded expected results. No sign of mutagenicity was observed with or without S9. The test material was cytotoxic at 5.0 mg/plate. It was concluded that citrus nobilis (mandarin orange) fruit extract was not mutagenic, with or without metabolic activation.

Citrus junos fruit extract (1.2% w/v; ethanol extract) was not mutagenic in an Ames assay using *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 and *Escherichia coli* strain WP2uvrA.[6] No further details were provided.

IRRITATION AND SENSITIZATION

Ocular Irritation

Citrus grandis (grapefruit) fruit extract (100% in powder form) was not a ocular irritant in an EpiOcular eye irritation test.[20] Citrus nobilis (mandarin orange) fruit extract was not an ocular irritant when tested up to 100% in a hen egg chorioallantoic membrane assay (HET-CAM).[21] Undiluted citrus sinensis (orange) fruit water (0.3 g) also was not an ocular irritant in a HET-CAM assay.[22] Hydrolyzed citrus aurantium dulcis (orange) fruit extract (8.5%) was slightly irritating when tested in 3 New Zealand rabbit eyes according to the method 405 of the Organisation for Economic Co-operation and Development (OECD).[5]

Dermal Irritation and Sensitization

Dermal irritation and sensitization studies are presented in Table 11. Citrus grandis (grapefruit) fruit extract (100% in powder form) was not a dermal irritant in an vitro study.[20] Citrus junos fruit extract (1.2%) was not irritating in a human irritation study.[6] Citrus junos fruit extract (1.2%) and hydrolyzed citrus aurantium dulcis (orange) fruit extract (8.5%) were not dermal irritants or dermal sensitizers in rabbit and guinea pig studies, respectively.[5,6] Fruit extracts of citrus aurantium bergamia (bergamot) (0.081525% in a lotion), citrus aurantium dulcis (orange) (1.2% in a night moisturizer), citrus limon (lemon) (1.2% in a night moisturizer), citrus nobilis (mandarin orange) (1%), and citrus grandis (grapefruit) (0.16% in a toner) and fruit waters of citrus aurantium dulcis (orange) (38% in an eye gel) and citrus limon (lemon) (1% in a skin cleansing product) were not sensitizing in human repeat insult patch tests (HRIPTs).[23-28]

Phototoxicity and Photosensitization

Phototoxicity and photosensitization studies are presented in Table 12. Phytophotodermatitis was observed in rats following exposure to undiluted lemon fruit juice.[29] No reactions were observed in human patients exposed to undiluted pure, or extracts of, orange mesocarp or fruit.[30]

Case Reports

Case reports describing reactions to *Citrus*-derived ingredients are summarized in Table 13. Phytophotodermatitis was noted in numerous patients exposed to the juices of lemons and limes.[31-43]

SUMMARY

The 80 *Citrus* fruit-derived ingredients described in this report function primarily as skin conditioning agents-miscellaneous and fragrance. Botanicals such as *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, photo-toxic furanocoumarin (psoralen) in *Citrus* fruits. Presently, CIR reviewed the information available on the potential toxicity of each *Citrus* fruit-derived ingredient as a whole, complex substance; CIR did not review the potential toxicity information on the individual constituents of which the *Citrus* fruit-derived ingredients are comprised.

Citrus limon (lemon) fruit extract has the most reported uses in cosmetic products, with a total of 571; more than half of the uses are in leave-on skin care preparations. The maximum use concentration range for citrus limon (lemon) fruit extract is 0.0001% to 1.2%, with 1.2% reported in night skin care products. Citrus aurantium amara (bitter orange) fruit extract has the second greatest number of overall uses reported, with a total of 295 more than half of those uses are in leave-on skin care preparations. Citrus aurantium amara (bitter orange) fruit extract had a maximum use concentration range of 0.00002% to 0.002%, with 0.002% reported in lipstick and eye makeup preparations. Most of the other use concentrations that were reported had similar ranges. However, maximum use concentrations as high as 19% were reported for citrus aurantium dulcis (orange) fruit water in paste masks and mud packs and as high as 15% for citrus grandis (grapefruit) fruit extract in face and neck products.

Under the rules governing cosmetic products in the European Union, *Citrus*-derived ingredients must have furocoumarin content below 1 mg/kg in sun-protection and bronzing products. 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 such oils are used in combination with other

phototoxic ingredients, the potential additive effect should be taken into consideration and use levels should be reduced accordingly.

The *Citrus* fruit-derived ingredients in this assessment are found in foods, and the daily exposure from food use would result in a much larger systemic dose than that resulting from use in cosmetic products. Essential oils, oleoresins (solvent-free), and natural extractives (including distillates) derived from some *Citrus* fruits are GRAS for their intended use in foods for human and animal consumption according to the FDA.

Citrus grandis (grapefruit) fruit extract (100% in powder form) and citrus nobilis (mandarin orange) fruit extract (up to 100%) were not ocular irritants in in vitro studies.

Citrus grandis (grapefruit) fruit extract (100% in powder form) was not a dermal irritant in an vitro study. Fruit extracts of citrus aurantium bergamia (bergamot) (0.081525%), citrus aurantium dulcis (orange) (1.2%), citrus limon (lemon) (1.2%), citrus nobilis (mandarin orange) (1%), and citrus grandis (grapefruit) (0.16%) and fruit waters of citrus aurantium dulcis (orange) (38%) and citrus limon (lemon) (1%) were not sensitizing in HRIPTs.

Phytophotodermatitis was observed in rats following exposure to undiluted lemon fruit juice. No reactions were observed in human patients exposed to 0.081525% citrus aurantium bergamia (bergamot) fruit extract or undiluted pure or extracts of orange mesocarp or fruit. Phytophotodermatitis was noted in numerous patients exposed to the juices of lemons or limes.

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* fruits 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 skin irritation and sensitization from topical exposures to the *Citrus* ingredients.

The Panel expressed concern about the potential for constituents in *Citrus* fruit-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.

The Panel noted that, because botanical ingredients are complex mixtures, there is concern that multiple botanical ingredients may each contribute to the final concentration of a single constituent. Therefore, when formulating products, manufacturers should avoid reaching levels in final formulation of botanical constituents that may cause sensitization or other adverse effects. Specific examples of constituents that could induce adverse effects are limonene, citral and other monoterpenes, and furocoumarins (such as 5- MOP and 7-methoxycoumarin).

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 activity may have been caused by repeated skin irritation and resultant proliferation of DMBA-treated basal cells, the Panel concluded that *Citrus*-derived peel oils could potentially act as tumor-promoters if formulated to reach irritant levels. While no skin irritation was reported following the use of *Citrus* fruit derived ingredients, the Panel felt that these botanical ingredients must be formulated to be non-irritating.

The Panel discussed the issue of incidental inhalation exposure from hair sprays and body and hand sprays. There were no inhalation toxicity data available. The Panel considered pertinent data indicating that incidental inhalation exposures to *Citrus* ingredients in such cosmetic products would not cause adverse health effects, including data characterizing the potential for *Citrus* ingredients to cause ocular or dermal irritation or sensitization. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols 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 *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).

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citrus aurantifolia (lime) juice
citrus aurantium amara (bitter orange) fruit extract
citrus aurantium amara (bitter orange) fruit juice extract*
citrus aurantium bergamia (bergamot) fruit extract
citrus aurantium bergamia (bergamot) fruit water*
citrus aurantium dulcis (orange) fruit extract
citrus aurantium dulcis (orange) fruit powder*
citrus aurantium dulcis (orange) fruit water
citrus aurantium dulcis (orange) juice
citrus aurantium sinensis (orange) fiber
citrus clementina fruit extract*
citrus clementina juice*
citrus depressa fruit extract*
citrus depressa fruit water*
citrus glauca fruit extract
citrus grandis (grapefruit) fruit extract
citrus grandis (grapefruit) fruit/peel water
citrus grandis (grapefruit) fruit water
citrus grandis (grapefruit) juice
citrus grandis/paradisi fruit water*
citrus hassaku fruit extract*
citrus hassaku/natsudaidai fruit juice*
citrus hassaku/natsudaidai fruit powder*
citrus iyo fruit extract*
citrus iyo fruit water*
citrus jabara juice*
citrus japonica fruit extract
citrus junos fruit extract
citrus junos fruit juice*
citrus junos fruit oil*
citrus junos fruit powder*
citrus junos fruit water*
citrus limon (lemon) fruit extract
citrus limon (lemon) fruit oil*
citrus limon (lemon) fruit powder*
citrus limon (lemon) fruit water
citrus limon (lemon) juice
citrus limon (lemon) juice extract
citrus limon (lemon) juice powder*
citrus madurensis fruit extract
citrus madurensis fruit juice*
citrus medica vulgaris fruit extract
citrus nobilis (mandarin orange) fruit extract
citrus nobilis (mandarin orange) fruit juice
citrus paradisi (grapefruit) fruit extract
citrus paradisi (grapefruit) fruit water*
citrus paradisi (grapefruit) juice*
citrus reticulata (tangerine) fruit*
citrus reticulata (tangerine) fruit extract
citrus reticulata (tangerine) fruit water*
citrus shunkokan fruit extract*
citrus sinensis (orange) fruit extract
citrus sinensis (orange) fruit water
citrus sphaerocarpa fruit juice*
citrus sudachi fruit extract*
citrus sudachi fruit juice*
citrus tachibana/reticulata fruit juice*
citrus tamurana fruit extract*
citrus tangelo fruit juice*
citrus tangelo fruit powder*
citrus tangerina (tangerine) fruit*
citrus tangerina (tangerine) fruit water*
citrus tankan fruit extract*
citrus tankan fruit water*
citrus unshiu/citrus reticulata/citrus iyo fruit water*
citrus unshiu fruit extract*
citrus unshiu fruit juice*
citrus unshiu fruit juice ferment extract filtrate
citrus unshiu fruit oil*
citrus unshiu fruit powder*
citrus unshiu fruit water*
citrus unshiu/sinensis/reticulata fruit extract*
defatted citrus unshiu fruit*
hydrolyzed citrus aurantium dulcis fruit extract
microcitrus australasica fruit extract*
microcitrus australis fruit 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.

FIGURES

Figure 1. Method of manufacturing of fruit waters.[44]

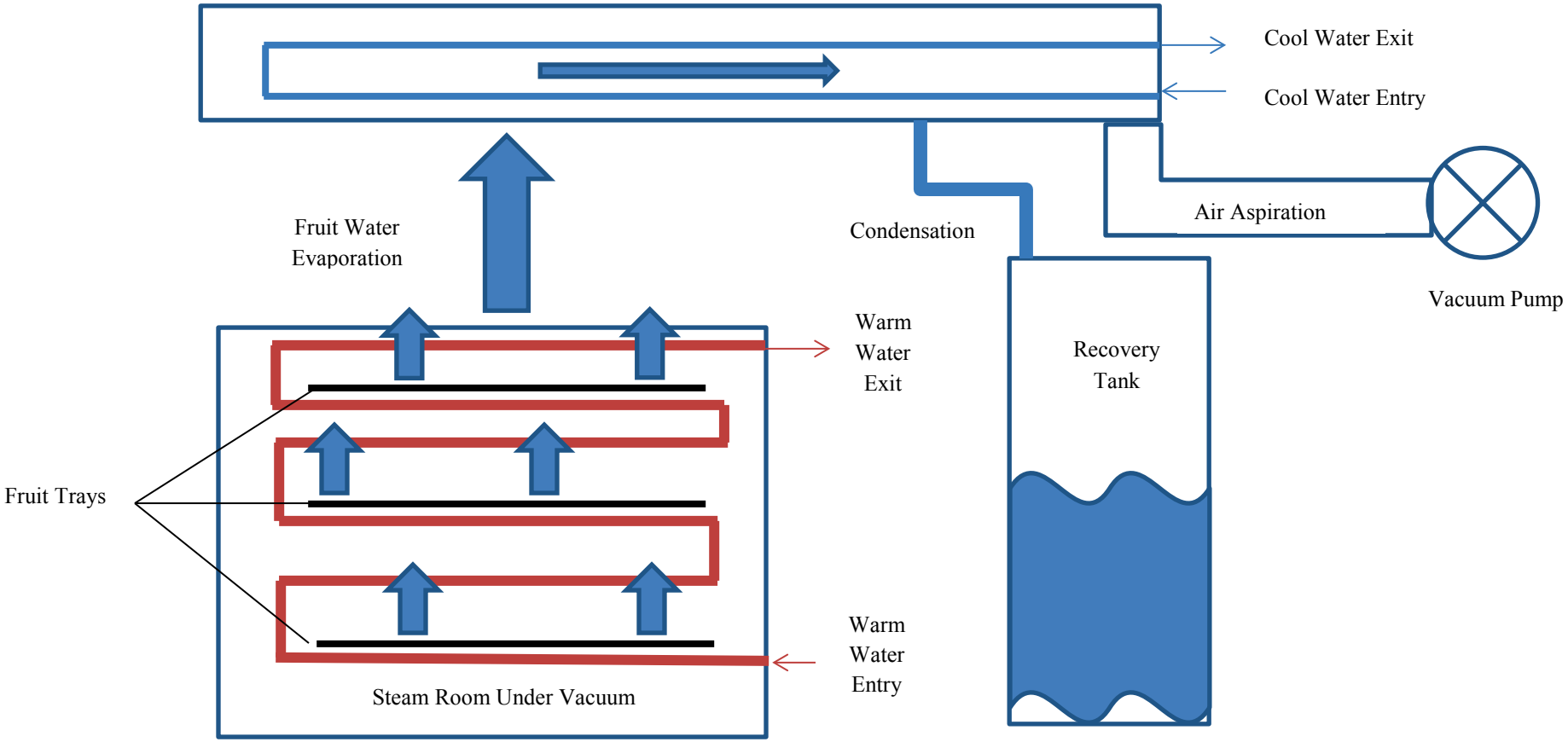


Figure 2. Manufacturing flow chart for citrus nobilis (mandarin orange) fruit extract.[45]

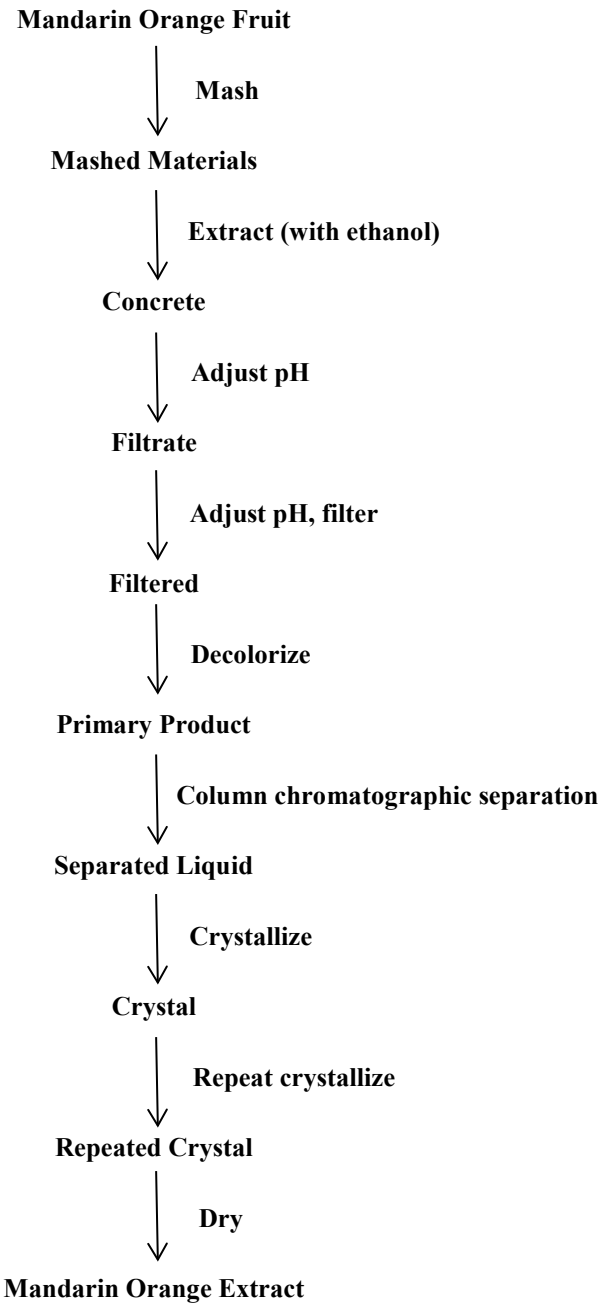
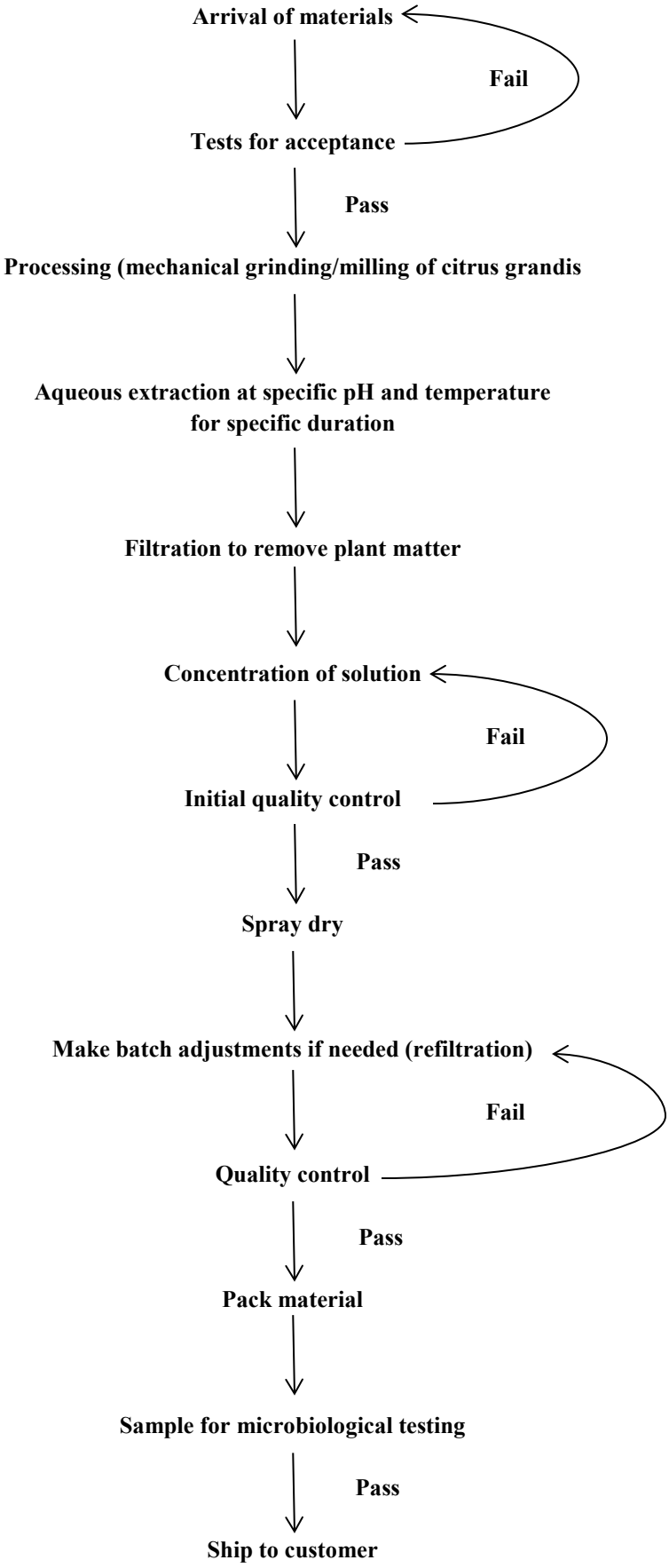


Figure 3. Manufacturing flow chart for citrus grandis (grapefruit) fruit extract – powder form.[46]



TABLES

Table 1. Definitions and functions of *Citrus*-derived ingredients. [4]

Ingredient	Definition	Function
Citrus Aurantifolia (Lime)/Citrus Limon (Lemon) Fruit Water	Citrus Aurantifolia (Lime)/Citrus Limon (Lemon) Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of *Citrus aurantifolia* and *Citrus limon.*	Skin-Conditioning Agents - Humectant
Citrus Aurantifolia (Lime) Fruit	Citrus Aurantifolia (Lime) Fruit is the fruit of *Citrus aurantifolia.*	Not reported
Citrus Aurantifolia (Lime) Fruit Extract CAS No. 90063-52-8	Citrus Aurantifolia (Lime) Fruit Extract is the extract of the fruit of *Citrus aurantifolia.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantifolia (Lime) Fruit Water	Citrus Aurantifolia (Lime) Fruit Water is an aqueous solution of the steam distillates obtained from the fruit of *Citrus aurantifolia.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantifolia (Lime) Juice	Citrus Aurantifolia (Lime) Juice is the liquid expressed from the fresh pulp of the lime, *Citrus aurantifolia.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Amara (Bitter Orange) Fruit Extract CAS No. 84625-25-2	Citrus Aurantium Amara (Bitter Orange) Fruit Extract is the extract of the fruit of *Citrus aurantium amara.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Amara (Bitter Orange) Fruit Juice Extract	Citrus Aurantium Amara (Bitter Orange) Fruit Juice Extract is the extract of the fruit juice of *Citrus aurantium amara.*	Hair Conditioning Agents; Nail Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Bergamia (Bergamot) Fruit Extract CAS No. 89957-91-5	Citrus Aurantium Bergamia (Bergamot) Fruit Extract is the extract of the fruit of *Citrus aurantium bergamia.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Bergamia (Bergamot) Fruit Water	Citrus Aurantium Bergamia (Bergamot) Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of *Citrus aurantium bergamia.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Dulcis (Orange) Fruit Extract CAS No. 84012-28-2	Citrus Aurantium Dulcis (Orange) Fruit Extract is the extract of the fruit of *Citrus aurantium dulcis.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Dulcis (Orange) Fruit Powder	Citrus Aurantium Dulcis (Orange) Fruit Powder is the powder obtained from the dried, ground fruit of *Citrus aurantium dulcis.*	Skin-Conditioning Agents - Miscellaneous
Citrus Aurantium Dulcis (Orange) Fruit Water	Citrus Aurantium Dulcis (Orange) Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of the orange, *Citrus aurantium dulcis.*	Flavoring Agents; Fragrance Ingredients
Citrus Aurantium Dulcis (Orange) Juice	Citrus Aurantium Dulcis (Orange) Juice is the liquid expressed from the pulp of the orange, *Citrus aurantium dulcis.*	Not reported
Citrus Aurantium Sinensis (Orange) Fiber	Citrus Aurantium Sinensis (Orange) Fiber is the fiber obtained from the pulp of *Citrus aurantium sinensis.*	Emulsion Stabilizers
Citrus Clementina Fruit Extract	Citrus Clementina Fruit Extract is the extract of the fruit of *Citrus clementina.*	Skin-Conditioning Agents - Miscellaneous
Citrus Clementina Juice	Citrus Clementina Juice is the juice expressed from the pulp of *Citrus clementina.*	Skin-Conditioning Agents - Miscellaneous
Citrus Depressa Fruit Extract	Citrus Depressa Fruit Extract is the extract of the fruit of *Citrus depressa.*	Skin-Conditioning Agents - Miscellaneous
Citrus Depressa Fruit Water	Citrus Depressa Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of *Citrus depressa.*	Skin-Conditioning Agents - Humectant
Citrus Glauca Fruit Extract CAS No. 1174331-62-4	Citrus Glauca Fruit Extract is the extract of the fruit of *Citrus glauca.*	Antistatic Agents; Hair Conditioning Agents; Skin-Conditioning Agents - Humectant
Citrus Grandis (Grapefruit) Fruit Extract	Citrus Grandis (Grapefruit) Fruit Extract is the extract of the fruit of *Citrus grandis.*	Preservatives; Skin-Conditioning Agents - Miscellaneous
Citrus Grandis (Grapefruit) Fruit/Peel Water	Citrus Grandis (Grapefruit) Fruit/Peel Water is the aqueous solution of the steam distillates obtained from the fruits and peels of the grapefruit, *Citrus grandis*.	Skin-Conditioning Agents - Humectant
Citrus Grandis (Grapefruit) Fruit Water	Citrus Grandis (Grapefruit) Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of *Citrus grandis.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Grandis (Grapefruit) Juice	Citrus Grandis (Grapefruit) Juice is the liquid expressed from the fresh pulp of the grapefruit, *Citrus grandis.*	Skin-Conditioning Agents - Miscellaneous
Citrus Grandis/Paradisi Fruit Water	Citrus Grandis/Paradisi Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of the hybrid of *Citrus paradisi* and *Citrus grandis.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Hassaku Fruit Extract	Citrus Hassaku Fruit Extract is the extract of the fruit of *Citrus hassaku.*	Skin-Conditioning Agents - Humectant
Citrus Hassaku/Natsudaidai Fruit Juice	Citrus Hassaku/Natsudaidai Fruit Juice is the juice expressed from the fruit of a hybrid of *Citrus hassaku* and *Citrus natsudaidai.*	Skin-Conditioning Agents - Humectant
Citrus Hassaku/Natsudaidai Fruit Powder	Citrus Hassaku/Natsudaidai Fruit Powder is the powder obtained from the dried, ground fruit of a hybrid of *Citrus hassaku* and *Citrus natsudaidai.*	Skin-Conditioning Agents - Emollient
Citrus Iyo Fruit Extract	Citrus Iyo Fruit Extract is the extract of the fruit of *Citrus iyo.*	Skin-Conditioning Agents - Emollient; Skin-Conditioning Agents - Humectant
Citrus Iyo Fruit Water	Citrus Iyo Fruit Water is the aqueous solution of the steam distillates obtained from the fruit of *Citrus iyo*.	Skin-Conditioning Agents - Humectant

Table 1. Definitions and functions of *Citrus*-derived ingredients. [4]

Ingredient	Definition	Function
Citrus Jabara Juice	Citrus Jabara Juice is the liquid expressed from the fruit of *Citrus jabara.*	Skin-Conditioning Agents - Miscellaneous
Citrus Japonica Fruit Extract	Citrus Japonica Fruit Extract is the extract obtained from the fruit of *Citrus japonica.*	Skin-Conditioning Agents - Miscellaneous
Citrus Junos Fruit Extract	Citrus Junos Fruit Extract is the extract of the fruit of *Citrus junos.*	Skin-Conditioning Agents - Miscellaneous
Citrus Junos Fruit Juice	Citrus Junos Fruit Juice is the juice expressed from the fruit of *Citrus junos.*	Skin-Conditioning Agents - Humectant
Citrus Junos Fruit Oil	Citrus Junos Fruit Oil is the volatile oil obtained from the fruit of *Citrus junos.*	Fragrance Ingredients
Citrus Junos Fruit Powder	Citrus Junos Fruit Powder is the powder obtained from the dried, ground fruit of *Citrus junos.*	Exfoliants
Citrus Junos Fruit Water	Citrus Junos Fruit Water is the aqueous solution of the steam distillates obtained the fruit of *Citrus junos.*	Fragrance Ingredients
Citrus Limon (Lemon) Fruit Extract CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Fruit Extract is the extract of the fruit of *Citrus limon.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous; Skin-Conditioning Agents - Occlusive
Citrus Limon (Lemon) Fruit Oil	Citrus Limon (Lemon) Fruit Oil is the volatile oil obtained from the fruit of *Citrus limon.*	Cosmetic Astringents
Citrus Limon (Lemon) Fruit Powder	Citrus Limon (Lemon) Fruit Powder is the powder obtained from the dried fruit of *Citrus limon.*	Skin-Conditioning Agents - Miscellaneous
Citrus Limon (Lemon) Fruit Water	Citrus Limon (Lemon) Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of *Citrus limon.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Limon (Lemon) Juice CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Juice is the liquid expressed from the fresh pulp of the lemon, *Citrus limon.*	Skin-Conditioning Agents - Miscellaneous
Citrus Limon (Lemon) Juice Extract CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Juice Extract is the extract of the juice of *Citrus limon.*	Skin-Conditioning Agents - Miscellaneous
Citrus Limon (Lemon) Juice Powder CAS No. 84929-31-7; 85085-28-5	Citrus Limon (Lemon) Juice Powder is the powder obtained from the dried juice of *Citrus limon.*	Skin-Conditioning Agents - Miscellaneous
Citrus Madurensis Fruit Extract	Citrus Madurensis Fruit Extract is the extract of the fruit of *Citrus madurensis.*	Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Citrus Madurensis Fruit Juice	Citrus Madurensis Fruit Juice is the juice expressed from the fruit of *Citrus madurensis*.	Flavoring Agents
Citrus Medica Vulgaris Fruit Extract CAS No. 92346-90-2	Citrus Medica Vulgaris Fruit Extract is the extract of the fruit of *Citrus medica vulgaris.*	Antioxidants; Chelating Agents
Citrus Nobilis (Mandarin Orange) Fruit Extract	Citrus Nobilis (Mandarin Orange) Fruit Extract is the extract of the fruit of *Citrus nobilis.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Nobilis (Mandarin Orange) Fruit Juice	Citrus Nobilis (Mandarin Orange) Fruit Juice is the liquid expressed from the fruit of the mandarin orange, *Citrus nobilis.*	Bath Soaps and Detergents
Citrus Paradisi (Grapefruit) Fruit Extract CAS No. 90045-43-5 (generic)	Citrus Paradisi (Grapefruit) Fruit Extract is the extract of the fruit of *Citrus paradisi.*	Skin-Conditioning Agents - Miscellaneous
Citrus Paradisi (Grapefruit) Fruit Water CAS No. 90045-43-5 (generic)	Citrus Paradisi (Grapefruit) Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of *Citrus paradisi.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Paradisi (Grapefruit) Juice CAS No. 90045-43-5 (generic)	Citrus Paradisi (Grapefruit) Juice is the liquid expressed from the fresh pulp of the grapefruit *Citrus paradisi.*	Skin-Conditioning Agents - Miscellaneous
Citrus Reticulata (Tangerine) Fruit	Citrus Reticulata (Tangerine) Fruit is the fruit of *Citrus reticulata.*	Skin-Conditioning Agents - Miscellaneous
Citrus Reticulata (Tangerine) Fruit Extract	Citrus Reticulata (Tangerine) Fruit Extract is the extract of the fruit of *Citrus reticulata.*	Drug Astringents - Skin Protectant Drugs
Citrus Reticulata (Tangerine) Fruit Water	Citrus Reticulata (Tangerine) Fruit Water is the aqueous solution of the steam distillates obtained from the fruit of *Citrus reticulata.*	Fragrance Ingredients
Citrus Shunkokan Fruit Extract	Citrus Shunkokan Fruit Extract is the extract of the fruit of *Citrus shunkokan.*	Antioxidants
Citrus Sinensis (Orange) Fruit Extract	Citrus Sinensis (Orange) Fruit Extract is the extract of the fruit of *Citrus sinensis.*	Antioxidants; Skin-Conditioning Agents - Miscellaneous
Citrus Sinensis (Orange) Fruit Water	Citrus Sinensis (Orange) Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of *Citrus sinensis.*	Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Sphaerocarpa Fruit Juice	Citrus Sphaerocarpa Fruit Juice is the juice expressed from the fruit of *Citrus sphaerocarpa.*	Skin-Conditioning Agents - Miscellaneous
Citrus Sudachi Fruit Extract	Citrus Sudachi Fruit Extract is the extract of the fruit of *Citrus sudachi.*	Skin-Conditioning Agents - Humectant
Citrus Sudachi Fruit Juice	Citrus Sudachi Fruit Juice is the juice expressed from the fruit of *Citrus sudachi.*	Skin-Conditioning Agents - Humectant
Citrus Tachibana/Reticulata Fruit Juice	Citrus Tachibana/Reticulata Fruit Juice is the juice expressed from the fruit of a hybrid of *Citrus tachbana* and *Citrus reticulata.*	Flavoring Agents; Skin-Conditioning Agents - Miscellaneous

Table 1. Definitions and functions of *Citrus*-derived ingredients. [4]

Ingredient	Definition	Function
Citrus Tamurana Fruit Extract	Citrus Tamurana Fruit Extract is the extract of the fruit of *Citrus tamurana.*	Skin-Conditioning Agents - Humectant
Citrus Tangelo Fruit Juice	Citrus Tangelo Fruit Juice is the juice expressed from the fruit of *Citrus tangelo.*	Skin-Conditioning Agents - Humectant
Citrus Tangelo Fruit Powder	Citrus Tangelo Fruit Powder is the powder obtained from the dried, ground fruit, *Citrus tangelo.*	Skin-Conditioning Agents - Emollient
Citrus Tangerina (Tangerine) Fruit	Citrus Tangerina (Tangerine) Fruit is the fruit of *Citrus tangerina.*	Not reported
Citrus Tangerina (Tangerine) Fruit Water	Citrus Tangerina (Tangerine) Fruit Water is an aqueous solution of the steam distillate obtained from the fruit of *Citrus tangerina.*	Skin-Conditioning Agents - Miscellaneous
Citrus Tankan Fruit Extract	Citrus Tankan Fruit Extract is the extract of the fruit of *Citrus tankan.*	Skin-Conditioning Agents - Humectant
Citrus Tankan Fruit Water	Citrus Tankan Fruit Water is the aqueous solution of the steam distillates obtained from the fruit of *Citrus tankan.*	Humectants
Citrus Unshiu/Citrus Reticulata/Citrus Iyo Fruit Water	Citrus Unshiu/Citrus Reticulata/Citrus Iyo Fruit Water is the aqueous solution of the steam distillates obtained from the fruit of *Citrus unshiu, Citrus reticulata* and *Citrus Iyo.*	Fragrance Ingredients
Citrus Unshiu Fruit Extract	Citrus Unshiu Fruit Extract is the extract of the fruit of *Citrus unshiu.*	Antioxidants; Hair Conditioning Agents; Skin Protectants; Skin-Conditioning Agents - Emollient; Sunscreen Agents
Citrus Unshiu Fruit Juice	Citrus Unshiu Fruit Juice is the juice expressed from the fruit of *Citrus unshiu.*	Skin-Conditioning Agents - Humectant
Citrus Unshiu Fruit Juice Ferment Extract Filtrate	Citrus Unshiu Fruit Juice Ferment Extract Filtrate is a filtrate of an extract of the product obtained by the spontaneous fermentation of Citrus Unshiu Fruit Juice.	Skin-Conditioning Agents - Miscellaneous
Citrus Unshiu Fruit Oil	Citrus Unshiu Fruit Oil is the volatile oil derived from the fruit of *Citrus unshiu.*	Skin-Conditioning Agents - Emollient
Citrus Unshiu Fruit Powder	Citrus Unshiu Fruit Powder is the powder obtained from the dried, ground fruit of *Citrus unshiu.*	Antioxidants; Exfoliants; Fragrance Ingredients; Skin-Conditioning Agents - Miscellaneous
Citrus Unshiu Fruit Water	Citrus Unshiu Fruit Water is the aqueous solution of the steam distillates obtained from the fruit of *Citrus unshiu.*	Hair Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Citrus Unshiu/Sinensis/Reticulata Fruit Extract	Citrus Unshiu/Sinensis/Reticulata Fruit Extract is the extract of the fruit of *Citrus unshiu*, *Citrus sinensis*, and *Citrus reticulata.*	Skin-Conditioning Agents - Miscellaneous
Defatted Citrus Unshiu Fruit	Defatted Citrus Unshiu Fruit is the dried, defatted fruit of *Citrus unshiu.*	Skin Protectants; Skin-Conditioning Agents - Miscellaneous
Hydrolyzed Citrus Aurantium Dulcis Fruit Extract	Hydrolyzed Citrus Aurantium Dulcis Fruit Extract is the hydrolysate of Citrus Aurantium Dulcis (Orange) Fruit Extract (q.v.) derived by acid, enzyme or other method of hydrolysis.	Skin Protectants
Microcitrus Australasica Fruit Extract	Microcitrus Australasica Fruit Extract is the extract of the fruit of *Microcitrus australasica.*	Skin-Conditioning Agents - Miscellaneous
Microcitrus Australis Fruit Extract	Microcitrus Australis Fruit Extract is the extract of the fruit of *Microcitrus Australis*.	Skin-Conditioning Agents - Miscellaneous

Table 2. Review of *Citrus* genus species names[1]

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 3. *Citrus*-ingredients that potentially function solely as fragrance ingredients.

Citrus Junos Fruit Oil
Citrus Junos Fruit Water
Citrus Reticulata (Tangerine) Fruit Water
Citrus Unshiu/Citrus Reticulata/Citrus Iyo Fruit Water

Table 4. Chemical and physical properties

Property	Value	Reference
Citrus limon (lemon) fruit extract		
Physical Form	clear, brownish yellow liquid	47-49
Odor	faint, fruity	47-49
Density (at 20ºC)	1.035-1.240	47-49
Refraction Index (at 20ºC)	1.425-1.460	47-49
pH	3.5-5.0	47-49
Citrus paradisi (grapefruit) fruit extract		
Physical Form	clear, yellowish liquid	50,51
Odor	faint, fruity	50,51
Density (at 20ºC)	1.040-1.215	50,51
Refraction Index (at 20ºC)	1.415-1.455	50,51
pH	4.0-5.0	50,51
Citrus aurantium dulcis (orange) fruit extract		
Physical Form	clear, yellow brown liquid	52,53
Odor	faint, fruity	52,53
Density (at 20ºC)	1.050-1.240	52,53
Refraction Index (at 20ºC)	1.425-1.465	52,53
pH	4.0-5.0	52,53
Citrus grandis (grapefruit) fruit extract		
Physical Form	clear to light yellow liquid or off-white to pale yellow powder	54-56
Odor	characteristic	54-56
Density (at 20ºC)	1.040-1.215	54
Refraction Index (at 25ºC)	1.385-1.400	54
pH	4.0-6.0 (in liquid at 25ºC); 2.0-5.0 (in powder at 1% in water)	54-56
Citrus aurantifolia (lime) fruit extract		
Physical Form	clear yellow to light amber liquid	57
Odor	characteristic	57
Specific Gravity	1.000-1.020	57
Boiling Point (ºC)	209	58
Freezing Point (ºC)	-50	58
Refraction Index	1.4350-1.4450	57
pH (at25ºC)		

Table 5. Potential constituents that are established contact allergens in humans, according to the SCCS

Constituent	**categorized according to number of patients reacting positively and to the number of patients tested (>1000 patients tested, unless indicated as r.t., i.e., rarely tested)** [59]
β-caryophyllene	≤10 (oxidized and non-oxidized)
carvone	≤10 (r.t.)
citral	101 to 1000
citronellol	11-100
coumarin	101 to 1000
farnesol	101 to 1000
geraniol	101 to 1000
linalyl acetate	≤10
α- and β-pinene	11-100
(DL)-limonene	11-100 (non-oxidized); 101 to 1000 (oxidized)
tepineol (mixture of isomers)/α-terpineol	≤10
terpinolene	11-100

Table 6. Cosmetic allergens certificate from a manufacturer of *Citrus* fruit waters and extracts [5,60-66]

Allergen	Citrus Sinensis (Orange) Fruit Water	Citrus Limon (Lemon) Fruit Water	Citrus Reticulata (Tangerine) Fruit Water	Citrus Paradisi (Grapefruit) Fruit Water	Citrus Aurantifolia (Lime) Fruit Extract	Citrus Grandis (Grapefruit) Fruit Extract	Hydrolyzed Citrus Aurantium Dulcis (Orange) Fruit Extract
Amyl cinnamal	NP	NP	NP	NP	NP	NP	NP
Benzyl alcohol	NP	NP	NP	NP	NP	NP	NP
Cinnamyl alcohol	NP	NP	NP	NP	NP	NP	NP
Citral	NP	Max. content < 100 ppm	NP	NP	NP	NP	NP
Eugenol	NP	NP	NP	NP	NP	NP	NP
Hydroxycitronellal	NP	NP	NP	NP	NP	NP	NP
Isoeugenol	NP	NP	NP	NP	NP	NP	NP
Amylcinnamyl alcohol	NP	NP	NP	NP	NP	NP	NP
Benzyl salicylate	NP	NP	NP	NP	NP	NP	NP
Cinnamal	NP	NP	NP	NP	NP	NP	NP
Coumarin	NP	NP	NP	NP	NP	NP	NP
Geranlol	NP	Max. content < 100 ppm	NP	NP	NP	NP	NP
Hydroxyisohexyl 3-cyclo hexane carboxaldehyde	NP	NP	NP	NP	NP	NP	NP
Anise alcohol	NP	NP	NP	NP	NP	NP	NP
Benzyl cinnamate	NP	NP	NP	NP	NP	NP	NP
Farnesol	NP	NP	NP	NP	NP	NP	NP
Butylphenyl methylpropional	NP	NP	NP	NP	NP	NP	NP
Linalool	Max. content < 10 ppm	Max. content < 100 ppm	NP	Max. content < 10 ppm	NP	NP	NP
Benyl benzoate	NP	NP	NP	NP	NP	NP	NP
Citronellol	NP	NP	NP	NP	NP	NP	NP
Hexyl cinnamal	NP	NP	NP	NP	NP	NP	NP
Limonene	NP	NP	NP	NP	NP	NP	NP
Methyl 2-octynoate	NP	NP	NP	NP	NP	NP	NP
Alpha-isomethyl ionone	NP	NP	NP	NP	NP	NP	NP
Evernia prunastri	NP	NP	NP	NP	NP	NP	NP
Evernia furfuracea	NP	NP	NP	NP	NP	NP	NP

Detection limit 2 ppm.
ND = unable to be detected by GCSM
NP = not present

Table 7. Constituents, components, and impurities in citrus fruit extract products. [5,6,47-53,55,57,67]

Constituent	Citrus Limon (Lemon) Fruit Extract – propylene glycol	Citrus Limon (Lemon) Fruit Extract – glycerin	Citrus Paradisi (Grapefruit) Fruit Extract – propylene glycol	Citrus Paradisi (Grapefruit) Fruit Extract - glycerin	Citrus Aurantium Dulcis (Orange) Fruit Extract – propylene glycol	Citrus Aurantium Dulcis (Orange) Fruit Extract - glycerin	Citrus Nobilis (Mandarin Orange) Fruit Extract-ethanol
fruit extract	50-75% (may have < 0.1% citrus limon (lemon) peel oil	50-75%	10-25%	10-25%	75-100%	25-50%	NR
propylene glycol	75-100%	NR	75-100%	NR	75-100%	NR	NR
glycerin	NR	75-100%	NR	50-75%	NR	75-100%	NR
ethanol	NR	NR	NR	NR	NR	NR	NR
butylene glycol	NR	NR	NR	NR	NR	NR	NR
limonene	0.015-0.03% max.	max. 0.015%	0.11% max	0.11% max	0.016% max.	0.01% max.	NR
citral	0.001- 0.002% max.	max. 0.001%	NR	NR	NR	NR	NR
tangeretin	NR	NR	NR	NR	NR	NR	>70%
furanocoumarins	NR	NR	NR	NR	NR	NR	NR
bactiphen or phenonip (phenoxyethanol, methylparaben, ethylparaben, propylparaben, butylparaben)	0-0.6%	NR	NR	NR	NR	NR	NR
lactic acid	0.1-1%	0.1-1%	0.1-1%	0.1-1%	0.1-1%	0.1-1%	NR
potassium sorbate	0-0.35%	0.3%	0.35%	0.35%	0.35%	0.4%	NR
sodium benzoate	0-0.35%	0.3%	0.35%	0.35%	0.35%	0.4%	NR
arsenic	NR	NR	NR	NR	NR	NR	limit: not more than 2 ppm
heavy metals	NR	NR	NR	NR	NR	NR	limit: not more than 20 ppm

Constituent	Citrus Aurantifolia (Lime) Fruit Extract – butylene glycol	Citrus Grandis (Grapefruit) Fruit Extract	Hydrolyzed Citrus Aurantium Dulcis (Orange) Fruit Extract	Citrus Junos Fruit Extract
fruit extract	20.0%	100%	8.5%	1.2%
propylene glycol	NR	NR	NR	NR
glycerin	NR	NR	NR	NR
ethanol	NR	NR	NR	NR
butylene glycol	79.5%	NR	NR	NR
limonene	NR	NR	NR	NR
citral	NR	NR	NR	NR
tangeretin	NR	NR	NR	NR
furanocoumarins	NR	< 1 ppm (limit)	do not contain or are below 10μg/ml	NR
bactiphen or phenonip (phenoxyethanol, methylparaben, ethylparaben, propylparaben, butylparaben)	0.5%	NR	NR	NR
lactic acid	NR	NR	NR	NR
potassium sorbate	NR	NR	NR	NR
sodium benzoate	NR	NR	NR	NR
arsenic	< 2 ppm	< 2 ppm	NR	not more than 2 ppm
heavy metals	< 20 ppm	< 20 ppm	nickel: 0.163 ppm; lead: 0.582 ppm	not more than 10 ppm

Table 8. Additional constituent data from various *Citrus* fruits.[68]

General Citrus
Carotenoids
Flavonoids as characterized a flavanones, flavones, and 3-hydroxyflavylium
-Flavanones may include: hesperidin, naringin, neohesperidin
-Flavones may include: apigenin, acacetin, luteolin
Limonoids including limonin, nomilin, ichangin, obacunaic acid, photolimonin I, deoxylimonin, obacunone, limonoic acid, limonilic acid, and limonol
Lipids
Inorganic elements (in juice):
-Major include: Ca, P, Fe, Mg, K, Na, Cl, and N
-Minor include: Si, Mn, B, Sr, Al, Cu, Li, Ni, Cr, V, Br, Zn, Pb, Sn, Co, As, Ba, Mo, Ag, Zn
Nitrogen content: 0.1-0.2% on net weight for whole *Citrus* fruit, 5-10% on total solids in fruit juice
Organic acids: mainly citric, malic, succinic; also tartaric, benzoic, oxalic, formic, adipic, iso-citric, aconitic, chlorogenic, citramalic, glacturonic, lactic, malonic, phosphoric, quinic, and 2-keto-glutaric.
Polysaccharides, including galacturonan-containing pectic substances, cellulose, glucan, arabinan, xylan, and starch
Simple polyphenolic compounds including phloroglucinol, phenolic acids, and coumarins
-Coumarins common to all species include: umbelliferone, scopoletin, citropten, bergaptol, aurapten, bergamottin, and byakangelicin
Sugars: 40%
Vitamins, including ascorbic acid, biotin, carotenoids, β-carotene, choline, folic acid, inositol, niacin, pantothenic acid, pyridoxine, riboflavin, and thiamine
Volatile flavoring constituents including essence oil, aroma oil, stripper oil, and *Citrus* essences
-Juice oil content is about 0.005%
Grapefruit
Coumarins including aurapten, auraptene, osthaol, auraptenol, bergaptene, herniarin, esulanten
Flavonoids including neohesperidin, rhoifolin, rutin, apigenin 7-β-rutinoside, tangeritin, nobiletin, naringin, poncirin
Lipids (in juice): 75-86 mg/100 ml
-major fatty acids: palmitic (21.7-23.7%), palmitoleic (3.1-4.3%), oleic (23.4-24.4%), linoleic (33.5-35.5%), linolenic (8.2-9.4%), others (5.8-7.2%)
Nitrogen content: total (3.58-6.64 g/l), amino nitrogen (0.218-0.422 g/l), ammonia nitrogen (1.2-2.8 mg/l), nitrates (0.33-0.76 mg/l)
Organic acids: citric (0.42-1.13%), malic (0.03-0.23%), succinic (0.06-0.86%)
Sugars (in juice): 5.0-8.3%, mainly fructose, glucose, and sucrose, as well as traces of other sugars
Vitamins, including 36-45 mg/100 ml ascorbic acid in juice
Lemons
Coumarins including imperatorin, 8-geranoxypsoralen, isopimpinellin, oxypeucedanin hydrate, phellopterin, 5-geranoxy-8-methoxysoralen
Flavonoids including neohesperidin, naringenin, eriocitrin, hesperidin, neohesperidoside, neodiosmin, rutinoside, diosmin
Lipids (in juice): 58-78 mg/100 ml)
-major fatty acids: palmitic (23.0-23.4%), palmitoleic (0.7-0.9%), oleic (9.5-9.5%), linoleic (34.8-36.0%), linolenic (18.8-19.0%), others (12.0-12.4%)
Nitrogen content: total (0.55-5.21 g/l), amino nitrogen (0.027-0.525 g/l), ammonia nitrogen (3.2-7.2 mg/l), nitrates (0.25-0.76 mg/l)
Organic acids: citric (4.00-4.38%), malic (0.07-0.26%)
Sugars (in juice): 0.81-3.70% , mainly fructose, glucose, and sucrose, as well as traces of other sugars
Vitamins, including 39.46 mg/100 g ascorbic acid in juice
Limes
Coumarins including bergaptene, imperatorin, 8-geranoxypsoralen, isopimpinellin, oxypeucedanin hydrate, phellopterin, 5-geranoxy-8-methoxysoralen, 5-isopentoxy-8-methoxypsoralen, 5-geranoxy-7-methoxycoumarin (2.2-3.2%), bergamottin (2.2-2.5%), citropten (0.89-1.70%), and bergapten (0.17-0.33%)
Polysaccharides including 24-30% pectin
Lipids
-major fatty acids: palmitic (21.7-22.3%), palmitoleic (5.4-5.6%), oleic (14.8-15.0%), linoleic (26.9-27.5%), linolenic (13.8-14.4%), others (16.0-16.6%)
Sugars (in juice): 0.76-1.39%, mainly fructose, glucose, and sucrose, as well as traces of other sugars
Mandarin Oranges
Coumarins including aurapten, auraptene, osthaol, auraptenol, and bergaptene
Flavonoids including hesperidin, neohespridin, and permethoxylated flavones
Organic acids: citric (0.86-1.22%), malic (0.08-0.21%)
Vitamins, including 68.39 mg/100 g ascorbic acid in juice
Oranges
Coumarins including aurapten, auraptene, osthaol, auraptenol, and bergaptene
Flavonoids including herperidin, narigenin, isosakuranetin, neohesperidin, naringin, poncirin, neoeriocitrin, rhoifolin, luteolin, neodiosmin, ruin, limoncitrin 3-β-D-glucoside
Lipids (in juice): 84-101 mg/100 ml
-major fatty acids: palmitic (21.2-23.3%), palmitoleic (4.0-4.6%), oleic (24.1-26.7%), linoleic (27.8-35.2%), linolenic (7.9-13.6%), others (5.9-7.1%)
Organic acids: citric (0.17-2.37%), malic (0.06-0.31%), succinic (trace-1.59%)
Sugars (in juice): 5.4-10.5%, mainly fructose, glucose, and sucrose, as well as traces of other sugars
Vitamins, including 35-56 mg/100 ml ascorbic acid in juice

Table 9. Frequency (2015) and concentration of use (2013) according to duration and type of exposure for *Citrus* fruit-derived ingredients.[9,10]

	# 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) Fruit Extract		**Citrus Aurantifolia (Lime) Juice**		**Citrus Aurantium Amara (Bitter Orange) Fruit Extract[d]**		**Citrus Aurantium (Bitter Orange) Fruit Water[e]**	
Totals[†]	**55**	**0.0001-0.2**	**1**	**NR**	**295**	**0.00002-0.002**	**9**	**NR**
Duration of Use								
Leave-On	21	0.0009-0.2	NR	NR	190	0.00002-0.002	6	NR
Rinse Off	32	0.0001-0.2	1	NR	103	0.0001	2	NR
Diluted for (Bath) Use	2	0.002	NR	NR	2	NR	1	NR
Exposure Type								
Eye Area	NR	NR	NR	NR	6	0.0001-0.002	2	NR
Incidental Ingestion	NR	NR	NR	NR	3	0.002	NR	NR
Incidental Inhalation-Spray	spray: NR possible: 13[a]; 3[b]	spray: 0.001 possible: 0.01[a]; 0.0009[b]	NR	NR	spray: 7 possible: 65[a]; 65[b]	NR	spray: NR possible: 2[a]	NR
Incidental Inhalation-Powder	powder: NR possible: 3[b]	0.0009[b]; 0.001-0.2[c]	NR	NR	powder: NR possible: 65[b]	powder: NR possible: 0.00002-0.0002[c]	NR	NR
Dermal Contact	46	0.0001-0.2	NR	NR	256	0.00002-0.002	9	NR
Deodorant (underarm)	NR	NR	NR	NR	spray: NR possible: 3[a]	NR	NR	NR
Hair - Non-Coloring	9	0.0005-0.01	1	NR	33	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	2	NR	NR	NR
Mucous Membrane	17	0.002-0.2	NR	NR	44	0.002	2	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Citrus Aurantium Dulcis (Orange) Fruit Extract		**Citrus Aurantium Dulcis (Orange) Fruit Water**		**Citrus Bergamia (Bergamot Orange) Fruit Extract**		**Citrus Glauca Fruit Extract**	
Totals[†]	**7**	**NR**	**23**	**2-19**	**24**	**0.000001-0.82**	**5**	**0.003-0.0051**
Duration of Use								
Leave-On	4	NR	19	2-10	13	0.000001-0.82	NR	NR
Rinse Off	3	NR	4	2-19	11	0.000001-0.0063	5	0.003-0.0051
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	3	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	spray: NR possible: 1[a]; 2[b]	NR	spray: 1 possible: 3[a]; 6[b]	NR	spray: NR possible: 4[a]; 6[b]	spray: 0.000001	NR	NR
Incidental Inhalation-Powder	powder: NR possible: 2[b]	NR	powder: NR possible: 6[b]	powder: NR possible: 3-10[c]	powder: NR possible: 6[b]	powder: NR possible: 0.0001-0.001	NR	NR
Dermal Contact	7	NR	22	2-19	9	0.0001-0.82	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	15	0.000001-0.0001	5	0.003-0.0051
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	NR	NR	NR	1	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 9. Frequency (2015) and concentration of use (2013) according to duration and type of exposure for *Citrus* fruit-derived ingredients.[9,10]

	# 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 Grandis (Grapefruit) Fruit Extract		**Citrus Grandis (Grapefruit) Fruit Water**		**Citrus Grandis (Grapefruit) Fruit/Peel Water**		**Citrus Grandis (Grapefruit) Juice**	
Totals[†]	**211**	**0.0000005-15**	**2**	**0.0029**	**NR**	**0.088-0.5**	**15**	**0.01**
Duration of Use								
Leave-On	102	0.0001-15	NR	NR	NR	0.088-0.5	11	NR
Rinse Off	107	0.0000005-8	2	0.0029	NR	0.1	4	0.01
Diluted for (Bath) Use	2	0.005-0.01	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	3	NR	NR	NR	NR	0.5	NR	NR
Incidental Ingestion	8	0.01-0.02	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	spray:4 possible: 42[a]; 33[b]	spray: 0.01 possible: 0.005-0.01[a]; 0.0001[b]	NR	NR	NR	spray: 0.088	spray: NR possible: 4[a]; 7[b]	NR
Incidental Inhalation-Powder	powder: 3 possible: 33[b]	powder: NR possible: 0.0001[b]; 0.0001-15[c]	NR	NR	NR	NR	powder: NR possible: 7[b]	NR
Dermal Contact	134	0.0001-15	2	0.0029	NR	0.5	15	0.01
Deodorant (underarm)	spray: NR possible: 1[a]	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	63	0.0000005-0.01	NR	NR	NR	0.088-0.1	NR	NR
Hair-Coloring	6	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	25	0.001-0.1	2	NR	NR	NR	3	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Citrus Japonica Fruit Extract		**Citrus Junos Fruit Extract**		**Citrus Limon (Lemon) Fruit Extract**		**Citrus Limon (Lemon) Juice**	
Totals[†]	**NR**	**0.0038**	**38**	**0.0005-0.002**	**571**	**0.0001-1.2**	**26**	**0.035-1**
Duration of Use								
Leave-On	NR	NR	31	0.0005-0.002	431	0.0001-1.2	13	0.05-1
Rinse Off	NR	0.0038	7	0.0005-0.001	138	0.002-0.5	13	0.035-0.05
Diluted for (Bath) Use	NR	NR	NR	NR	2	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	6	NR	13	NR	NR	NR
Incidental Ingestion	NR	NR	NR	0.001	7	0.03	NR	NR
Incidental Inhalation-Spray	NR	NR	spray: 1 possible: 6[a]; 12[b]	spray: 0.0005-0.001	spray: 17 possible: 199[a]; 108[b]	spray: NR possible: 0.001[a]	spray: NR possible: 6[a]; 7[b]	spray: NR possible: 0.05[a]
Incidental Inhalation-Powder	NR	NR	powder: NR possible: 12[b]	powder: NR possible: 0.0005-0.002[c]	powder: NR possible: 108[b]	powder: NR possible: 0.0001-0.5[c]	powder: NR possible: 7[b]	powder: NR possible: 1[c]
Dermal Contact	NR	NR	37	0.0005-0.002	478	0.0001-1.2	17	0.035-1
Deodorant (underarm)	NR	NR	NR	NR	spray: NR possible: 1[a]	NR	NR	NR
Hair - Non-Coloring	NR	0.0038	1	NR	83	0.002-0.005	8	0.05
Hair-Coloring	NR	NR	NR	NR	NR	NR	1	NR
Nail	NR	NR	NR	NR	3	0.0001-0.5	NR	NR
Mucous Membrane	NR	NR	2	0.0005-0.001	44	0.0028-0.04	2	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 9. Frequency (2015) and concentration of use (2013) according to duration and type of exposure for *Citrus* fruit-derived ingredients.[9,10]

	# 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 Madurensis Fruit Extract		**Citrus Medica Limonum (Lemon)Fruit Water**		**Citrus Medica Limonum (Lemon) Juice Extract**		**Citrus Medica Vulgaris Fruit Extract**	
Totals[†]	**NR**	**0.0005**	**3**	**1**	**4**	**0.05-0.2**	**11**	**NR**
Duration of Use								
Leave-On	NR	0.0005	2	NR	2	0.2	6	NR
Rinse Off	NR	NR	1	1	2	0.05	5	NR
Diluted for (Bath) Use	NR	0.0005	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	spray: 1 possible: 1[b]	NR	spray: NR possible: 2[b]	NR	spray: 1 possible: 2[a]; 2[b]	NR
Incidental Inhalation-Powder	NR	powder: NR possible: 0.0005	powder: NR possible: 1[b]	NR	powder: NR possible: 2[b]	powder: NR possible: 0.2[c]	powder: NR possible: 2[b]	NR
Dermal Contact	NR	0.0005	3	1	3	0.05-0.2	8	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	spray: NR possible: 1[a]	NR
Hair - Non-Coloring	NR	NR	NR	NR	1	NR	3	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	0.0005	1	NR	1	NR	4	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Citrus Nobilis (Mandarin Orange) Fruit Extract[f]		**Citrus Paradisi (Grapefruit) Fruit Extract**		**Citrus Paradisi (Grapefruit) Fruit Juice**		**Citrus Reticulata (Tangerine) Fruit Extract**	
Totals[†]	**27**	**0.001-0.04**	**59**	**0.005-1.5**	**2**	**NR**	**5**	**NR**
Duration of Use								
Leave-On	7	0.001-0.04	35	0.05-1.5	1	NR	3	NR
Rinse Off	19	0.001-0.04	24	0.005-0.2	1	NR	1	NR
Diluted for (Bath) Use	1	NR	NR	NR	NR	NR	1	NR
Exposure Type								
Eye Area	NR	NR	2	NR	NR	NR	1	NR
Incidental Ingestion	NR	NR	1	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	spray: NR possible: 4[a]; 2[b]	spray: 0.0075 possible: 0.001-0.01[a]	spray: NR possible: 7[a]; 15[b]	NR	spray: NR possible: 1[b]	NR	spray: NR possible: 1[b]	NR
Incidental Inhalation-Powder	powder: NR possible: 2[b]	powder: NR possible: 0.0018-0.04[c]	powder: NR possible: 15[b]	powder: NR possible: 0.05-1.5[c]	powder: NR possible: 1[b]	NR	powder: NR possible: 1[b]	NR
Dermal Contact	18	0.0018-0.04	52	0.05-1.5	2	NR	5	NR
Deodorant (underarm)	spray: NR possible: 1[a]	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	9	0.001-0.01	6	0.005	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	11	0.002-0.04	5	NR	1	NR	2	NR
Baby Products	NR	NR	1	NR	NR	NR	1	NR

Table 9. Frequency (2015) and concentration of use (2013) according to duration and type of exposure for *Citrus* fruit-derived ingredients.[9,10]

	# 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 Sinensis (Orange) Fiber		**Citrus Sinensis (Orange) Juice**		**Citrus Sinensis (Orange) Powder**		**Citrus Sinensis (Sweet Orange) Fruit Extract**	
Totals†	**3**	**NR**	**1**	**0.000038**	**1**	**NR**	**12**	**0.00003-1.2**
Duration of Use								
Leave-On	3	NR	1	0.000038	1	NR	6	0.00003-1.2
Rinse Off	NR	NR	NR	NR	NR	NR	6	0.00003-0.25
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	0.1
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	spray: NR possible: 3[b]	NR	spray: NR possible: 1[b]	spray: NR possible: 0.000038[a]	spray: NR possible: 1[b]	NR	spray: 1 possible: 1[a]	spray: NR possible: 0.001[a]
Incidental Inhalation-Powder	powder: NR possible: 3[b]	NR	powder: NR possible: 1[b]	NR	powder: NR possible: 1[b]	NR	NR	powder: NR possible: 0.0005-0.32[c]
Dermal Contact	3	NR	1	NR	1	NR	10	0.00003-1.2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	0.000038	NR	NR	2	0.0007-0.25
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	0.2
Mucous Membrane	NR	NR	NR	NR	NR	NR	3	0.004-0.041
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	Citrus Sinensis (Sweet Orange) Fruit Water		**Citrus Tangerina (Tangerine) Extract**		**Hydrolyzed Citrus Aurantium Dulcis Fruit Extract**	
Totals†	**4**	**NR**	**16**	**NR**	**15**	**0.00002-5**
Duration of Use						
Leave-On	3	NR	4	NR	15	0.00002-0.11
Rinse Off	1	NR	12	NR	NR	0.048-5
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	1	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	spray: NR possible: 1[a]; 1[b]	NR	spray: 1 possible: 1[a]; 1[b]	NR	spray:6 possible: 3[a]; 3[b]	spray: NR possible: 0.00002-0.11[a]
Incidental Inhalation-Powder	powder: NR possible: 1[b]	NR	powder: NR possible: 1[b]	NR	powder: NR possible: 3[b]	powder: NR possible: 0.0068[c]
Dermal Contact	4	NR	5	NR	15	0.0068-5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	11	NR	NR	0.00002-0.048
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	2	NR	NR	5
Baby Products	NR	NR	NR	NR	NR	NR

NR = Not reported.

† Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

[a.] It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

[b.] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

[c.] It is possible these products may be powders, but it is not specified whether the reported uses are powders.

[d] Listed as Citrus Aurantium (Bitter Orange) Fruit Extract in the VCRP database.

[e] Only listed in the VCRP database, not in the INCI dictionary

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

Table 10. Ingredients that are not reported to be in use

Citrus Aurantifolia (Lime)/Citrus Limon (Lemon) Fruit Water
Citrus Aurantifolia (Lime) Fruit
Citrus Aurantifolia (Lime) Fruit Water
Citrus Aurantium Amara (Bitter Orange) Fruit Juice Extract
Citrus Aurantium Bergamia (Bergamot) Fruit Water
Citrus Aurantium Dulcis (Orange) Fruit Powder
Citrus Clementina Fruit Extract
Citrus Clementina Juice
Citrus Depressa Fruit Extract
Citrus Depressa Fruit Water
Citrus Grandis/Paradisi Fruit Water
Citrus Hassaku Fruit Extract
Citrus Hassaku/Natsudaidai Fruit Juice
Citrus Hassaku/Natsudaidai Fruit Powder
Citrus Iyo Fruit Extract
Citrus Iyo Fruit Water
Citrus Jabara Juice
Citrus Junos Fruit Juice
Citrus Junos Fruit Oil
Citrus Junos Fruit Powder
Citrus Junos Fruit Water
Citrus Limon (Lemon) Fruit Oil
Citrus Limon (Lemon) Fruit Powder
Citrus Limon (Lemon) Juice Powder
Citrus Madurensis Fruit Juice
Citrus Paradisi (Grapefruit) Fruit Water
Citrus Paradisi (Grapefruit) Juice
Citrus Reticulata (Tangerine) Fruit
Citrus Reticulata (Tangerine) Fruit Water
Citrus Shunkokan Fruit Extract
Citrus Sphaerocarpa Fruit Juice
Citrus Sudachi Fruit Extract
Citrus Sudachi Fruit Juice
Citrus Tachibana/Reticulata Fruit Juice
Citrus Tamurana Fruit Extract
Citrus Tangelo Fruit Juice
Citrus Tangelo Fruit Powder
Citrus Tangerina (Tangerine) Fruit
Citrus Tangerina (Tangerine) Fruit Water
Citrus Tankan Fruit Extract
Citrus Tankan Fruit Water
Citrus Unshiu/Citrus Reticulata/Citrus Iyo Fruit Water
Citrus Unshiu Fruit Extract
Citrus Unshiu Fruit Juice
Citrus Unshiu Fruit Oil
Citrus Unshiu Fruit Powder
Citrus Unshiu Fruit Water
Citrus Unshiu/Sinensis/Reticulata Fruit Extract
Defatted Citrus Unshiu Fruit
Microcitrus Australasica Fruit Extract
Microcitrus Australis Fruit Extract

Table 11. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
DERMAL IRRITATION - ALTERNATIVE STUDIES					
citrus grandis (grapefruit) fruit extract	100% in powder form	reconstructed human epidermal model	EpiDerm dermal irritation test	-non-irritating	[20]
DERMAL IRRITATION – NON-HUMAN					
citrus junos fruit extract	1.2%	3 rabbits	-primary skin irritation test	-not-irritating	[6]
hydrolyzed citrus aurantium dulcis (orange) fruit extract	8.5% tested neat	3 rabbits	-acute dermal irritation/corrosion test according to OECD 404 -patches semi-occluded for 4 h	-not-irritating	[5]
DERMAL IRRITATION –HUMAN					
citrus junos fruit extract	1.2%	25 subjects	-human single insult patch test; occluded	-not-irritating	[6]
DERMAL SENSITIZATION – NON-HUMAN STUDIES					
citrus junos fruit extract	1.2%	30 guinea pigs	-guinea pig sensitization assay	-not-sensitizing	[6]
hydrolyzed citrus aurantium dulcis (orange) fruit extract	8.5% tested neat and at 50% dilution	10 albino guinea pigs	-Magnusson and Kligman maximization test according to OECD 406 -patches occluded	-not sensitizing	[5]
DERMAL SENSITIZATION – HUMAN STUDIES					
citrus aurantium bergamia (bergamot) fruit extract	0.081525% in a white lotion	105 subjects	-modified Draize HRIPT -during induction phase, 0.2 ml test material was applied for 24 h to skin sites on the scapular back with an occlusive Webril patch -total of 9 induction patches were completed over 3 weeks -after a 2 week rest, the same dose was applied during the challenge phase to naïve sites via occlusive patch -patches were removed after 24 h and sites were evaluated at 48 and 72 h post-application	-test material did not induce irritation or sensitization	[25]
citrus aurantium dulcis (orange) fruit extract and citrus limon (lemon) fruit extract	1.2% each in a night moisturizer	100 subjects	-modified Draize HRIPT -product was tested neat, not occluded -during the induction phase, test material was applied to the back and allowed to air dry -total of 9 induction patches were completed over 3 weeks -after a 2 week rest, the test material was applied to naïve sites and the sites were scored 24 and 48 h post-application	-test material did not induce irritation or sensitization	[27]
citrus aurantium dulcis (orange) fruit water	38% in an eye gel	214 subjects	-HRIPT -0.2 g test material applied by a 2 cm^2 Webril patch to back or upper arm and occluded -total of 9 induction patches were completed over 3 weeks -after a 2 week rest, the test material was applied for 24 h to naïve sites and the sites were scored 48 and 72 h post-application	-test material did not induce sensitization -1 subject experienced erythema during induction, but no reactions were observed when subject received test material on a new test site	[26]

Table 11. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
citrus nobilis (mandarin orange) fruit extract	1% in dioctyl adipate/octyl palmitate/octyl stearate	107 subjects	-HRIPT -0.2 ml test material applied by a 1 in^2 patch to upper back and semi-occluded -total of 9 induction patches were completed over 3 weeks -after a 2 week rest, the test material was applied to naïve sites and the sites were scored 24 and 72 h post-application	-test material did not induce irritation or sensitization	[23]
citrus limon (lemon) fruit water	1% in a skin cleansing product	102 subjects	-HRIPT -0.2 ml test material applied by a 3/4 in^2 patch to upper back and semi-occluded -total of 9 induction patches were completed over 3 weeks -after a 2 week rest, the test material was applied to naïve sites and the sites were scored 24 and 72 h post-application	-test material did not induce sensitization -2 subjects experienced mild to moderate erythema during the induction phase, but did not have sensitivity reactions	[24]
citrus grandis (grapefruit) fruit extract	0.16% in a toner	206 subjects	-HRIPT -0.15 ml test material applied by 2 cm^2 patch to back and occluded -total of 9 induction patches were completed over 3 weeks -after a 2 week rest, the test material was applied for 24 h to naïve sites and the sites were scored 24, 48, and 72 h post-application	-test material did not induce irritation or sensitization	[28]
citrus sinensis (orange) fruit water	undiluted	25 subjects	-HRIPT -20 µl test material applied by 50 mm^2 Finn Chamber and occluded -total of 9 induction patched were completed over 3 weeks -after week rest, test material as applied for 24 h to naïve sites and the sites were scored 24, 48, and 72 h post-application	-test material was non-irritating and non-sensitizing	[69]

Table 12. Photosensitization and phototoxicity studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			NON-HUMAN		
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	[29]
			HUMAN		
sweet orange peel, mesocarp, and fruit and 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 48 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	[30]
citrus aurantium bergamia (bergamot) fruit extract	0.081525% in a white lotion	20 subjects with type I to type III skin	-patches of ¾ in^2 area containing 0.2 ml test material that volatilized for at least 30 min were applied to test site and occluded -patches were removed after 24 h and the test sites were irradiated with 0.5 MED of UVB light followed by 20 J of UVA -light source was a 150 W xenon arc lamp with WG-320 and UG-11 filters, emission spectrum for UVA and UVB ranges was 290-400 nm -test sites were examined at 24 and 48 h after irradiation	-no contact dermal phototoxic responses observed	[70]

Table 13. Case reports

Mode of Contact	Patient(s)	Presentation	Reference
limeade made from the juice of Mexican limes; exposure to lime juice was at least 15 min in duration; minimal sunlight exposure for 1 h while swimming outdoors	6-year-old boy	-initial presentation was marked symmetric, painful erythema of both hands that abruptly stopped at the wrists; skin had a wrinkled appearance similar of an early second-degree burn or severe contact allergy -8 h later, dramatic bullae developed over the dorsum of both hands	[31]
fresh limes used in an arts-and-crafts activity at a summer camp	12 children initially	-skin eruptions consistent with phototoxic dermatitis confined to hands, wrists, and forearms -eruptions observed as discreet and confluent polymorphous patches and linear streaks -eruptions were also macular, hyperpigmented, and nonpruritic -clinical examination of 622 children, 104 counselors, and 57 adult staff at the camp found 97 (16%) of the children, 7 of the counselors (7%), and none of the adult staff with a similar rash	[32]
fresh limes and lime juice while making salsa on vacation in the Bahamas	28-year-old male active duty sailor	-hyperpigmented macules on the dorsa of both hand and right forearm; macules were uniformly brown in color and well demarcated with minimal erythema -lesions were observed near the knuckles and between the thumb and forefinger, with guttate macules scattered along the radial right forearm -large bullous lesion also developed on the dorsum of the patient's left hand -no reactions were observed on the palms and there were no other related cutaneous mucosal lesions -based on physical examination and patient history, the patient was diagnosed with phytophotodermatitis.	[33]
fresh limes used to wash clothing and scrubbed directly on the skin during travel to beaches in Mexico, Belize, and Guatemala	22-year-old female	-painful, streaky, hyperpigmented rash on lateral surface of right thigh, with an associated area of blistering and erythema -similar rash on the dorsal aspect of both hands -rash started with painful burning erythema and progressed to blister formation in linear pattern -rash began shortly after the patient started washing her clothes in freshly squeezed lime juice and after spending time in the sun -patient was diagnosed with phytophotodermatitis from psoralen and UV light exposure	[34]
fresh lemon that was accidentally mixed with sunscreen	3-year-old girl	-erythema, hyperpigmentation, and ulcerated areas on the trunk except on areas that had been covered with a bathing suit -child's mother had similar hypercromic patches on her hand -mother had been eating seafood with lemon prior to applying sunscreen on the child -diagnosis was phytophotodermatitis	[35]
fresh lime in gin and tonic	52-year-old female	-patient presented with a 4-month history of an eczematous rash on the side of the mouth and lips -initially diagnosed as angular chelitis by general practitioner -months prior to medical examination, the patient had begun sucking on limes from gin and tonics for up to 1 min -patient also had a history of mild hand eczema and eyelid dermatitis -dermatological examination showed an eczematous eruption on the lips, left corner of the mouth, left chin and eyelids -patch test to the British Contact Dermatitis Society extended standard series, cosmetics, balsams and perfumes, hairdressers series, lemon and lime peel yielded positive reactions to *Myroxylon pereirae*, fragrance mix, santolite resin, geraniol 2%, geranium oil, rose oil Bulgarian, and lime peel on days 2 and 4	[36]

Table 13. Case reports

Mode of Contact	Patient(s)	Presentation	Reference
fresh lemon	13-year-old female	-patient with a history of psoriasis and sports-related musculosketal injuries presented with a week-long painless erythematous rash on right thigh -rash began while on a beach vacation following exposure to lemons -physical examination showed erythematous, hyperpigmented streaks on thigh and 3 well-demarcated erosion on distal thigh that were in the shape of her hand -diagnosis was phytophotodermatitis from exposure to psoralens and UVA light	[37]
liniment containing lime juice	26-year-old female	-patient presented with a residual maculopapular rash on right thigh and several hyperpigmented linear track on right leg -two weeks prior, the patient was thought to have been stung by a jellyfish while surfing and had treated the skin with a liniment containing turmeric, vinegar, and lime juice -3 days after treatment, several pigmented linear tracks appeared on right leg, some extending down to knee and 2 reaching down to the lateral part of the right foot -diagnosis was phytophotodermatitis and not jellyfish envenomation based on delayed reaction and hyperpigmented skin lesions	[38]
lime juice	6-year-old girl	-5 days after squeezing limes, patient presented with large blisters on the dorsum of both hands and thighs with some visible streaking equivalent to a superficial burn surface area of 4% -lime juice exposure was followed by exposure to the sun -diagnosis was phytophotodermatitis	[39]
lime juice	11-year-old girl	-5 days after squeezing limes, patient presented with large blisters to the dorsum of both hands, equivalent to a superficial burn surface area of 2.5% -lime juice exposure was followed by exposure to the sun -diagnosis was phytophotodermatitis	[39]
lime juice	14-year-old girl	-5 days after preparing limes, patient presented with apparent superficial burns to the dorsum of both hands, equivalent to a burn surface area of 1% -lime juice exposure was followed by exposure to the sun -diagnosis was phytophotodermatitis	[39]
key lime juice	24-year-old female	-patient presented with irregularly shaped but well demarcated rash on hands and wrists. Rash had erythematous patches and plaques and was tender with noted edema on the dorsum of the hands -rash developed 2 days prior with tender erythema and swelling, with some vesicle and blister formation -several hours before the development of the lesions, the patient had made a key lime pie from scratch, including hand squeezing limes, and then walked outside on a sunny day -diagnosis was lime phytophotodermatitis	[40]

Table 13. Case reports

Mode of Contact	Patient(s)	Presentation	Reference
limes	23-year-old female	-patient presented with a 3-day history of painful, erythematous, blistering rash on sun-exposed skin -prior to the onset of the rash, patient had spent 2 days at the beach where she had prepared mojitos with limes -in the subsequent 24 h, a burning erythema developed and later blistered -physical examination found tender skin with vesicles and tense bullae atop erythematous, edematous plaques on her dorsal hands, forearms, and chest. Symmetric, discrete, erythematous patches studded with tiny vesicles were found on her back -diagnosis was phytophotodermatitis	[41]
lime juice	32-year-old female	-patient presented with a linear eruption consisting of erythema and hyperpigmentation over the chest, abdomen, and legs. The eruption was only mildly painful and showed no pruritus or blistering -eruption occurred during the final days of a cruise where the patient had inserted limes into bottles of Mexican beer and sprayed the beer and lime juice over lower trunk and legs -diagnosis was lime phytophotodermatitis	[42]
lime juice	24-year-old female	-patient presented with a linear array of hyperpigmentation on the left side of the neck and in a fingerprint smudge pattern on the right side of the neck -five days prior, the patient had been drinking Mexican beer with limes at a festival and had splashed lime juice on her neck -diagnosis was lime phytophotodermatitis	[42]
limes	21-year-old female	-patient developed a raised, pruritic, 10 cm x 30 cm lesion on right lateral chest wall during a vacation in Florida, initially thought to be having an allergic reaction -five days after returning home, rash was diagnosed with herpes zoster due to multiple vesicles in dermatomal distribution on right side of torso -four days later, patient presented to primary care physician due to continuation of occurrence of hyperpigmentation around mouth, chin, upper chest, breasts, thighs, and forearms. Original lesions on right lateral thorax had dried, crusted, and was peeling -while on vacation, the patient was exposed to the sun and had consumed citrus beverages and fresh limes -final diagnosis was phytophotodermatitis	[43]

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