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Safety Assessment of Citrus-Derived Peel Oils as Used in Cosmetics

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Abstract

The Cosmetic Ingredient Review Expert Panel assessed the safety of 14 citrus-derived peel oil ingredients and concluded that these ingredients are safe for use in cosmetic products when finished products, excluding rinse-off products, do not contain more than 0.0015% (15 ppm) 5-methoxypsoralen, and when formulated to be nonsensitizing and nonirritating. The citrus-derived peel oil ingredients are most frequently reported to function in cosmetics as fragrances and/or skin conditioning agents. The Panel reviewed the available animal and clinical data to determine the safety of these ingredients. Because final product formulations may contain multiple botanicals, each containing the same 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.

Keywords

cosmetics, safety, citrus peel oils

Introduction

Citrus-derived peel oils are widely used as cosmetic ingredients 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 14 citrus-derived peel oils:

Citrus aurantifolia (lime) peel oil
Citrus aurantium amara (bitter orange) peel oil
Citrus aurantium currassuviensis peel oil
Citrus aurantium dulcis (orange) peel oil
Citrus clementina peel oil
Citrus grandis (grapefruit) peel oil
Citrus iyo peel oil
Citrus junos peel oil
Citrus limon (lemon) peel oil
Citrus medica vulgaris peel oil
Citrus nobilis (mandarin orange) peel oil
Citrus reticulata (tangerine) peel oil
Citrus tachibana/reticulata peel oil
Citrus tangerina (tangerine) peel oil

The citrus ingredients in this assessment are found in foods, and daily exposure from food use would result in much larger systemic exposures than those from use in cosmetic products. Additionally, essential oils, oleoresins (solvent-free), and natural extracts (including distillates) derived from some citrus fruits are generally recognized as safe (GRAS) for their intended use in foods for human and animal consumption according to the US Food and Drug Administration (FDA). Volatile oils of limes, lemons, grapefruits, bitter oranges, oranges, and tangerines are described as flavoring agents in the US Pharmacopeia (USP) Food Chemicals Codex.[1] Thus, the systemic toxicity potential of citrus-derived peel oils via oral exposure is not addressed further in this report. The primary focus of this safety assessment of these citrus ingredients as used in cosmetics is on the potential for irritation and sensitization from dermal exposure.

The Cosmetic Ingredient Review (CIR) does not review ingredients that function only as fragrance ingredients because, as fragrances, the safety of these ingredients is evaluated by the Research Institute for Fragrance Materials (RIFM). Three of the citrus-derived peel oils in this report function only as

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

Ingredient	Definition[2]	Function[2]
Citrus aurantifolia (lime) peel oil	*C aurantifolia* (lime) peel oil is the volatile oil obtained from the peel of *C aurantifolia*	Fragrance ingredients
Citrus aurantium amara (bitter orange) peel oil CAS No. 68916-04-1	*C aurantium* amara (bitter orange) peel oil is the volatile oil obtained from the peel of *C aurantium amara*	Fragrance ingredients; skin conditioning agents-miscellaneous
Citrus aurantium currassuviensis peel oil	*C aurantium currassuviensis* peel oil is the volatile oil derived from the peel of the laraha orange, *C aurantium currassuviensis*	Fragrance ingredients
Citrus aurantium dulcis (orange) peel oil CAS No. 8008-57-9	*C aurantium dulcis* (orange) peel oil is the volatile oil obtained by expression from the peel of *Citrus sinensis*	Fragrance ingredients; skin conditioning agents-miscellaneous
Citrus clementina peel oil	*C clementina* peel oil is the volatile oil obtained from the peel of *C clementina*	Fragrance ingredients; skin conditioning agents-miscellaneous
Citrus grandis (grapefruit) peel oil CAS No. 8016-20-4	*C grandis* (grapefruit) peel oil is the volatile oil obtained from the peel of the grapefruit, *C grandis*	Fragrance ingredients; skin conditioning agents-miscellaneous
Citrus iyo peel oil	*C iyo* peel oil is the volatile oil obtained from the peel of *C iyo*	Skin conditioning agents-emollient
Citrus junos peel oil	*C junos* peel oil is the volatile oil obtained from the peel of *C junos*	Cosmetic astringents
Citrus limon (lemon) peel oil CAS Nos. 8008-56-8; 8020-19-7; 84929-31-7; 85085-28-5	*C limon* (lemon) peel oil is the volatile oil obtained from the peel of *C limon*	Fragrance ingredients; skin conditioning agents-miscellaneous
Citrus medica vulgaris peel oil	*C medica vulgaris* peel oil is the volatile oil obtained from the peel of *C medica vulgaris*	Fragrance ingredients
Citrus nobilis (mandarin orange) peel oil CAS No. 8008-31-9; 84696-35-5	*C nobilis* (mandarin orange) peel oil is the oil obtained from the peel of the mandarin orange, *C nobilis*	Fragrance ingredients; skin conditioning agents-miscellaneous
Citrus reticulata (tangerine) peel oil CAS No. 8008-31-9	*C reticulata* (tangerine) peel oil is the volatile oil obtained from the peel of *C reticulata*	Deodorant agents; flavoring agents; fragrance ingredients
Citrus tachibana/reticulata peel oil	*C tachibana/reticulata* peel oil is the volatile oil obtained from the peel of the hybrid of *C tachibana* and *C reticulata*	Skin conditioning agents-emollient
Citrus tangerina (tangerine) peel oil	*C tangerina* (tangerine) peel oil is the volatile oil obtained from the peel of *C tangerina*	Fragrance ingredients; skin conditioning agents-miscellaneous

Table 2. Citrus Ingredients That Potentially Function Solely as Fragrance Ingredients.

Citrus aurantifolia (lime) peel oil
Citrus aurantium currassuviensis peel oil
Citrus medica vulgaris peel oil

fragrance ingredients, according to the *International Cosmetic Ingredient Dictionary and Handbook* (see Table 2).[2] However, RIFM has not confirmed that these 3 ingredients function only as fragrances and therefore within its purview; thus, CIR is reviewing the safety of these ingredients.

Botanicals such as those derived from citrus contain hundreds of constituents, some of which have the potential to cause toxic effects. For example, bergapten (also known as 5-methoxypsoralenor [5-MOP]) is a naturally occurring phototoxic furanocoumarin (psoralen) in citrus peel oils. In this assessment, CIR is reviewing information available to evaluate the potential toxicity of each of the citrus-derived peel oils as a whole, complex substance. Except for specific constituents of concern, CIR is not reviewing information that may be available to assess the potential toxicity of the individual constituents of which the citrus-derived ingredients are composed. Cosmetic Ingredient Review requested information on the concentrations (including ranges, means, upper 95%confidence limits, detection limits, etc) of individual constituents in citrus-derived peel oils used in cosmetics to facilitate the safety assessment of these ingredients. Such information on constituents that have been identified as constituents of concern by the Panel in previous safety assessments, or by other recognized scientific expert review bodies, is especially important.

Some toxicological data on lemon oil and sweet orange oil (synonyms: lemon, ext. and orange, sweet, extract, respectively) reviewed in this safety assessment were obtained from robust summaries of data submitted to the European Chemical Agency (ECHA) by companies as part of the REACH chemical registration process. These data are available on the ECHA website.[3,4]

Note that, in many of the published studies included in this assessment, the information provided is not sufficient to determine how well the substance being tested represents the cosmetic ingredient. In this safety assessment, if a substance tested in a study is not clearly a cosmetic ingredient, because of lack of information on the genus and species from which the substance was derived and/or the method of extraction used, the test substance will be referred to by a common name (eg, lime oil). If the substance is clearly a cosmetic ingredient, the International Nomenclature of Cosmetic Ingredients (INCI) name

will be used (eg, "*C aurantifolia* [lime] peel oil"). In some instances, the part of the plant from which the oil was expressed is not known but, based on the method of manufacture, the oil could have been expressed from the peels of the citrus fruit. Additionally, some inconsistencies were noted in both taxonomic and INCI naming conventions. For example, this report includes the sweet orange ingredient described as *C aurantium dulcis* (orange) peel oil in the *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*).[2] In contrast, most of the published literature and the FDA refer to this ingredient as *Citrus sinensis* (sweet orange) peel oil. Another example of a naming inconsistency is *C grandis* (grapefruit) peel oil; *C grandis* is generally considered a name for a pummelo and is more commonly called *Citrus maxima*. The INCI Committee of the Personal Care Products Council (Council) is working to correct some of these errors.

Chemistry

Definition and General Characterization

The definitions and functions of the citrus-derived peel oils 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 essential oils are hydrophobic, liquid, and volatile aroma compounds from plants. These are typically mixtures of small molecules, but their chemical structures can vary widely. The volatile nature of essential oils makes them likely to be useful as fragrances but does not preclude other functions for them in cosmetics.

There are numerous *Citrus* varieties distributed throughout the world; most citrus fruits are grown in the temperate and tropical zones in both the northern and southern hemispheres.[5] Citrus can be propagated and new varieties can be produced by cultivating asexual nuclear or chance seedlings or by crossing or mutation.

Physical and Chemical Properties

Physical and chemical properties of the citrus-derived peel oils are provided in Table 3.

Method of Manufacturing

A suitable antioxidant can be added to citrus oil during preparation.[1]

Bitter orange oil and orange oil are obtained using a cold-pressed extraction method from the fresh peel of the fruit of *Citrus aurantium* and *C sinensis*, respectively.[1] *Citrus grandis* oil[6] and *C junos* oil[7] are also extracted using a cold-press method. Tangerine oil (cold-pressed) is obtained from the peels of the ripe fruit of the Dancy tangerine, *C nobilis* or *C reticulata*, and from some other closely related varieties.[1]

Lemon oil and lime oil, expressed, are produced by pressing the outer rind of the ripe fruit manually or by machine.[8] More economical processes involve an integrated juice-oil procedure. These oils can also be produced by distillation of expressed oils or direct distillation of fruit; distilling (rectifying) removes terpenes. Steam distillation removes nonvolatile furocoumarins.

Citrus iyo oil is produced by removing the peel from the fruit, homogenization of the peel with distilled water, and lyophilization.[9] The oil is purified using vacuum distillation.

Mandarin peel oil, expressed (identified in the literature as *C reticulata*), is prepared by expression of the peels of the ripe fruit of the mandarin orange.[10]

Constituents/Composition

The citrus-derived peel oils 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 apomixis (ie, 1 or more of several types of asexual reproduction).[11] The composition of citrus oils will vary based on the location where the plant is grown, the maturity of the plant, and storage conditions.[5] The method of extraction will also affect the composition.

Citrus oils contain large amounts of monoterpene hydrocarbons. Limonene is the constituent present in the greatest amount, often comprising greater than 90% of the oil, and the amount present can vary within the oil; for example, limonene is reported to compose 38.1% to 95.8% *C limon* (lemon) peel essential oils, cold-pressed.[12,13] Citrus oils also contain sesquiterpene hydrocarbons, which are responsible for the characteristic flavors of these oils.[12] Table 4 lists the chemical compositions of cold-pressed,[6,7,11-16] hydrodistilled,[17-21] lyophilization/vacuum distillation,[9] and steam-distilled[22] peel oils sorted by citrus plant species; Table 5 presents the typical levels of 5-MOP found in some of the oils; and Table 6 provides the levels of major coumarins and furocoumarins in lemon and lime oil. Table 7 lists citrus constituents that are established contact allergens, according the European Commission's Scientific Committee on Consumer Safety.

Use

Cosmetic

Table 8 presents the current product-formulation use data for citrus-derived peel oils. These ingredients are most frequently reported to function as fragrances and/or skin conditioning agents-miscellaneous.[2]

According to information supplied to the FDA by industry as part of the Voluntary Cosmetic Registration Program (VCRP), *C limon* (lemon) peel oil has the most reported uses in cosmetic and personal care products, with a total of 490; more than half of the uses are in leave-on skin care preparations.[23] *Citrus aurantium dulcis* (orange) peel oil (reported as *C sinensis* [sweet orange] peel oil by the VCRP) has the second greatest number of overall uses reported, with a total of 289; about half of those uses are in leave-on skin care preparations.

In a use concentration survey conducted by the Council, *C limon* (lemon) peel oil had a maximum use concentration range

Table 3. Physical and Chemical Properties of Citrus-Derived Peel Oils.

Property	Description	Reference
Citrus aurantifolia (lime) oil		
Color	Colorless to greenish yellow	8
Odor	Fresh citrus, intense	8
Optical rotation	+34° to +47°	8
Solubility	Insoluble in water, soluble in ethanol and propylene glycol	8
Refractive index	1.4477-1.4745	8
Specific gravity	0.855-0.863	8
C aurantifolia or *Citrus latifolia* (lime) oil (distilled)		
Color	Colorless to greenish yellow	1
Odor	Mild citrus, floral	1
Optical rotation/angular rotation	+34° to +47°	1
Solubility	Soluble in most fixed oils and mineral oil; insoluble in glycerin and propylene glycol	1
Solubility in alcohol	1-mL sample dissolves in 5 mL of 90% alcohol	1
Aldehydes	Between 0.5% and 2.5% of aldehydes, calculated as citral	1
Refractive index	1.474-1.477 at 20°C	1
Specific gravity	0.855-0.863	1
C aurantifolia (lime) oil (cold-pressed)		
Color	Yellow to brown-green to green liquid	1
Odor	Fresh lime peel	1
Optical rotation/angular rotation	Mexican type: +35° to +41°; Tahitian type: +38° to +53°	1
Solubility	Soluble in most fixed oils and mineral oil; insoluble in glycerin and propylene glycol	1
Aldehydes	Mexican type: no less than 4.5% and no more than 8.5% of aldehydes, calculated as citral; Tahitian type: no less than 3.2% and no more than 7.5% of aldehydes, calculated as citral	1
Refractive index	Mexican type: 1.482-1.486; Tahitian type: 1.476-1.486	1
Residue of evaporation	Mexican type: 10.0%-14.5%; Tahitian type: 5.0%-12.0%	1
Specific gravity	Mexican type: 0.872-0.881; Tahitian type: 0.858-0.876	1
UV absorbance	Max. at 315 nm; Mexican type: no less than 0.45; Tahitian type: no less than 0.24	1
Citrus aurantium (bitter orange) oil (cold-pressed)		
Color	Pale yellow or yellow-brown liquid	1
Odor	Characteristic aromatic odor of the Seville orange	1
Optical rotation/angular rotation	+88° to +98°	1
Solubility	Miscible with absolute alcohol and with an equal volume of glacial acetic acid; soluble in fixed oils and mineral oil; slightly soluble in propylene glycol; relatively insoluble in glycerin	1
Aldehydes	No less than 0.5% and no more than 1.0% of aldehydes, calculated as decyl aldehyde	1
Refractive index	1.472-1.476 at 20°C	1
Residue of evaporation	2.0%-5.0%	1
Specific gravity	0.845-0.851	1
Citrus clementina		
Color	Orange to brownish liquid	43
Odor	Characteristic	43
Optical rotation	+89 to +97° (15°C)	43
Solubility	Insoluble in water; soluble in ethyl alcohol	43
Refractive index	1.5640-1.4820 (20°C)	43
Specific gravity	0.840-0.875 (15°C)	43
Citrus limon (lemon) oil		
Color	Pale to deep yellow or greenish yellow	8
Odor	Fresh citrus, intense	8
Optical rotation	+57 to +65.6	8
Solubility	Insoluble in water, soluble in ethanol and propylene glycol	8
Refractive index	1.474-1.467	8
Specific gravity	0.849-0.855	8
C limon (lemon) oil (distilled)		
Color	Colorless to pale yellow liquid	1
Odor	Fresh lemon peel	1
Optical rotation/angular rotation	+55° to +75°	1
Solubility	Soluble in most fixed oil, mineral oil, and alcohol (with haze); insoluble in glycerin and propylene glycol	1
Solubility in alcohol	1-mL sample dissolves in 5 mL of 90% alcohol	1

(continued)

Table 3. (continued)

Property	Description	Reference
Aldehydes	Between 1.0% and 3.5% of aldehydes, calculated as citral	1
Refractive index	1.470-1.475 at 20°C	1
Specific gravity	0.842-0.856	1
UV absorbance	Maximum at 315 nm, no less than 0.01	1
C limon (lemon) oil (cold-pressed)		
Color	Pale to deep yellow or green-yellow	1
Odor	Fresh lemon peel	1
Optical rotation/angular rotation	California and Italian types: +57° to +65.6°; desert type: +67° to +78°	1
Solubility	Miscible with dehydrated alcohol and glacial acetic acid	1
Solubility in alcohol	1 mL of sample dissolves in 3 mL of 95% alcohol, slight haze possible	1
Aldehydes	Desert type: no less than 1.7% of aldehydes, calculated as citral; California type: no less than 2.2% and no more than 3.8% of aldehydes, calculated as citral; Italian type: no less than 3.0% and no more than 5.5% of aldehydes, calculated as citral	1
Refractive index	1.473-1.476 at 20°C	1
Residue of evaporation	Between 5.0% and 14.5%	1
Specific gravity	Desert type: 0.846-0.851; California and Italian types: 0.849-0.855	1
UV absorbance	Maximum at 315 nm; desert and California types: no less than 0.2; Italian type: no less than 0.49	1
Citrus nobilis or Citrus reticulata (tangerine) oil (cold-pressed)		
Color	Red-orange to brown-orange	1
Odor	Pleasant, orange	1
Optical rotation/angular rotation	+88° to +96°	1
Solubility	Soluble in most fixed oils and mineral oil; slightly soluble in propylene glycol; relatively insoluble in glycerin	1
Aldehydes	0.8% to 1.9% of aldehydes, calculated as decyl aldehyde	1
Refractive index	1.473-1.476 at 20°C	1
Residue of evaporation	2.3%-5.8%	1
Specific gravity	0.844-0.854	1
Citrus reticulata peel oil		
Physical state and appearance	Clear, mobile, dark orange to reddish-orange or Brownish-orange liquid	10
Odor	Orange-like	10
Optical rotation	+63° to +78°	10
Refractive index	1.4730-1.4770 (20°C)	10
Specific gravity	0.847-0.853 (25/25°C)	10
Citrus sinensis (orange) oil (distilled)		
Color	Colorless to pale yellow liquid	1
Odor	Mild citrus floral	1
Optical rotation/angular rotation	+94° to +99°	1
Solubility	Soluble in most fixed oil, mineral oil, and alcohol (with haze); insoluble in glycerin and propylene glycol	1
Solubility in alcohol	1-mL sample dissolves in 5 mL of 90% alcohol	1
Refractive index	1.471-1.474 at 20°C	1
Specific gravity	0.840-0.844	1
UV absorbance	Maximum at 330 nm, no less than 0.01	1
Citrus sinensis (orange) oil (cold-pressed)		
Color	Intensely yellow, orange, or deep orange liquid	1
Odor	Characteristic of fresh, sweet orange peel	1
Optical rotation/angular rotation	+94° to +99°	1
Solubility	Miscible with dehydrated alcohol and carbon disulfide; soluble in glacial acetic acid	1
Aldehydes	No less than 1.2% and no more than 2.5% of aldehydes, calculated as decyl aldehyde	1
Refractive index	1.472-1.474 at 20°C	1
Specific gravity	0.842-0.846	1
UV absorbance	Maximum at 330 nm; California type: no less than 0.130; Florida type: no less than 0.240	1

Abbreviation: UV, ultraviolet.

of 0.0001% to 0.5%, with 0.5% reported in "other" skin care preparations.[24] *Citrus aurantium dulcis* (orange) peel oil had a maximum use concentration range of 0.00002% to 29%, with 29% reported in noncoloring hair conditioners.

In some cases, reports of uses were received from the VCRP, but no concentration of use data were provided. For example, *C junos* peel oil is reported to be used in 6 formulations, but no use concentration data were available. In other

Table 4. Chemical Composition (%) of Citrus Peel Oils.[a]

	Citrus aurantifolia (lime) peel oil		*Citrus aurantium amara* (bitter orange) essential oil				*Citrus aurantium dulcis* (orange) essential oil		*Citrus clementina* Peel essential oil		*Citrus grandis* (grapefruit) peel essential oil		*Citrus iyo* peel essential oil		*Citrus junos* peel essential oil	
	Cold-pressed[13]		Cold-pressed[14]		Hydrodistilled[18,20]		Cold-pressed[14]		Hydrodistillation[17]		Cold-pressed[6]		Lyophilization/vacuum distillation[9]		Cold-pressed[7] or not specified[16]	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Essential oil content (%)					0.12[18]-1.67[20]							0.12[6]		1.5[9]		
Constituent																
Limonene	39.9	94.4			67.9	94.67			93.77	96.19		94.8	79	89	63.1	77.44
(E)-α-Bergamotene															Trace	
(E)-β-farnesene	Trace	0.1													Trace	
(E)-β-ocimene	Trace	0.5			0.02	0.5									ND	Trace
(E)-decenal															ND	Trace
(E)-carvone												0.005-0.05				
(E)-caryophyllene	0.1	0.5														
(E)-caryophyllene oxide												Trace				
(E)-linalool oxide															ND	Trace
(E)-nerolidol															Trace	
(E)-p-mentha-2,8-dienol												0.1				
(E)-p-2,8-menthadien-1-ol												Trace				
(E, E)-α-farnesene	0.3	1.9										0.1				
(E, E)-farnesyl acetate															ND	Trace
(E, Z)-2,6-nonadien-1-ol											ND					
(Z)-β-ocimene	Trace	0.7													Trace	
Z-carveol												0.005-0.05				
(Z)-carvone												0.1				
(Z)-β-farnesene															0.9	1.3
(Z)-limonene oxide															ND	Trace
(Z)-piperitol												0.005-0.05				
1-Octanol																
1,3,8-p-Menthatriene															Trace	
1,8-Cineole	0.5	0.6			Trace	14.72										
2Z.6E-farnesol					Trace											
3-Carene	Trace	0.3														
3,3',4',5,6,7-Heptamethoxyflavone			X				X									
3,3',4',5,6,7-Hexamethoxyflavone							X									
3',4',5,6,7,8-Hexamethoxyflavone			X													
3',4',5,6,7-Pentamethoxyflavone							X									
4',5,6,7-Tetramethoxyflavone			X				X									
4',5,6,7,8-Pentamethoxyflavone			X				X									
5-Methoxypsoralen			X													
(5-(6',7'-Dihydroxy-geranyloxy)psolaren)			X													
(5-(6',7'-Epoxy-geranyloxy)psolaren)			X													
5,7-Dimethoxycoumarin			X													
6-Methylhept-5-en-2-one		Trace														
7-Methoxy-8(2',3'-dihydroxy)isopentyloxycoumarin			X													
7-Methyoxy-8(2',3'-epoxy)isopentenylcoumarin			X													
7-Methyoxy-8-isopentenylcoumarin			X													
7-Methoxy-8-(2'-one-isopentyl)coumarin)			X													
30 carvacrol					Trace	0.69										
Allo-ocimene		Trace														
Aromadendrene															ND	Trace
Bicycloelemene															Trace	
Bicyclogermacrene	Trace	0.4													0.7	2.0
Borneol					0.08	0.16										

(continued)

Table 4. (continued)

	Citrus aurantifolia (lime) peel oil		*Citrus aurantium amara* (bitter orange) essential oil				*Citrus aurantium dulcis* (orange) essential oil		*Citrus clementina* Peel essential oil		*Citrus grandis* (grapefruit) peel essential oil		*Citrus iyo* peel essential oil		*Citrus junos* peel essential oil	
	Cold-pressed[13]		Cold-pressed[14]		Hydrodistilled[18,20]		Cold-pressed[14]		Hydrodistillation[17]		Cold-pressed[6]		Lyophilization/vacuum distillation[9]		Cold-pressed[7] or not specified[16]	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Bornyl acetate	Trace	Trace			Trace											
Camphene	Trace	0.2			Trace	0.24									Trace	
Camphor					0.17	6.37										
Caryophyllene															ND	Trace
Caryophyllene oxide	Trace	0.1			0.08	0.21						Trace				
Cedrol											Trace					
cis-Dihydrocarvone							0.03	0.28								
cis-Limonene-1,2-oxide	Trace	0.1														
cis- Linalool oxide THF		Trace			Trace	3.4										
cis-β-Ocimene						0.30										
cis-Sabinene hydrate					Trace	0.18									Trace	0.1
Citronellal	Trace	1.6							0.03	0.08		0.1				
Citronellol	Trace	0.6					Trace	0.07							ND	Trace
Citronellyl acetate	0.1	0.2														
Cumin aldehyde												0.005-0.05				
Decanal	Trace	0.3				0.16						0.3			Trace	
Dihydrocarveol											Trace					
Dodecanol		Trace										0.1			ND	Trace
Elemol											Trace				Trace	
Eugenol															ND	Trace
Geranial	0.5	6.1										0.1				
Geraniol	Trace	0.3														
Geranyl acetate	0.1	2.4			Trace	0.11										
Geranyl propionate											Trace					
Germacrene B															0.1	0.2
Germacrene D	Trace	1.0			0.04	0.25									0.3	0.4
Germacrene D-4-ol															0.3	0.4
Globulol		0.1														
Guaiene															ND	Trace
Heptyl acetate												0.3				
Isothyujol												0.005-0.05				
Limonen-10-ol											Trace					
Linalool	0.1	1.4			Trace	0.76			0.03	0.08		0.1	1.3	7.3	1.6	2.8
Linalool oxide																
Linalyl acetate	Trace	Trace			0.01	0.18						0.1				
Methyl-N-methyl anthranilate												0.005-0.05				
Myrcene	0.8	2.0			0.07	2.0			0.73	0.78			X		0.4	3.2
Neral	Trace	3.1									Trace					
Nerol	Trace	0.1			0.03	0.12					Trace				ND	Trace
Nerolidyl acetate											Trace					
Neryl acetate	Trace	2.0				0.10										
Nonanal	Trace	0.1			Trace	0.18						0.005-0.05			Trace	
Nonanoic acid												Trace				
Nootkatone												0.1.				
Octanal	Trace	0.1			0.02	1.59						0.4			Trace	
Octyl acetate	Trace	Trace														
p-Cymene	Trace	5.3			Trace	0.09									0.4	0.6
p-Cymenene		0.1														
p-Mentha-1-en-9-ol											Trace					

(continued)

Table 4. (continued)

	Citrus aurantifolia (lime) peel oil		*Citrus aurantium amara* (bitter orange) essential oil				*Citrus aurantium dulcis* (orange) essential oil		*Citrus clementina* Peel essential oil		*Citrus grandis* (grapefruit) peel essential oil		*Citrus iyo* peel essential oil		*Citrus junos* peel essential oil	
	Cold-pressed[13]		Cold-pressed[14]		Hydrodistilled[18,20]		Cold-pressed[14]		Hydrodistillation[17]		Cold-pressed[6]		Lyophilization/vacuum distillation[9]		Cold-pressed[7] or not specified[16]	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Perillaldehyde											Trace				Trace	
Perillyl alcohol															Trace	
Perillyl aldehyde												0.005-0.05				
Piperitenone		Trace													Trace	
Pseudolimonene															Trace	
Sabina ketone												0.1				
Sabinene	0.1	19.6			Trace	0.200.18						0.4			0.4	0.5
Santal-10-en-2-ol	Trace	Trace														
Spathulenol					Trace	0.21									ND	Trace
Terpinen-4-ol	Trace	1.7			0.01	0.54									Trace	0.1
Terpinolene	Trace	1.1			0.02	0.22					ND				0.6	0.7
Terpinyl acetate	Trace	Trace														
Tetradecane															ND	Trace
Tetradecenal											Trace					
Thymol															0.2	0.3
Thymyl methyl oxide	1.2	1.6														
trans-α-Bergamotene	0.2	1.6														
trans-Limonene-1,2-oxide	Trace	0.2														
trans-Sabinene hydrate	Trace	0.1													Trace	0.1
Tri-Cyclen					0	0.75										
Undecanal	Trace	0.1														
Valencene					0.04	0.2										
(−)-α-Copaene															Trace	0.1
α-Cadinene																0.1
α-Cadinol															ND	Trace
α-Cedrene												Trace				
α-Copaene												0.005-0.05				
α-Cubebene												0.1			Trace	
α-Farnesene															ND	Trace
α-Humulene	Trace	0.2			0.03	0.13										0.1
α-Muurolene															Trace	
α-p-Dimethyl styrene															Trace	
α-Phellandrene	Trace	0.1													0.7	0.9
α-Pinene	0.2	2.7			0.03	0.53			0.15	0.31		0.5			2.0	2.7
α-Sinensal																
α-Terpinene	Trace	0.4			0.91	1.66						1.8	X			0.3
α-Terpineol	Trace	4.7			0.07	0.35			0.04	0.09		0.1			0.2	0.3
α-Terpinyl acetate					Trace	1.4										
α-Thujene	Trace	0.7			0.14	0.44					ND					
α-Thujone					Trace	0.35										
α-ylangene															ND	Trace
β-Bisabolene	0.3	2.4														
β-Caryophyllene												0.1				0.3
β-Cubebene															Trace	0.1
β-Eleme	Trace	0.8														0.1
β-Eudesmol															Trace	
β-Ionone															ND	Trace
β-Phellandrene	0.2	0.8													2.16	5.4
β-Pinene	Trace	19.2			0.07	0.62			0.06	0.36		0.005-0.05			0.9	1.1

(continued)

Table 4. (continued)

	Citrus aurantifolia (lime) peel oil		*Citrus aurantium amara* (bitter orange) essential oil				*Citrus aurantium dulcis* (orange) essential oil		*Citrus clementina* Peel essential oil		*Citrus grandis* (grapefruit) peel essential oil		*Citrus iyo* peel essential oil		*Citrus junos* peel essential oil	
	Cold-pressed[13]		Cold-pressed[14]		Hydrodistilled[18,20]		Cold-pressed[14]		Hydrodistillation[17]		Cold-pressed[6]		Lyophilization/vacuum distillation[9]		Cold-pressed[7] or not specified[16]	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
β-Sesquiphellandrene															0.1	
β-Sinensal	Trace	0.1									Trace					
γ-Terpinene	Trace	21.5			0.14	0.31						0.005-0.05			11.4	12.3
δ-Carene															ND	Trace
δ-Elemene											Trace				0.1	0.2
δ-3-Carene						0.17										
Δ3-Carene					Trace	0.01										

	Citrus limon (lemon) peel essential oils				*Citrus nobilis* (mandarin orange) essential oil		*Citrus sinensis* (orange) peel oil						*Citrus reticulata* (tangerine) peel oil	
	Cold-pressed[12,13]		Hydrodistilled[18]		Cold-pressed[14]		Cold-pressed[11,12,15,16]		Hydrodistilled[44]		Steam-distilled[22]		Hydrodistilled[21,44]	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Essential oil content (%)	1.1212		1.318				0.98-1.2112		0.24-1.0744		2.4922		0.30-0.5044	
Constituent														
Limonene	38.1	95.8	37.631	69.71			61.08	96.57	66.8	80.9		77.49	64.1	92.4
(*E*)-β-Farnesene	Trace	0.2												
(*E*)-β-Ocimene	Trace	0.4						0.1						
(*E*)-Caryophyllene	Trace	0.7												
(*E*)-Nerolidol	Trace	Trace												
(Z)-β-Ocimene	Trace	0.3	Trace	0.5						0.34				0.28
Z-Carveol									0.68	4.53				1.29
1-Octanol													0.55	0.95
1,3,8-*p*-Menthatriene									1.21	1.69				
1,8-Cineole			Trace	0.82										
2Z.6E-farnesol			Trace											
3-Carene	Trace	Trace												
3-Furanacetic acid										3.0				
3,3′,4′,5,6,7-Heptamethoxyflavone					X									
3′,4′,5,6,7,8-Hexamethoxyflavone					X									
4-Carene									0.61	0.85				
4-Carvon methanol														0.95
4-Terpineol												0.43		
4-Vinyl guaiacol									1.21	1.27			0.87	2.32
4′,5,6,7-tetramethoxyflavone					X									
4′,5,6,7,8-Pentamethoxyflavone					X									
6-Methylhept-5-en-2-one	Trace	Trace												
30 Carvacrol			Trace	0.69										
Allyl isovalerate														0.36
Benzaldehyde		0.11												
Bicyclogermacrene								Trace						
Borneol		0.16	0.33	2.54				7.63						
Bornyl acetate	Trace	Trace	Trace	0.01										
Camphene	Trace	0.13	Trace	0.24				0.32						
Camphor			Trace	0.58										
Capraldehyde							0.35	5.62						
Caprinaldehyde		0.26						2.10						

(continued)

Table 4. (continued)

	Citrus limon (lemon) peel essential oils				*Citrus nobilis* (mandarin orange) essential oil		*Citrus sinensis* (orange) peel oil						*Citrus reticulata* (tangerine) peel oil	
	Cold-pressed[12,13]		Hydrodistilled[18]		Cold-pressed[14]		Cold-pressed[11,12,15,16]		Hydrodistilled[44]		Steam-distilled[22]		Hydrodistilled[21,44]	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Caryophyllene oxide	Trace	0.3	Trace											
Carvone												0.17	0.47	0.62
d-Carvone										0.39				
Cephrol												0.15		
cis-Carveol												0.22		
cis-Dihydrocarvone			Trace	0.29										
cis-Limonene-1,2-oxide	Trace	0.5												
cis-Linalool oxide THF			0	0.49										
cis-Sabinene hydrate			Trace	0.05										
cis-β-Farnesene														0.1
cis-β-Ocimene								0.26						
Citral		0.27					1.74	7.74						
Citronellyl acetate							0.01	0.22						
Citronellal	Trace	0.4					0.06	0.2					0.45	0.78
Citronellol	Trace	0.15	Trace	0.04				4.18	0.71	1.6			0.8	1.2
Citronellyl acetate	Trace	0.3										0.12		
Copaene														0.89
Decanal	Trace	Trace						0.21	0.71	1.02		0.11	2.33	7.71
Decanol								0.35						
Dehydrolinalool												0.40		
Dodecanol								0.03					0.42	0.65
Elemol													0.35	0.89
Eugenol										0.53				
Farnesol														1.14
Geranial	0.1	2.9					Trace	0.11						
Geraniol	Trace	0.2												
Geranyl acetate	Trace	3.2	Trace	0.56										
Germacarene													0.30	1.07
Germacrene D	Trace	0.8	0.019	1.35				0.08				0.27		
n-Heptane														0.4
Hexadecane								0.2						
Isophorone									1.09	2.92				
Isopropyl cresol														1.36
Lemonol												0.28		
Limonene oxide										0.76				
Linalool	0.1	25.1	0	1.59			0.12	2.32	1.52	2.1		0.22	0.7	2.56
Linalool oxide									0.48	1.12				0.6
Linalyl acetate	Trace	31.2	Trace	2.61			Trace					0.28		0.4
Longipinene														0.4
Menthadien-1-ol														0.42
Myrcene	0.7	10.16	Trace	1.54				2.5				6.27		
Neral	Trace	1.5						0.06						
Nerol	Trace	0.1	Trace	0.24										
Neryl acetate	0.1	3.9						0.04						
Nikkol									5.7					
Nonanal	Trace	0.3	Trace					0.08						
n-Nonane								0.2						
Nootkatone								0.01					0.30	3.95
Octanal	Trace	0.1	0.02	1.59			0.34	0.8					1.06	1.15

(continued)

Table 4. (continued)

	Citrus limon (lemon) peel essential oils				*Citrus nobilis* (mandarin orange) essential oil		*Citrus sinensis* (orange) peel oil						*Citrus reticulata* (tangerine) peel oil	
	Cold-pressed[12,13]		Hydrodistilled[18]		Cold-pressed[14]		Cold-pressed[11,12,15,16]		Hydrodistilled[44]		Steam-distilled[22]		Hydrodistilled[21,44]	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Octyl acetate	Trace	0.1												
p-Cymene	0.1	7.8	0.23	9.84										
p-Cymenene	Trace	0.3												
Pentadecane								0.2						
Perillaldehyde								0.03					1.64	1.65
Piperitenone										0.42				
Sabinene	Trace	6.3	3.8	6.48			0.21	0.5	0.37	0.62		1.29		0.49
Spathulenol	Trace	0.1	Trace											
Terpineol-4	Trace	0.1												
Terpinen-4-ol			Trace	1.28										0.1
Terpinolene	Trace	0.8	0.02	0.22				0.08						
Terpinyl acetate		0.5	Trace	0.15										
Tetradecane								0.2						
Thymol	Trace	1.1						Trace						
trans-α-Bergamotene	0.2	1.3												
trans-Carveol												0.44		
trans-Limonene oxide								0.01				0.20		
trans-Limonene-1,2-oxide	Trace	0.6												
trans-Linalool oxide THF	Trace	Trace												
trans-p-1,8-Dienol														0.52
trans-*p*-menth-2-en-1-ol	Trace	0.1												
trans-p-2,8-Menthadien-1-ol									0.79	1.07				
trans-Sabinene hydrate	Trace	0.1												
Tri-Cyclen			0.02	0.16										
Valencene			Trace	0.37				0.05	0.41	1.2				
α-Bisabolene		0.2												
α-Cadinol														0.46
α-Copaene								0.04						
α-Cubebene										0.7				0.48
α-Farnesene													0.36	0.48
α-Humulene	Trace	0.2	Trace	0.04										
α-Phellandrene	Trace	0.6								0.46				
α-Pinene	0.1	2.63	1.14	5.9			0.35	1.4	1.65	2.48		1.49	0.6	1.67
α-Sinensal									0.35	0.49			0.93	5.0
α-Terpinene	Trace	0.4	Trace	1.05										
α-Terpineol			0.93	1.7										1.51
α-Terpineol	Trace	0.4						0.07	2.34	3.1		0.14	0.2	1.1
α-Terpinolene		0.25					1.56	2.06				0.38		0.1
α-Thujene	Trace	1.7	Trace	0.38			0.04	0.11				0.11		
α-Thujone			Trace	0.35										
β-Bisabolene	0.2	2.0												
β-Caryophyllene												0.21		1.39
β-Cubebene								0.03						0.37
β-Eleme	Trace	0.5						0.1						
β-Elemene												0.17		
β-Farnesene												3.64		
β-gurjurene								0.0						
β-Myrcene								1.88	3.76	4.41			3.27	4.05
β-Ocimene												0.27		
β-Phellandrene	0.1	4.2												1.8

(continued)

Table 4. (continued)

	Citrus limon (lemon) peel essential oils				*Citrus nobilis* (mandarin orange) essential oil		*Citrus sinensis* (orange) peel oil						*Citrus reticulata* (tangerine) peel oil	
	Cold-pressed[12,13]		Hydrodistilled[18]		Cold-pressed[14]		Cold-pressed[11,12,15,16]		Hydrodistilled[44]		Steam-distilled[22]		Hydrodistilled[21,44]	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
β-Pinene	0.1	15.8	0.63	31.49			Trace	5.45				0.41	0.2	0.4
β-Sinensal									0.33	0.83				0.67
γ-Eudesmol														1.08
γ-Munrolene														1.16
γ-Terpinene	Trace	18.57	0.04	9.96			0.2	1.21				3.34	0.23	2.6
δ-Amorphene								0.05						
δ-Cadinene										0.32				0.88
δ-3-Carene								0.14				0.69		
Δ3-Carene	0.1	4.2	Trace						0.78	1.03				

Abbreviation: ND, none detected.

[a]Information on various cultivars and/or harvest times. X denotes these compounds were present; however, the amount present was not specified.

Table 5. Typical Levels of 5-Methoxypsoralen (5-MOP).

Ingredient	5-MOP level[26]
Tangerine oil cold-pressed	50 ppm
Mandarin oil cold-pressed	250 ppm

Table 6. Levels of Major Coumarins and Furocoumarins in Lemon Oil and Lime Oil.

Compound	% in lemon oil[8]	% in lime oil[8]	Photosensitizing activity[8]
5-Geranoxypsoralen	0.0387	2.2-2.5	0
5-Geranoxy-7-methoxycoumrin	0.0603	2.2-5.2	0
5-Geranoxy-8-methoxypsoralen	Not analyzed	0.945	0
5,7-Dimethoxycoumarin	0.0295	0.464	0
5,8-Dimethoxypsoralen	Not analyzed	0.508	0
Oxypeucedanin	0.005-0.073	0.0025	+
5-Methoxypsoralen	0.0001-0.0087	0.17-0.33	++++

Table 7. 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 rt, ie, rarely tested)[45]
β-Caryophyllene	≤10 (oxidized and nonoxidized)
Carvone	≤10 (rt)
Citral	101-1000
Citronellol	11-100
Coumarin	101-1000
Farnesol	101-1000
Geraniol	101-1000
Linalyl acetate	≤10
α- and β-pinene	11-100
(DL)-Limonene	11-100 (nonoxidized); 101-1000 (oxidized)
Terpineol (mixture of isomers)/ α-terpineol	≤10
Terpinolene	11-100

Abbreviations: rt, room temperature; SCCS, Scientific Committee on Consumer Safety.

cases, no reported uses were identified by the VCRP, but a maximum use concentration was provided in the industry survey. For example, *C grandis* (grapefruit) peel oil was not reported in the VCRP database to be in use, but the industry survey indicated that it is used at concentrations up to 0.05%. It should be presumed that *C grandis* (grapefruit) peel oil is used in at least 1 cosmetic formulation.

Table 9 lists the 7 citrus-derived peel oils not indicated to be in use based on the VCRP data and the results of the Council concentration of use survey.

Under the rules governing cosmetic products in the European Union, citrus-derived ingredients must have furocoumarin content below 1 mg/kg in sun protection products and in bronzing products.[25] The International Fragrance Association (IFRA) has issued standards for citrus oils and other furocoumarin-containing essential oils.[26] Thus, 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 0.0075%, or 75 ppm, in a fragrance compound 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 ingredients, the potential for an additive effect should be considered and use levels should be reduced accordingly. Restrictions for furocoumarin-containing essential oils have been recommended for bitter orange oil expressed, grapefruit oil expressed, lemon oil cold-pressed, and lime oil expressed.

An IFRA standard also has been issued for 7-methoxycoumarin, which is prohibited for use in fragrance compounds.[27] 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. An example of a maximum concentration based on this standard is 0.1% for lime cold-pressed oil.

Additionally, IFRA has set a standard stating that D-, L-, and DL-limonene and natural products containing substantial amounts of it should only be used when the level of peroxides is kept to the lowest practical level; such products should have a peroxide value of <20 mmol/L.[28] This standard is also cited by the European Commission.[29] The European Union also states that limonene must be included in the list of ingredients when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products.

The IFRA has also set limits on the amounts of some citrus-derived oils in finished products. For leave-on products applied to skin areas exposed to direct sunlight, these limits include 1.25% bitter orange peel expressed,[30] 4% grapefruit oil expressed,[31] 2% lemon oil cold-pressed,[32] and 0.7% lime oil expressed.[33] There are no restrictions for any of these oils in rinse-off products and products that are not applied to the skin. International Fragrance Association specified that if combinations of phototoxic fragrance ingredients are used, the use levels must be reduced accordingly, so that the sum of the concentrations of all phototoxic fragrance ingredients, expressed as a percentage of their respective recommended maximum levels, shall not exceed 100% in the consumer product. Additionally, the IFRA general standard described above for "Citrus oils and other furocoumarins-containing essential oils" must be considered.

Table 8. Frequency (2014) and Concentration of Use (2013) According to Duration and Type of Exposure for Citrus-Derived Ingredients.[23,24]

	Number of use[46]	Maximum concentration of use (%)	Number of uses	Maximum concentration of use (%)	Number of uses	Maximum concentration of use (%)	Number of uses	Maximum concentration of use (%)
	Citrus aurantium amara (bitter orange) peel oil		*Citrus aurantium dulcis* (orange) peel oil (Listed as *Citrus sinensis* (sweet orange) peel oil in VCRP)		*Citrus grandis* (grapefruit) peel oil		*Citrus junos* peel oil	
Totals[a]	127	0.05-2	289	0.00002-29	NR	0.00004-0.05	6	NR
Duration of use								
Leave-on	74	0.2-2	156	0.00038-0.54	NR	0.0004-0.0008	4	NR
Rinse-off	45	0.05-0.25	110	0.00002-29	NR	0.00004-0.05	2	NR
Diluted for (bath) use	8	NR	23	0.33	NR	0.0014	NR	NR
Exposure type								
Eye area	2	NR	3	0.1	NR	NR	NR	NR
Incidental ingestion	1	0.75	4	NR	NR	NR	NR	NR
Incidental inhalation—Spray	27[b]; 28[c]	NR	56[b]; 55[c]	0.00038[b]	NR	NR	2	NR
Reported spray	NR	NR	NR	NR	NR	NR	NR	NR
Incidental inhalation—Powder	28[c]	0.9-2[d]	3[d]; 55[c]	0.03-0.4[d]	NR	0.0004[d]	1	NR
Reported powder	NR	NR	NR	NR	NR	NR	NR	NR
Dermal contact	115	0.05-2	218	0.001-0.4	NR	0.00004-0.05	6	NR
Deodorant (underarm)	NR	NR	1[b]	NR	NR	NR	NR	NR
Reported spray	NR	NR	NR	NR	NR	NR	NR	NR
Reported as not spray	NR	NR	NR	NR	NR	NR	NR	NR
Hair—Noncoloring	11	NR	65	0.00002-29	NR	0.005	NR	NR
Hair—Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	2	0.5-0.54	NR	NR	NR	NR
Mucous membrane	21	0.25-0.75	56	0.1-0.33	NR	0.0014	1	NR
Baby products	6	NR	8	NR	NR	NR	NR	NR

	Number of use[46]	Maximum concentration of use (%)	Number of uses	Maximum concentration of use (%)	Number of uses	Maximum concentration of use (%)	Number of uses	Maximum concentration of use (%)
	Citrus limon (lemon) peel oil		*Citrus nobilis* (mandarin orange) peel oil		*Citrus reticulata* (mandarin orange) peel oil[e]		*Citrus sinensis sanguinello* (blood orange) peel oil[e]	
Totals[a]	490	0.0001-0.5	152	0.00005-0.1	2	NR	8	NR
Duration of use								
Leave-on	297	0.0001-0.5	86	0.00005-0.1	1	NR	4	NR
Rinse-off	165	0.0006-0.001	58	0.00005-0.03	1	NR	4	NR
Diluted for (bath) use	28	0.012	8	NR	NR	NR	NR	NR
Exposure type								
Eye area	9	NR	NR	NR	NR	NR	NR	NR
Incidental ingestion	8	NR	1	0.0099	NR	NR	NR	NR
Incidental inhalation—Spray	84[b]; 96[c]	0.06[c]	45[b]; 26[c]	NR	1[c]	NR	1[b]; 2	NR
Reported spray	NR	NR	NR	NR	NR	NR	1	NR
Incidental inhalation—Powder	1[d]; 96[c]	0.001-0.14[d]; 0.06[c]	26[c]	0.00005-0.14	1[c]	NR	2[c]	NR
Reported powder	NR	NR	NR	NR	NR	NR	NR	NR

(continued)

Table 8. (continued)

	Number of use[46]	Maximum concentration of use (%)	Number of uses	Maximum concentration of use (%)	Number of uses	Maximum concentration of use (%)	Number of uses	Maximum concentration of use (%)
	Citrus limon (lemon) peel oil		*Citrus nobilis* (mandarin orange) peel oil		*Citrus reticulata* (mandarin orange) peel oil[e]		*Citrus sinensis sanguinello* (blood orange) peel oil[e]	
Dermal contact	411	0.0001-0.5	136	0.00005-0.1	2	NR	8	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Reported spray	NR	NR	NR	NR	NR	NR	NR	NR
Reported as not spray	NR	0.002	NR	NR	NR	NR	NR	NR
Hair—Noncoloring	67	NR	15	0.00005-0.03	NR	NR	NR	NR
Hair—Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	3	0.0001-0.14	NR	0.012	NR	NR	NR	NR
Mucous membrane	96	0.001-0.012	40	0.0099	NR	NR	4	NR
Baby products	8	NR	NR	NR	NR	NR	NR	NR

	Number of use[46]	Maximum concentration of use (%)	Number of uses	Maximum concentration of use (%)	Number of uses	Maximum concentration of use (%)	Number of uses	Maximum concentration of use (%)
	Citrus tangerina (tangerine) peel oil							
Totals[a]	34	0.0000013						
Duration of use								
Leave-on	18	0.0000013						
Rinse-off	15	0.0000013						
Diluted for (bath) use	1	NR						
Exposure type								
Eye area	NR	NR						
Incidental ingestion	1	NR						
Incidental inhalation—Spray	5[b]; 8[c]	0.0000013b						
Reported spray	1	NR						
Incidental inhalation—Powder	8[c]	NR						
Reported powder	NR	NR						
Dermal contact	26	NR						
Deodorant (underarm)	NR	NR						
Reported spray	NR	NR						
Reported as not spray	NR	NR						
Hair—Noncoloring	7	0.0000013						
Hair—Coloring	NR	NR						
Nail	NR	NR						
Mucous membrane	7	NR						
Baby products	NR	NR						

Abbreviations: INCI, International Nomenclature of Cosmetic Ingredient; NR, not reported; VCRP, Voluntary Cosmetic Registration Program.
[a]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.
[b]It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.
[c]Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.
[d]It is possible these products may be powders, but it is not specified whether the reported uses are powders.
[e]Use in a spray product has been reported in response to a survey conducted by the Council.

Table 9. Ingredients That Are Not Reported to Be in Use.

Citrus aurantifolia (lime) peel oil
Citrus aurantium currassuviensis peel oil
Citrus clementina peel oil
Citrus iyo peel oil
Citrus medica vulgaris peel oil
Citrus reticulata (Tangerine) peel oil
Citrus tachibana/reticulata peel oil

Noncosmetic

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: *C aurantifolia* (lime), *C aurantium* (bitter orange; the flowers and peel), *C limon* (lemon), *C reticulata* (tangerine), *Citrus reticulata blanco* (mandarin), *C sinensis* (orange; the leaf, flowers, and peel), and citrus peels (species not specified; 21CFR182.20). These essential oils, oleoresins (solvent-free), and natural extractives (including distillates) of these citrus fruits are GRAS for their intended use in animal drugs, feeds, and related products (21CFR582.20).

Citrus essential oils are used in the pharmaceutical industry as flavoring agents to mask the unpleasant taste of drugs.[18] *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.[34]

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.[1] Therefore, 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 dermal exposure to these citrus ingredients as used in cosmetic products.

Acute Toxicity

Dermal—Nonhuman

Lemon oil. The dermal LD_{50} of lemon oil was greater than 10 g/kg in rabbits.[3] An occlusive patch of undiluted oil was applied to the skin of 6 animals for 24 hours. One animal died during the observation period.

Mandarin oil—Expressed (C reticulata). The dermal LD_{50} of mandarin peel oil (C reticulata) was greater than 5 g/kg in rabbits.[10] An occlusive patch of undiluted oil was applied to the skin of seven animals for 24 hours.

Orange oil. The dermal LD_{50} of sweet orange oil was greater than 5 g/kg in female New Zealand White rabbits.[4] An occlusive patch of undiluted oil was applied to the skin of 10 animals for 24 hours. Signs of skin irritation were reported, including moderate redness in 10 of 10 animals, slight edema in 3 of 10 animals, and moderate edema in 5 of10 animals.

Reproductive and Developmental Toxicity

No published reproductive and developmental studies on citrus-derived peel oils were identified in a literature search for these ingredients, and no unpublished data were submitted.

Genotoxicity

Genotoxicity studies for in vitro assays are summarized in Table 10. No genotoxic effects were observed for lemon oil or sweet orange oil in bacterial reverse mutation assays, mouse lymphoma cell mutation assays, and Chinese hamster chromosome aberration assays.[3,4]

Carcinogenicity

Orange Oil, Lemon Oil, Grapefruit Oil, and Lime Oil

Tumor-promoting activity was observed in mouse skin exposed to essential oils of orange (sweet), lemon, grapefruit, or lime.[35] Chemical constituents of these oils were not fully identified in this study, although the terpene and nonterpene fractions were separated. Groups of 10 male and 10 female strain 101 mice received a single application of 9,10-dimethyl-1,2-benzanthracene (DMBA) in acetone (300 μg in 0.2 mL in 4 groups, 225 μg in 0.15 mL in a fifth group). Group 1 was a control group that received no further treatments. Groups 2 through 5 received weekly applications of 0.25 mL of the test substances 3 weeks after the application of DMBA.

By the fifth week, papillomas were observed in group 3 (lemon oil), group 4 (grapefruit oil), and group 5 (lime oil). Papillomas were observed in group 2 (orange oil) by the 12th week. After 33 weeks, 10 of 20 mice in the lemon oil and lime oil treatment groups and 13 of 20 mice in the grapefruit oil and orange oil groups had papillomas. Only 1 mouse in the control group had papillomas after 33 weeks, and the affected site was not the treated skin. Additionally, one female mouse of the lemon oil group developed a sebaceous-gland tumor of the nipple. No malignant skin tumors were observed in the orange oil group: Treatment for this group was stopped after 42 weeks. Squamous cell carcinomas of the skin were observed in 2 mice from the lemon oil group and2 mice of the grapefruit oil group between weeks 36 and 55. One malignant skin tumor was observed in the lime oil group at week 34; however, the mouse was found dead and a proper histological examination was not possible. No malignant skin tumors were observed in the control group. Nondermal tumors during the treatment period were observed in one mouse of the orange oil group (a hemangioma

Table 10. Genotoxicity.

Test article	Concentration/ dose	Procedure	Results	Reference
In vitro				
Lemon oil in ethanol	10-5000 μg/plate	Reverse mutation assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2uvrA, with and without S9 metabolic activation	Toxicity was observed in all test strains except WP2uvrA with and without S9; no significant dose-related increases in the number of revertant colonies in any test strain at any dose level, with or without metabolic activation; controls yielded expected results; lemon oil was not mutagenic in this assay	[3]
Lemon oil in ethanol	40-100 μg/mL	Cell mutation assay in mouse lymphoma L5178Y TK ± cells in accordance with OECD guideline 476 in 2 independent experiments; with and without S9 metabolic activation	No significant increases in the mutation frequency were observed in either experiment, with or without S9 activation; controls yielded the expected results; lemon oil did not induce gene mutations in mouse lymphoma cells	[3]
Lemon oil in ethanol	Up to 0.125 mg/mL	Chromosome aberration study using Chinese hamster lung fibroblasts (CHL) in accordance with OECD guideline 473, without metabolic activation, 100 metaphases examined	The incidence of polyploidy cells at 24 hours post-treatment was 1.0%, and the incidence of cells with structural chromosome aberrations at 24 hours after treatment was 2.0%; the test material did not significantly induce chromosomal aberrations in CHL cells; lemon oil was not considered clastogenic	[3]
Sweet orange oil in ethanol	1-5000 μg/plate	Reverse mutation assay using *S typhimurium* strains TA98, TA100, TA1535, and TA1537 and *E coli* strain WP2uvrA, with and without S9 metabolic activation	Cytotoxicity was observed in all test strains except WP2uvrA with and without S9; no significant dose-related increases in the number of revertant colonies in any test strain at any dose level, with or without metabolic activation; controls yielded expected results; sweet orange oil was not mutagenic in this assay	[4]
Sweet orange oil in ethanol	40-100 μg/mL	Cell mutation assay in mouse lymphoma L5178Y TK ± cells in accordance with OECD guideline 476 in 2 independent experiments; with and without S9 metabolic activation	The test material did not induce a significant increase in the mutation frequency in both experiments, with or without metabolic activation; sweet orange oil did not induce gene mutations in mouse lymphoma cells	[4]
Sweet orange oil in ethanol	Up to 0.125 mg/mL	Chromosome aberration study using CHL fibroblasts in accordance with OECD guideline 473, without metabolic activation, 100 metaphases examined	The incidence of polyploidy cells at 48 hours post-treatment was 1.0%, and the incidence of cells with structural chromosome aberrations at 48 hours after treatment was 1.0%; the test material did not significantly induce chromosomal aberrations in CHL cells; sweet orange oil was not considered clastogenic	[4]

Abbreviation: OECD, Organisation for Economic Co-operation and Development.

of the subcutaneous tissue starting at week 7) and in one mouse of the grapefruit oil group (a spindle cell sarcoma of the subcutaneous tissues). No tumors of the internal organs were observed. The survival of all the mice, including the controls, in this experiment was poor because of a very high incidence of renal disease.[35]

Orange Oil

Tumor-promoting activity was observed in mouse skin exposed to orange (sweet) oil.[35] In the study, groups of 10 male and 10 female strain 101 mice received a single application of DMBA in acetone (300 μg in 0.15 mL). One group (15 mice of each

Table 11. Dermal Irritation Studies for Citrus-Derived Ingredients.

Test article	Concentration/ dose	Test population	Procedure	Results	Reference
Nonhuman					
Lemon oil	5 mL/kg	6 New Zealand White rabbits	Acute dermal toxicity limit test scored under the Draize method; 24-hour occlusive patches on intact and abraded skin	Irritating	3
Orange oil, cold-pressed	0.5 mL of undiluted material	3 male albino rabbits	Skin irritation study conducted according to OECD guideline 404; semi-occluded patch for 4 hours	Mean erythema/eschar scores were 2.0, 1.7, and 2.0; mean edema scores were 2.0, 1.3, and 1.3; irritating to skin	4
Mandarin peel oil, expressed (described as *Citrus reticulata*)	5 mg/kg	7 rabbits	24-hour occlusive, single dose study	Slight erythema and edema	10
Mandarin peel oil, expressed (described as *C reticulata*)	Not reported	Hairless mice and miniature swine; details not provided	Open patch tests; details not provided	2 of 3 samples were irritating	10
Human					
Lemon oil	0.3%, 2%, or 20%; multiple vehicles	34 patients at 0.3%, 30 subjects at 2%, and 35 patients at 20%	24-72 hours occlusive patch tests	No irritation at 0.3% and 20%, 1 $\pm$ reaction at 2%	36
Mandarin peel oil, expressed (described as *C reticulata*)	8% in petrolatum	5 patients	48 hours closed patch test; details not provided	No irritation	10

Abbreviation: OECD, Organisation for Economic Co-operation and Development.

sex) was a control group that received no further treatments. Two groups received weekly applications of 0.25 mL of 40% orange oil in acetone or 80% orange oil in acetone 3 weeks after the initial application of DMBA. The applications continued for 37 weeks.

Papillomas were observed in both groups treated with orange oil starting on the 12th week. After 33 weeks, 5 of 10 mice treated with 40% orange oil and 10 of 10 mice treated with 80% orange oil had papillomas, and at study end, only 1 tumor of each group was found outside the treated area. Four mice in the control group had papillomas by week 33, but these tumors were outside the treated area of the skin. Malignant tumors were observed in one mouse of each treatment group, arising from the preexisting papilloma. Both tumors were squamous cell carcinomas, infiltrating the panniculus muscle. Additionally, tumors of the urethral orifice were observed in 4 female mice of the 40% orange oil group. The survival of all the mice in this experiment was poor due to a very high incidence of renal disease.

In the same study, tumor-promoting activity was observed in mice exposed to undiluted orange oil after pretreating the mice with either dermal or intraperitoneal injections of urethane. The effect was weak compared to the effects observed after DMBA induction.

A similar experiment performed in the same study tested the carcinogenic effects of orange oil without pretreatment with DMBA or urethane. The mice were treated once weekly with 0.25 mL of 40% or 80% orange oil in acetone or undiluted orange oil for 38 (diluted) or 46 (undiluted) weeks. This study found no evidence of direct tumorigenic effects on the treated mouse skin. Urethral orifice tumors were observed in one female mouse of the 40% orange oil group and in one female mouse of the 80% orange oil group. A papilloma was observed on the head of a mouse (outside the treatment site) that was treated with 80% orange oil.[35]

Irritation and Sensitization

Dermal Irritation

Dermal irritation studies are summarized in Table 11. Lemon oil, orange oil, and mandarin peel oil all produced some reaction in irritation studies in animals, but in human patients, no irritation was observed after topical exposure to lemon oil (up to 20%) or mandarin peel oil (8%).[3,4,10,36]

Ocular Irritation

Lemon oil. Lemon oil tested at 5% was not irritating to the eyes of 3 albino rabbits.[3] Each rabbit had 0.1 mL of the test material

Table 12. Sensitization Studies for Citrus-Derived Ingredients.

Test article	Concentration/ dose	Test population	Procedure	Results	Reference
Human: Patch					
Bitter orange oil	2% in paraffin	200 patients with dermatitis tested with 35 essential oils plus an additional 50 patients with balsam sensitivity	Sensitization patch study, details not provided	6 positive reactions	37
Lemon oil	2% in paraffin	200 patients with dermatitis tested with 35 essential oils plus an additional 50 patients with balsam sensitivity	Sensitization patch study, details not provided	4 positive reactions, details not provided	37
Lemon oil	Not reported	100 patients	Marzulli-Maibach sensitization technique; open patches	2% of the patients had a positive skin reaction at the first reading after challenge, no reactions were noted at the 48 and 72 hours readings, study concluded the test material was not sensitizing	3
Mandarin oil, expressed (described as *Citrus reticulate*)	8% in petrolatum	25 patients	Maximization study, details not provided	Not sensitizing	10
Sweet orange oil	2% in paraffin	200 patients with dermatitis tested with 35 essential oils plus an additional 50 patients with balsam sensitivity	Sensitization patch study, details not provided	3 positive reactions, details not provided	37
Sweet orange oil	Not reported	100 patients	Marzulli-Maibach sensitization technique; open patches	4% of the patients had positive skin reaction at the first reading after challenge, no reactions were noted at the 48 and 72 hours readings, study concluded the test material was not sensitizing	4

instilled into the right eye with no further treatment. The left eye served as the control. Eyes were examined every 24 hours for 4 days and then again on the seventh day. No corneal opacity or iris congestion was observed. An intense conjunctival irritation involving chemosis and discharge occurred. Treated eyes were normal on the seventh day.

Orange oil. Orange oil tested undiluted did not induce significant or irreversible damage to the eyes of 3 male New Zealand White rabbits.[4] The test was performed in accordance with Organisation for Economic Co-operation and Development Test Guideline 405. The test material (0.1 mL) was instilled into one eye of each rabbit. The mean scores calculated for the 3 animals across 3 scoring times were 0.0 for corneal opacity and iris lesions and 1.0 for reddening of the conjunctivae.

Sensitization

Sensitization studies are presented in Table 12. Mandarin peel oil (8% in petrolatum) was not sensitizing in human maximization tests. In studies of 250 patients with dermatitis, less than 2.5% had positive reactions to bitter orange oil, lemon oil, or sweet orange oil tested at 2% in paraffin.[3,4,10,37]

Phototoxicity and Photosensitization

Phototoxicity and photosensitization studies are presented in Table 13. Phototoxic potential was observed for sweet orange oil and lemon oil in in vitro studies. No phototoxic responses were noted in some animal studies of lime oil, lemon oil, grapefruit oil, mandarin oil, or tangerine oil; however, signs of phototoxicity were observed in response to undiluted lime oil and lime oil diluted to concentrations of 15%, undiluted bitter orange oil, and undiluted lemon oil and lemon oil diluted to concentrations of 50%. In human studies, phototoxic reactions were observed in response to undiluted bitter orange oil, lemon oil (1%), sweet orange oil (1%), and undiluted and diluted expressed lime oil (30%). Many of the citrus-derived peel oils contain constituents that are photoactive agents, although those noted to be furocoumarin free tended not to induce photosensitization.[19,30,38-41]

Occupational Exposure

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

Table 13. Photosensitization and Phototoxicity Studies.

Test article	Concentration/dose[a]	Test population	Procedure	Results	Reference
Alternative studies					
Sweet orange oil, including deterpenated kind	Concentrations not reported; tested in PBS, ethanol, or DMSO with samples from 3 suppliers	3T3 Balb/c fibroblasts	- 3T3 neutral red uptake phototoxicity test - Light source was a doped mercury-metal halide lamp, filtered with 50% transmission at 335 nm to diminish UVB	Borderline phototoxic, positive phototoxic results observed more frequently with the vehicles PBS and ethanol with certain supplied samples	38
Lemon oil, including deterpenated kind	Same as above	Same as above	Same as above	Borderline phototoxic, positive phototoxic results observed in all 3 vehicles, but were more prominent in the deterpenated sample	38
Sweet orange oil, including deterpenated kind	Up to 3.16% in water with samples from 3 suppliers	Same as above	Same as above	Potential for phototoxicity observed	38
Lemon oil, including deterpenated kind	Same as above	Same as above	Same as above	Cytotoxicity observed with deterpenated lemon oil; potential for phototoxicity observed	38
Nonhuman					
Lime oil, distilled (psoralen-free)	Undiluted; 20 μL	Hairless mice, 6/group	- A single dose was applied to a 2 cm^2 area on the back; animals were exposed to irradiation 30 minutes after dosing - One group was exposed to a compact-arc xenon lamp for 2 minutes (wavelengths $<$295 nm or 320-280 nm excluded) - One group was exposed to a long-arc xenon lamp for 40 minutes at a distance of 1 m; the weighted energy was 0.1667 W/m^2 - One group was exposed to 4 fluorescent black light lamps (UVB eliminated) for 1 hour at an integrated UVA intensity of 3 W/m^2 - Positive controls were treated with 0.01% 8-methoxypsoralen in methanol; negative controls with an appropriate vehicle - Test sites were examined 4, 24, 48, 72, and 96 hours after exposure	- A phototoxic response was not observed with any of the light sources	40
Lime oil, distilled (psoralen-free)	Undiluted; 20 μL	Miniature swine, 2/group	As above	- A phototoxic response was not observed with any of the light sources	40
Lime oil, expressed	Undiluted and diluted; 20 μL	Hairless mice, 6/group	As above	- A phototoxic response was observed with all 3 light sources - The lowest phototoxic concentration was 15%	40
Lime oil, expressed	Undiluted and diluted; 20 μL	Miniature swine, 2/group	As above	- A phototoxic response was observed with all 3 light sources - The lowest phototoxic concentration was 30%	40
Grapefruit oil	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	Not photosensitizing	40

(continued)

Table 13. (continued)

Test article	Concentration/dose[a]	Test population	Procedure	Results	Reference
Lime oil distilled (psoralen-free)	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	Not photosensitizing	[40]
Lime oil; expressed and rectified	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	Not photosensitizing	[40]
Lime oil Persian Florida; expressed and rectified	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	Not photosensitizing	[40]
Mandarin oil	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	Not photosensitizing	[40]
Mandarin oil, Italian	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	Not photosensitizing	[40]
Oil of lemon, California	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	Not photosensitizing	[40]
Oil of lemon, distilled	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	Not photosensitizing	[40]
Oil mandarin, Italian	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	Not photosensitizing	[40]
Oil of tangerine	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	Not photosensitizing	[40]
Orange oil; cold-pressed	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	Not photosensitizing	[40]
California lemon oil	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	- A phototoxic response was observed	[40]
Italian lemon oil	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	- A phototoxic response was observed	[40]
Oil lemon, Greek; cold-pressed	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	- A phototoxic response was observed	[40]
Oil lemon, Italian	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	- A phototoxic response was observed	[40]
Oil lemon, IC (not defined)	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	- A phototoxic response was observed	[40]
Lime oil, expressed	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	- A phototoxic response was observed	[40]
Oil limes, Persian	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	- A phototoxic response was observed	[40]
Oil limes, expressed and rectified	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	- A phototoxic response was observed	[40]
Lime oil, expressed and rectified	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	- A phototoxic response was observed	[40]
Bitter orange oil	Undiluted; 20 μL	6 hairless mice and 2 miniature swine	- As above	- A phototoxic response was observed	[40]
Lemon oil from multiple regional sources	20%, 50%, or 100% in ethanol; 0.02 mL	Albino guinea pigs	- The oil was applied to the shaved back of the animals - The animals were then exposure to UVA radiation (320-400 nm, 13 J/cm^2)	- Concentrations of 50% and 100% elicited phototoxicity in most of the samples tested - Lemon oils from different regions had different phototoxicity potencies	[41]

(continued)

Table 13. (continued)

Test article	Concentration/dose[a]	Test population	Procedure	Results	Reference
			- Erythema was evaluated 24, 48, and 72 hours after irradiation - The samples were then fractionated subsequent phototoxicity testing of the isolated components was performed	- Oxypeucedanin and 5-methoxypsoralen (furocoumarins) were identified as phototoxic	
Human					
Bitter orange peel oil	Undiluted; 5 $\mu L/cm^2$	8 patients	- An occlusive patch was applied to a 2 cm $\times$ 2 cm area - 1 cm site on each patient was exposed to visible light of 20 J/cm^2 UVA - The test sites were scored after 24 and 48 hours	All patients reacted (details not provided)	30
Lemon oil, including deterpenated kind	Up to 1% in water from samples from 3 supplier; dose not provided	5 female patients	-2 occlusive 10 mm diameter Finn Chambers on both sides of the lower back - Exposure time to test material was 1 hour - Irradiation immediately to 1 site after patch removal at a dose of 5 J/cm^2as measured in the UVA range - Test sites scored after 24, 48, and 72 hours - Light source was a doped mercury-metal halide lamp, filtered with 50% transmission at 335 nm to diminish UVB	- Phototoxic reactions concurrent with an irritation reactions were observed in lemon oil at 1% in 4 of 5 patients up to 72 hours after irradiation - Phototoxic reactions were observed in deterpenated lemon oil at 0.1% in 2 of 5 patients at 48 and 72 hours after irradiation - No reactions were observed at concentrations of 0.1% or lower in lemon oil and 0.01% in deterpenated lemon oil	38
Sweet orange oil, including deterpenated kind	Same as above	Same as above	- Same as above	- Phototoxic reaction were observed in orange oil at 1% in 3 of 5 patients at 24 hours and 2 of 5 patients at 48 and 72 hours after irradiation - No reactions were observed at concentrations of 0.1% or lower in orange oil or 0.1% and 0.01% in deterpenated orange oil	38
Lime oil, distilled	Undiluted	10 Caucasian patients	- A single dose was applied to a 2-cm^2 area on the back - 30 minutes after dosing, patients were exposed to sunlight for 30 minutes or a compact-arc xenon lamp for 2 minutes (wavelengths $<$295 nm or 320-280 nm excluded) - Positive controls were treated with 0.01% 8-methoxypsoralen in methanol; negative controls with an appropriate vehicle - Test sites were examined 4, 24, 48, 72, and 96 hours after exposure	No phototoxic response was observed	40

(continued)

Table 13. (continued)

Test article	Concentration/dose[a]	Test population	Procedure	Results	Reference
Lime oil, expressed	Undiluted and diluted; 20 μL	10 Caucasian patients	- A single dose was applied to a 2 cm^2 area on the back - 30 minutes after dosing, 1 treated site and the control untreated site were exposed to sunlight for 30 minutes, a compact-arc xenon lamp for 2 minutes (wavelengths <295 nm or 320-280 nm excluded), or 4 fluorescent black light lamps (UVB eliminated) for 1 hour at an integrated UVA intensity of 3 W/m^2 - Positive controls were treated with 0.01% 8-methoxypsoralen in methanol; negative controls with an appropriate vehicle - Test sites were examined 4, 24, 48, 72, and 96 hours after exposure	- A phototoxic response was observed with all 3 light sources - The lowest phototoxic concentration with the simulated light sources was 30%	[40]

Abbreviations: DMSO, dimethyl sulfoxide; PBS, phosphate-buffered saline; UVA, ultraviolet A; UVB, ultraviolet B.
[a]The solvent is specified when known.

the patients had positive skin prick test reactions to lemon peel.[42]

Summary

The 14 citrus-derived peel oils 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 (as known as 5-MOP) is a naturally occurring, phototoxic furanocoumarin (psoralen) in citrus peel oils. Presently, CIR reviewed the information available on the potential toxicity of each of the citrus peel oil–derived ingredients as a whole, complex substance; CIR did not review the potential toxicity information on the individual constituents of which the citrus-derived ingredients are comprised. Cosmetic Ingredient Review requested information on the concentrations (including ranges, means, upper 95% confidence limits, detection limits, etc) of individual constituents in the citrus peel oil–derived ingredients used in cosmetics, to facilitate the safety assessment of these ingredients. Such information on constituents that have been identified as of concern by the Panel in previous safety assessments, or by other recognized scientific expert review bodies, is especially important.

Citrus oils contain large amounts of monoterpene hydrocarbons; limonene is present in the greatest amount, composing 38.1% to 95.8% of the oils. Citrus oils also contain sesquiterpene hydrocarbons, which are responsible for the characteristic flavor of these oils.

Citrus limon (lemon) peel oil has the most reported uses in cosmetics and personal care products, with a total of 490; more than half of the uses are in leave-on skin care preparations. The range of highest maximum use concentrations for *C limon* (lemon) peel oil is 0.0001% to 0.5%, with 0.5% reported in "other" skin care preparations. *Citrus aurantium dulcis* (orange) peel oil (reported as *C sinensis* [sweet orange] peel oil to the VCRP) has the second greatest number of overall uses reported, with a total of 289; about half of those uses are in leave-on skin care preparations. *Citrus aurantium dulcis* (orange) peel oil had a highest maximum use concentration range of 0.00002% to 29%, with 29% reported in noncoloring hair conditioners.

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. International Fragrance Association 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. Restrictions for furocoumarin-containing essential oils and limits on the amounts of citrus-derived oils in finished products have been recommended for bitter orange oil expressed, grapefruit oil expressed, lemon oil cold-pressed, and lime oil expressed.

The European Union also set standards for limonene, stating that limonene must be included in the list of ingredients when its concentration exceeds 0.001% in leave-on products and 0.01% in rinse-off products.

The citrus peel oils 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.

The dermal LD_{50} of undiluted mandarin peel oil (*C reticulata*) and undiluted sweet orange oil was greater than 5 g/kg in rabbits. In undiluted lemon oil, the dermal LD_{50} was greater than 10 g/kg in rabbits.

No genotoxic effects were observed in lemon oil or sweet orange oil in bacterial reverse mutation assays, mouse lymphoma cell mutation assays, and Chinese hamster chromosome aberration assays. Tumor-promoting activity was observed in mouse skin exposed to undiluted essential oils of orange (sweet), lemon, grapefruit, or lime after pretreatment with DMBA. Related studies of 40%, 80%, or 100% orange oil following pretreatment with DMBA or urethane also reported tumor-promoting activity, although the effect was weaker in the mice induced with urethane. No tumorigenic effects were observed in mice tested with orange oil without pretreatment with DMBA or urethane. Survival rates of the mice, including controls, in these experiments were poor because of a very high incidence of renal disease.

Irritation was observed in animals treated with unspecified concentrations of mandarin peel oil. In human patients, no irritation was observed after topical exposure to lemon oil (up to 20%) or mandarin peel oil (8%).

In rabbits, lemon oil tested at 5% was not irritating and orange oil tested undiluted did not induce significant or irreversible damage to the eyes. Mandarin peel oil (8% in petrolatum) was not sensitizing in human maximization tests. In studies of 250 patients with dermatitis, less than 2.5% had positive reactions to bitter orange oil, lemon oil, or sweet orange oil tested at 2% in paraffin.

Phototoxic potential was observed for sweet orange oil and lemon oil in in vitro studies. No phototoxic responses were noted in some animal studies of lime oil, lemon oil, grapefruit oil, mandarin oil, or tangerine oil; however, phototoxic reactions were observed in response to undiluted lime oil and lime oil diluted to concentrations of 15%, undiluted bitter orange oil, and undiluted lemon oil and lemon oil diluted to concentrations of 50%. In human studies, phototoxic reactions were observed in response to undiluted bitter orange oil, lemon oil (1%), sweet orange oil (1%), and undiluted and diluted expressed lime oil (30%). Many of the citrus-derived peel oils contain constituents that are photoactive agents, although those noted to be furocoumarin free tended not to induce photosensitization.

A retrospective occupational study of food handlers noted positive reactions to orange and lemon peels. No published studies on reproductive and development toxicity of citrus-derived peel oils were discovered and no unpublished data were submitted to address these topics.

Discussion

The citrus ingredients in this assessment are found in foods, and daily exposures from the consumption of foods can be expected to yield much larger systemic exposures to these ingredients than those from the use of cosmetic products. Essential oils, oleoresins (solvent-free), and natural extracts (including distillates) derived from some citrus 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 irritation and sensitization from dermal exposures to the citrus ingredients.

Most of the reports that the Panel reviewed were not sufficiently detailed to enable determining how well the substances tested represent the cosmetic ingredients included in this safety assessment. For example, the genus and species of the plants from which the test substances were derived, the cultivation methods used to grow the plants, and the methods of extraction are not specified in many of these studies.

The Panel expressed concern about the potential for constituents in citrus-derived peel oils, including the furocoumarin 5-MOP, to cause phototoxicity. International Fragrance Association has issued standards for citrus oils and other furocoumarin-containing essential oils, and the Panel agreed that adherence to the IFRA standards for such constituents will prevent phototoxicity. According to these standards, finished products that are applied to the skin, excluding rinse-off products, must not contain more than 0.0015%, or 15 ppm, 5-MOP. An IFRA standard also has been issued for 7-methoxycoumarin; based on established maximum levels of this substance from commercially available natural sources (like essential oils, extracts, and absolutes), exposure to 7-methoxycoumarin from the use of these oils and extracts is regarded to be acceptable if the level of 7-methoxycoumarin in the finished product does not exceed 100 ppm.

Additionally, based on the 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. Thus, these botanical ingredients must be formulated to be nonirritating.

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

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 to limit impurities.

Conclusion

The CIR Expert Panel concluded the citrus-derived peel oils are safe for use in cosmetic products, excluding rinse-off products, do not contain more than 0.0015% (15 ppm) 5-MOP, and when formulated to be nonsensitizing and nonirritating.

C aurantifolia (lime) peel oil*
Citrus aurantium amara (bitter orange) peel oil
Citrus aurantium currassuviensis peel oil*
Citrus aurantium dulcis (orange) peel oil
Citrus clementina peel oil*
Citrus grandis (grapefruit) peel oil
Citrus iyo peel oil*
Citrus junos peel oil
Citrus limon (lemon) peel oil
Citrus medica vulgaris peel oil*
Citrus nobilis (mandarin orange) peel oil
Citrus reticulata (tangerine) peel oil*
Citrus tachibana/reticulata peel oil*
Citrus tangerina (tangerine) peel oil *

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

Author's Note

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

Author Contributions

Burnett, C. contributed to conception and design; acquisition, analysis, and interpretation; drafted manuscript; and critically revised manuscript. Fiume, M., Gill, L., and Heldreth, B. contributed to analysis and interpretation and critically revised manuscript. Bergfeld, W., Belsito, D., Hill, R., Klaassen, C., Liebler, D., Marks, J. Shank, R., Slaga, T., and Snyder, P. contributed to conception and design; analysis and interpretation; and critically revised manuscript; and gave final approval. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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