



HOTLIST INGREDIENT REVIEW

Risk Assessment Division

Consumer and Hazardous Products Safety Directorate (CHPSD)

Hotlist Ingredient Review

Furocoumarins and Imperatorin

Date Approved: January 11, 2024

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EXECUTIVE SUMMARY

Purpose

Furocoumarins are naturally occurring constituents of botanically-derived ingredients. They are produced by plants as a natural defense mechanism against pests and predators. In human skin, when exposed to UV radiation, furocoumarins may cause phototoxic reactions resulting in burns or erythema. Some furocoumarins such as 5-methoxypsoralen (5-MOP or bergapten) and 8-methoxypsoralen (8-MOP) are also recognized internationally to be photomutagenic and photocarcinogenic.

'Furocoumarins' are covered under their own individual entry on the Hotlist and restricted to 1 mg/kg (1 ppm ~ 0.0001%) in sun-tanning products. For unknown reasons, '*Imperatorin*,' is captured separately on the Hotlist as prohibited and it is not subject to the same concentration allowance and exemptions as other furocoumarins. Although their presence on the Hotlist appears justified by phototoxicity concerns that are well documented in the scientific literature, no internal records of decision or policy statements have been identified to substantiate their current Hotlist status or the level of restriction.

This review aims to: 1) verify the scientific support behind the current Hotlist status regarding the use of furocoumarins (including imperatorin) or furocoumarin-containing ingredients in cosmetic products; 2) assess if the current level of restriction for furocoumarins sufficiently protects human health; and 3) recommend further revisions to the current status and conditions, if appropriate.

Note: Other significant botanical sources of furocoumarins such as "*Ammi majus* and its galenical preparations" and "*Ficus carica* absolute" are currently described as prohibited on the Hotlist. However, due to their known therapeutic function, these ingredients are addressed under separate hazard-based reviews¹ of prohibited drug ingredients on the Hotlist. They are excluded from the scope of this HIR. There is also an entry for "*Citrus reticulata* leaf oil", which is described as restricted. As there is an ongoing CMP assessment of Mandarin/Tangerine oil that would include this ingredient, and the main components identified in the assessment are not furocoumarins, the ingredient will be addressed in a separate review.

Disclaimer: The recommendations put forward by this document are intended to inform an upcoming Hotlist update, as supported by the currently available scientific evidence. However, the HIR is a dynamic document which may be updated as required, should new information become available.

¹ "*Ficus Carica* absolute" was addressed as part of the "Review of certain prohibitions for drugs that are on the cosmetic ingredient Hotlist". "*Ammi majus* and its galenical preparations" falls under the scope of the "Review of prohibited drugs with INCI names".

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Recommendations/Conclusions

Due to their known phototoxic, photomutagenic and photocarcinogenic potentials, the presence of furocoumarins on the Hotlist is scientifically justified.

In the EU and other international jurisdictions, furocoumarins are listed as ingredients prohibited from use in cosmetics, except for normal content in natural essences and in sun protection and bronzing products where the allowable level is restricted to 1 mg/kg (1 ppm).

The current Hotlist entry for furocoumarins reads as follows:

- 1 ppm maximum permitted concentration for intentionally added furocoumarins in sun-tanning products
- no specific conditions for naturally occurring furocoumarins

It is not clear if the intent of the Hotlist entry was to harmonize with Health Canada's international counterparts. However, the presence of the entry on the restricted portion of the Hotlist changes its overall interpretation compared to other international jurisdictions.

Health Canada has concerns relating to the presence of furocoumarins in any product with potential exposure to sunlight, such as leave-on products.

Current notification data do not indicate that furocoumarin ingredients are individually notified in cosmetic products. Health Canada expects furocoumarins may be present in a wide range of cosmetic products, because they are naturally occurring constituents of various botanically derived sources. In 1990, the Scientific Committee of Cosmetology (SCC) set a class-based limit of 1 mg/kg (1 ppm) total furocoumarin content in sun-tanning cosmetic products. At that time, available scientific, technical, and epidemiological data could not demonstrate that furocoumarin content "above a minimum level" would be without risk in sun-tanning and bronzing products. The potential phototoxic, photomutagenic and photocarcinogenic hazards of furocoumarins were recognized internationally. This overarching conclusion relied on a conservative interpretation of the hazard profile of bergapten (5-methoxypsoralen or 5-MOP), a major photomutagenic furocoumarin, intentionally added as a tanning accelerator to sun protection and bronzing products. The SCC conclusion did not account for differences in toxicity of other furocoumarins or the cumulative exposure from multiple products that may contain them.

Although the regulatory status of "imperatorin" aligns with other international jurisdictions, no record of decision or other scientific lines of evidence were found to explain why imperatorin poses a disproportionately higher risk than other furocoumarins, in order to warrant its own individual prohibition, irrespective of source. Although no authoritative opinions or risk assessments have been conducted on imperatorin, comparative studies suggest that this furocoumarin displays lower phototoxic and photomutagenic potentials relative to 5-MOP. No other properties of concern have been identified at this time for cosmetic use. Recent preclinical investigations (predominantly *in vitro*) have found imperatorin to be a substance of potential therapeutic value, due to its wide spectrum of

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pharmacological activity including but not limited to vasodilation, anti-inflammatory, anti-proliferative, hepatoprotective and neuroprotective effects. Based on information available at this time, there is no indication that imperatorin would be deliberately added as a cosmetic ingredient, although it may be present at low levels in botanically derived ingredients that are not presently restricted in cosmetics.

The intentional addition of furocoumarin substances to cosmetic formulations should be prohibited, in alignment with other international jurisdictions. Until further evidence becomes available to support a revision to the existing threshold for dermally applied furocoumarins, it is recommended that the phrasing of the furocoumarins entry be revised to clarify that the allowance of 1 ppm only applies to the content of furocoumarins when naturally occurring in plant extracts. The conditions of use by product type should be expanded to include products with leave-on application, rather than only sun-tanning products. While recommending limits on individual botanically-derived essential oils and extracts goes beyond the scope of this HIR, the additive effect should be taken in consideration when co-formulating multiple furocoumarin-containing ingredients such that the level of total furocoumarins does not exceed 1 ppm in the finished product.

To reduce redundancy on the Hotlist, consideration should be given to removing the listing for imperatorin and adding it to the scope of the revised entry on furocoumarins.

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1.0 INGREDIENT SUMMARY

(1) Furocoumarins, except for naturally occurring in plant extracts

INCI Name: N/A

Synonyms: Psoralen; Ficusin; 7*H*-Furo[3,2-*g*][1]benzopyran-7-one; 2-Propenoic acid, 3-(6-hydroxy-5-benzofuranyl)-, δ -lactone; 6,7-Furanocoumarin (Pubchem, 2021; NCI Global, 2021)

CAS RN: 66-97-7 (PubChem, 2023)

* CAS numbers and synonyms of other furocoumarin derivatives that lack INCI names but are expected to be found in cosmetics are listed in [Appendix 1](#).

(2) Imperatorin

INCI Name: N/A

Synonyms: 5-Benzofuranacrylic acid, 6-hydroxy-7-((3-methyl-2-butenyl)oxy)-, δ -lactone; 5-hydroxy-8-(1,1-dimethylallyl)psoralen; 8-(3-Methyl-2-butenyloxy)psoralen (NCI Global, 2023; PubChem, 2023)

CAS RN: 482-44-0 (PubChem, 2023)

* See full list of synonyms in [Appendix 1](#).

2.0 BACKGROUND ON SUBSTANCE

2.1 Regulatory Status of Substance in Cosmetics

Furocoumarins have a restricted status on the Cosmetic Ingredient Hotlist. Based on the current phrasing of the entry, their intentional use is only restricted in sun-tanning products at a maximum combined concentration of 1 mg/kg (1 ppm ~ 0.0001%). When naturally occurring in plant extracts, furocoumarins are exempt from the Hotlist restriction (HC, 2022).

The European Commission prohibits the use of furocoumarins except for normal content in natural essences used in cosmetic formulations, under Annex II/358 (list of substances prohibited in cosmetic products) of Cosmetics Regulation (EC) No. 1223/2009. The EU allows a maximum concentration of 1 mg/kg in sun protection and bronzing products. Except for the US, other verified international jurisdictions align with EU regulations. Switzerland however, applies the limit of 1 mg/kg total furocoumarin content to products that are leave-on and/or products with potential for direct exposure to sunlight, and provides an exemption for certain perfumery products (e.g. eau de toilette).

Imperatorin is prohibited on the Cosmetic Ingredient Hotlist. The European Commission prohibits it from use in cosmetic formulations, under Annex II/34 of the Cosmetics

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Regulation (EC) No. 1223/2009. Other verified international jurisdictions, except for US, align with this prohibition.

This ingredient is not subject to restrictions when sold as part of cosmetic products marketed in the US.

Please refer to [Appendix 2](#), for a detailed comparison of the cosmetic regulations applicable to these ingredients in other international jurisdictions.

2.1.1 Policy Statements and Decisions Regarding Cosmetics and Cosmetic Regulations

None identified.

2.2 Status of Ingredient in Other Cosmetic Lists or Databases

a. Cosmetics Notifications (Health Canada):

There is no indication that furocoumarin ingredients are individually notified in cosmetic formulations.

However, a number of botanical ingredients noted by IFRA to be significant sources of furocoumarins (angelica root oil, bergamot oil expressed, cumin oil, lemon oil cold-pressed) are present in a number of leave-on products with potential for sun exposure upon application (at up to 100%). Because disclosure of the raw material composition of the individual ingredients as well as the method of extraction (e.g. cold-pressed, steam distilled) is not required at the time of notification, the total content of furocoumarins present in the notified cosmetic formulations cannot be estimated.

Based on the restrictions recommended by the IFRA code of practice and the maximum notified concentrations of the potential botanical sources of furocoumarin in the finished product, it is *theoretically* possible that the concentration of furocoumarins may exceed the 1 ppm allowance set by the EU (see Tables 4 & 5, [Appendix 3](#)).

[Redacted]

b. Personal Care Products Council (PCPC) INCI Dictionary:

Alloimperatorin is reported to function as a skin conditioning agent (PCPC, 2023).

c. International Fragrance Association (IFRA) Standards (49th ed.):

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Furocoumarins are captured as “citrus oils and other furocoumarins containing essential oils” under the 49th Amendment of IFRA Standards, in the “Restricted” category, last amended 01/2020.

The IFRA recommends individual restrictions in the finished product for a number of fragrance ingredients (extracts) considered to be significant sources of furocoumarins. These are available for reference in Table 4 ([Appendix 3](#)).

- Angelica root oil
- Bergamot oil expressed
- Bitter orange oil expressed
- Cumin oil
- Grapefruit oil expressed
- Lemon oil cold pressed
- Lime oil expressed
- Rue oil

Several essential oils that contain small amounts of phototoxic furocoumarins were identified by IFRA:

- Petitgrain mandarin oil (50 ppm)
- Tangerine oil cold pressed (50 ppm)
- Parsley leaf oil (20 ppm)

The IFRA considers the levels of furocoumarins in these botanical extracts to not be high enough to warrant restrictions when used individually in a product; however, if they are used in combination, or along with other significant sources of furocoumarin-containing ingredients as listed above, the total concentration of 5-MOP in the finished product should not exceed 15 ppm.

(IFRA, 2020)

2.3 Status of Ingredient in Other Non-Cosmetic Databases

Natural and Non-Prescription Health Products Directorate (NNHPD):

The NNHPD database identifies several substances which contain furocoumarins, including essential oils or citrus plant components as flavouring agents, aromatherapeutic agents and skin-conditioners. These substances are classified as natural health products under Schedule 1 of the *Natural Health Product Regulations* and include Grapefruit oil (cold pressed), Mandarin essential oil (cold pressed), Bergamot essential oil, *Citrus Aurantium Amara* (Bitter Orange) peel, *Citrus Aurantifolia* (Lime) oil, and *Citrus Aurantium Bergamia* (Bergamot) fruit oil.

Restrictions applied to these ingredients are based on the European limits

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with the NNHPD citing the European Commission limit of 1 ppm for furocoumarins in these material sources.

(HC, 2023)

California Environmental Protection Agency:

Listed as “**5-methoxypsoralen** with ultraviolet A therapy” and “**8-methoxypsoralen** with ultraviolet A therapy”, under “Chemicals known to the state to cause cancer or reproductive toxicity”.

(California EPA, 2021)

International Agency for Research on Cancer (IARC):

5-methoxypsoralen (5-MOP) is specified on the IARC class of carcinogenicity list as Group 2A, a substance that is “probably carcinogenic to humans”. (Volume 40, Sup 7, 1987).

Methoxsalen (8-methoxypsoralen) plus ultraviolet A radiation is specified on the IARC class of carcinogenicity list as Group 1, a substance that is carcinogenic to humans (Volume 24, Sup 7, 100A, 2012).

The following furocoumarin substances are specified on the IARC class of carcinogenicity list as Group 3, unclassifiable as to their carcinogenicity to humans (Volume 40, Sup 7, 1987):

- 3-Carbethoxypsoralen
- 4,5',8-Trimethylpsoralen
- Pyrido[3,4-c]psoralen
- 4,4'-Dimethylangelicin plus ultraviolet A radiation
- 4,5'-Dimethylangelicin plus ultraviolet A radiation
- Angelicin plus ultraviolet A radiation
- 5-Methylangelicin plus ultraviolet A radiation
- 4,4',6-Trimethylangelicin plus ultraviolet A radiation

(IARC, 2023)

The ingredients were not found in the following sources:

Domestic Substances List (DSL)

List of all Challenge Substances, Chemicals Management Plan (CMP);

Food and Drug Regulations (C.R.C, c. 870);

Lists of Permitted Food Additives (HC);

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New Drugs List (aka Listing of Drugs Currently Regulated as New Drugs) (TPD)
Drug Product Database (DPD);
Licensed Natural Health Products Database
Prescription Drug List (HC);
Australian Government Poisons Standard (as of July, 2023);
Danish List of Undesirable Substances.

3.0 SCIENTIFIC JUSTIFICATION

3.1 Background

Furocoumarins are synthetic or naturally occurring components of plants and plant extracts, some of which are used as cosmetic ingredients. Furocoumarins as a class have a limited distribution in the plant kingdom and are characteristic of certain plant families, primarily *Apiaceae*, *Moraceae*, *Rosaceae*, and *Rutaceae* (Christensen, 2018). Members of these families are often known to cause phytophotodermatitis, a cutaneous phototoxic inflammatory eruption resulting from concomitant exposures to light-sensitizing botanical substances and long-wave ultraviolet A (UV-A, 320-380 nm) radiation (Baugh, 2019).

The phototoxicity of furocoumarins is correlated with their ability to react with nucleobases in the DNA under the influence of UV-A radiation; the subsequent formation of inter-strand cross-linkages in the DNA leads to characteristic acute bullous lesions. No allergic mechanism is involved in these phototoxic reactions, although furocoumarins may be occasional sensitizers. The major allergenic furocoumarins are isobergaptene and sphondin, but they are considered to have poor phototoxic potential (Christensen, 2018).

The risk and degree of phototoxicity depends on the identity and the amount of phototoxic substance present as well as the extent of exposure to UV light. Botanicals that typically cause phytophotodermatitis contain primarily linear furocoumarins such as psoralen, bergapten (5-MOP) and methoxsalen (8-MOP) (see Figure 1).

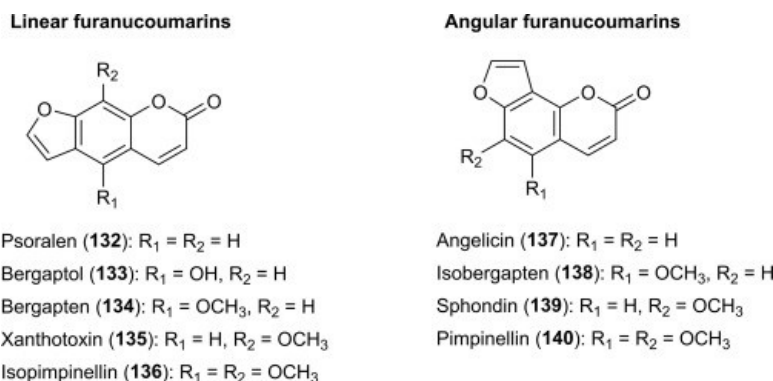


Figure 1. Linear vs. Angular furocoumarins (Christensen, 2018)

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These have a high degree of phototoxicity and they are known to have photomutagenic and photocarcinogenic potentials in the presence of UVA radiation. Other linear furocoumarins such as bergamottin, bergaptol and isopimpinellin have negligible phototoxicity and have either negligible, unlikely or unknown potentials for photomutagenicity and photocarcinogenicity. Angular furocoumarins such as angelicin or isobergaptin generally have lower phototoxicity relative to linear furocoumarins (Tisserand & Young, 2014, see Figure 2).

In the absence of light, furocoumarins, linear or angular, can insert into the DNA double helix. The difference in toxicity is mechanistically linked to the ability of linear furocoumarins to induce (upon photoactivation) *both* mono- and inter-strand cross-linked bi-adducts. In contrast, angular furocoumarins can only form mono-adducts with the DNA. While mono-adducts are believed to be responsible for the therapeutic application of furocoumarins in suppressing DNA replication, the crosslink formation is associated with cutaneous phototoxicity and photocarcinogenicity (Melough & Chun, 2018; Young et al., 1990).

Constituent	Degree of phototoxicity	Photomutagenic	Photocarcinogenic	Type ^a
Psoralen	Strong	Yes	Yes	LF
Methoxsalen	Strong	Yes	Yes	LF
Bergaptin	Strong	Yes	Yes	LF
Angelicin (isopsoralen)	Moderate	Yes	Weak	AF
Imperatorin	Moderate	Yes	Not known	LF
Citropten	Moderate	Yes	Not known	Lac
Oxypeucedanin	Moderate	Not known	Not known	LF
Isoimperatorin	Weak	Not known	Not known	LF
Bergamottin	Negligible	Negligible	Not known	LF
Isobergaptin	Negligible	Not known	Not known	AF
Isopimpinellin	Zero	No	Unlikely	LF
Bergaptol	Zero	No	Unlikely	LF
7-Methoxy-5-geranoxycoumarin	Not known	Not known	Not known	Lac

These are listed in approximate descending order of phototoxic potency
^aLF, linear furanocoumarin (psoralen); AF, angular furanocoumarin (angelicin); Lac, lactone

Figure 2. Light-related risks of some furocoumarins and lactones (Tisserand & Young, 2014)

Bergaptin (5-MOP) is present in the expressed (cold-pressed) oil of bergamot and other phototoxic citrus oils at 100-3000 ppm (IARC, 1986b; SCC, 1990; Tisserand & Young, 2014). Since the mid-1970's, a number of products became available in Europe which contained the furocoumarin bergaptin (5-MOP) at 15-60 ppm in commercially sold sun-tanning products (Clark & Wilkinson, 1998; SCC, 1990). Upon photoactivation by UVA radiation (320-400 nm), bergaptin-containing preparations were expected to promote sunlight-induced melanogenesis (i.e. tanning) while protecting against UVB-induced damage. The levels of bergaptin used in these products were subsequently found to cause

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photocarcinogenic effects in mice (Young et al., 1990). However, bergapten was claimed to produce overall less phototoxic reactions than methoxalen (8-MOP), another commonly used sun-tanning activator in sunscreen preparations (Cartwright & Walter, 1983). Synthetic forms of methoxsalen (8-MOP) and bergapten (5-MOP) have been widely used as oral and topical drugs in skin photochemotherapy, in combination with UVA radiation, to treat symptoms of psoriasis, vitiligo and mycosis fungoides. Even the short-term use of psoralens in skin photochemotherapy has been associated with phototoxicity, including erythema, localized edema, and blistering while the long-term use was found to increase the risk of non-melanoma skin cancers and possibly cutaneous melanoma (Aronson, 2015).

Furocoumarins have been isolated from various parts of plants from which cosmetic ingredients may be sourced – including bark, leaf, fruit, root, peel, seed and pulp (EFSA, 2012). In perfumes, the concentrations of 5-MOP have been reported in the range of 0-100 µg/mL (up to 100 ppm) (IARC, 1986b). Reducing the concentration of 5-MOP and other non-volatile furocoumarins is possible by steam or fractional distillation. However, the resulting “furocoumarin-free” oil is considered to have an inferior fragrance to the cold-pressed variety (Young *et al.* 1990; CIR, 2019). In spite of that, Ashwood-Smith and colleagues (1980) reported that nearly all the bergamot oil sold in the US for use in consumer products is produced through steam-distillation, and is thus considered “furocoumarin-free”.

Based on the available notification data, there is no evidence that furocoumarins are intentionally added as discrete ingredients to cosmetic products. However, they may be/are likely present in cosmetics as the result of formulating using naturally occurring sources. The current Hotlist entry reads “Furocoumarins, except for naturally occurring in plant extracts”. As such, there are no specific conditions described on the Hotlist for most botanically derived oils (e.g. bergamot oil, angelica root oil, lemon oil, etc.) that may contain furocoumarins. Two other botanical sources of furocoumarins, *Ammi majus* L (Bishop’s Weed) and *Ficus carica* L. are already described as prohibited on the Hotlist. The rationales for prohibiting those are partly based on their potential to cause severe phototoxic reactions.

Imperatorin is a naturally occurring linear furocoumarin described in scientific literature as having moderate phototoxicity and significantly lower photomutagenic potential relative to 5-MOP and 8-MOP (Schimmer & Abel, 1986; Tisserand & Young, 2014). There is no indication that imperatorin would be an intentionally added ingredient, because it has no INCI name or reported cosmetic function at this point in time. However, it may be present in a finished cosmetic formulation from natural sources of imperatorin such as *Angelica dahurica*, *Angelica archangelica*, *Angelica sinensis*, *Petroselinum crispum* (parsley), and *Foeniculum vulgare* Mill (fennel), (Deng et al., 2020; PCPC, 2021).

3.2 Relevant Toxicokinetics

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Because furocoumarins are naturally occurring constituents of various botanically derived ingredients, which can be added to a wide range of cosmetic product types, all routes of exposure are considered relevant during cosmetic use.

When ingested orally, furocoumarins are rapidly absorbed through the gastro-intestinal tract, bound to proteins (primarily albumin) and distributed to many tissues. When distributed to the skin, phototoxic reactions can follow with exposure to UV radiation (Melough & Chun, 2018). Various authors have estimated that the skin furocoumarin concentration reaches peak level at between 1-4 hours post-consumption (Lauharanta et al., 1982; Tegeder et al., 2002).

Bergapten (5-MOP) showed high (69.5 – 94.0%) bioavailability in rats upon oral administration, and may also be absorbed through the skin (SCC, 1990; Yu et al., 2016). In a study where bergamot oil was applied to the skin of five volunteers, the blood concentration of 5-methoxypsoralen (5-MOP) was significantly increased 4 hours after application, suggesting that furocoumarins are readily absorbed through dermal contact (Wang & Tso, 2002).

In oral rat studies, high concentrations of 8-MOP were found in the liver, kidney and adrenal glands. Other animal studies have identified the intestines, adipose tissue, muscle, and skin as tissues accumulating relatively high concentrations of 8-MOP compared to the levels reported in blood plasma (Melough & Chun, 2018). Several furocoumarins, including imperatorin have been shown to cross the blood-brain barrier in mice (Wan et al., 2013). Urinary excretion is the major route of elimination for ingested furocoumarins.

Overall, both the ingestion of furocoumarins as well as skin contact with furocoumarin-containing botanically derived ingredients can lead to systemic absorption and adverse phototoxic responses.

3.3 Authoritative Opinions and Risk Assessments

Scientific opinions with direct relevance to cosmetics are available for furocoumarins. They are presented below in chronological order, from most to least recent, along with their final conclusions:

- *Safety Assessment of Citrus Peel-Derived Ingredients as Used in Cosmetics*
 - The CIR Expert Panel concluded that the 47 peel-derived ingredients under review are safe in the present practices of use and concentration in both rinse-off and leave-on cosmetic products when formulated to be non-sensitizing and non-irritating, provided that leave-on products do not contain more than 0.0015% (15 ppm) 5-methoxypsoralen (5-MOP) (Burnett et al., 2021a)
- *Safety Assessment of Citrus Fruit-Derived Ingredients as Used in Cosmetics*

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- The CIR Expert Panel concluded that 80 Citrus fruit-derived ingredients under review are safe in the present practices of use and concentration in both rinse-off and leave-on cosmetic products when formulated to be non-sensitizing and non-irritating, provided that leave-on products do not contain more than 0.0015% (15 ppm) 5-methoxypsoralen (5-MOP) (Burnett et al., 2021b)
- *Safety Assessment of Citrus-Derived Peel Oils as Used in Cosmetics*
 - The CIR Expert Panel concluded that 14 citrus-derived peel essential oils under review are safe in the present practices of use and concentration in both rinse-off and leave-on cosmetic products when formulated to be non-sensitizing and non-irritating, provided that leave-on products do not contain more than 0.0015% (15 ppm) 5-methoxypsoralen (5-MOP) (Burnett et al., 2019)
- *Opinion of the Scientific Committee on Consumer Products (SCCP) on Furocoumarins in Cosmetic Products (SCCP, 2005)*
 - *Overall, the available data received by the SCCP do not rule out the phototoxicity of any of the known furocoumarins*
 - As the consumer is exposed to sunlight after using various types of cosmetic products, not only bronzing or sun protection products, and in the absence of any additional data demonstrating the safety of any of the furocoumarin-like substances, the SCCP reemphasized the earlier conclusion of the scientific committee that total concentrations of furocoumarins exceeding 1 ppm in any finished cosmetic product will be of concern with regard to consumer safety
 - The opinion applies to the content of furocoumarins in finished cosmetic formulations, *irrespective of the source of these substances*
- *Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) Concerning Bergamottin (SCCNFP, 2003a)*
 - Photomutagenicity and photocarcinogenicity are the main effects of concern in relation to the use of furocoumarins in cosmetics. The data submitted by European Flavour & Fragrance Association (EFFA) on bergamottin was not found to be adequate for evaluation of the safety of the substance in relation to photomutagenicity and photocarcinogenicity
- *Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) Concerning Furocoumarins in Sun Protection and Bronzing Products (SCCNFP, 2003b)*
 - SCCNFP concluded that the data available from *in vitro* short-term studies, experimental studies in animals, and epidemiological studies on humans on the effect of furocoumarins in sun protection and sun-bronzing products do not justify a higher limit than 1 ppm (not to be intentionally added)

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- *Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) Concerning Isopimpinellin (SCCNFP, 2003c)*
 - Photomutagenicity and photocarcinogenicity are the main effects of concern in relation to the use of furocoumarins in cosmetics. The data submitted by European Flavour & Fragrance Association (EFFA) on isopimpinellin was not found to be adequate for evaluation of the safety of the substance in relation to photomutagenicity and photocarcinogenicity
- *Opinion of the SCC Concerning Bergasol Suntan Products Containing 5-MOP (SCC, 1990)*
 - It is not possible to conclude that sunscreen products containing 15-60 ppm or more 5-MOP (bergapten) are without risk of producing harm due to their potential for photomutagenicity and photocarcinogenic effects; therefore the maximum amount of 5-MOP in all sun-tanning products should be 1 ppm.

3.3.1 Restrictions Recommended by Industry

A recent IFRA standard published in 2020 (49th amendment) restricts the use citrus oils and other furocoumarin-containing essential oils, citing phototoxicity as the intrinsic property driving risk management (IFRA, 2020). The standard stipulates that for products applied on areas of skin exposed to UV radiation, the total level of bergapten (5-methoxypsoralen, or 5-MOP) in the consumer products should not exceed 0.0015% (15 ppm). The IFRA notes that rinse-off products or those that may come in incidental contact with the skin are excluded from the application of this standard. When several furocoumarin-containing oils are used in combination, the standard recommends that additive effects be taken into consideration and the concentration levels of the ingredients be adjusted accordingly to prevent exceeding the threshold of 15 ppm bergapten in the finished product.

The IFRA standard on citrus oils and other furocoumarin containing essential oils is based on several publications:

As part of an international cooperative study on bergamot oil, Young *et al.* (1990) investigated the photocarcinogenic potential of 5-methoxypsoralen (5-MOP) at low concentrations in the albino mouse skin model (Skh 1). Female hairless albino mice (Skh 1) were exposed to test samples containing 5-MOP at 0, 5, 15 and 50 ppm, formulated with or without sunscreen ingredients (0.5%), in the presence or absence of simulated solar radiation (SSR), over a period of up to 75 weeks. There were 12 treatment groups and 5 control groups, each containing 30 mice. The results showed a significant dose-response, with the lowest concentration of 5-MOP (5 ppm) demonstrating enhanced photocarcinogenic potential. Non-irradiated control groups as well as the control group treated with bergapten-free bergamot oil, did not show evidence of skin tumor formation.

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Similarly, the group exposed to 5-MOP at the highest concentration (50 ppm) did not show evidence of tumorigenesis in the absence of SSR.

Study results also indicated that 5-MOP is the active phototumorigenic agent in bergamot oil, rather than other furocoumarin constituents (e.g. bergamottin) that may be present at higher concentrations. Additionally, the statistical analysis presented in the study provided a strong indication that the threshold concentration for a positive effect of 5-MOP is 5 ppm or less. In the 5 and 15 ppm test groups, the low concentrations of sunscreens (0.5%) provided photoprotective effects, by reducing or completely eliminating the risk of skin cancer development associated with 5-MOP exposure.

A follow-up study by Dubertret and colleagues (1990) investigated the phototoxic properties of perfume samples containing 5-MOP at different concentrations (0, 5, 15 and 50 ppm) on human subjects. Hydroalcoholic perfumes (ethanol:water, 80:20, w/w) were prepared using bergamot oil. Some samples were combined with sunscreen ingredients (UVA or UVB) alone or in combination, at 0.5-1% concentration. A total of 18 healthy, 20-25 year old volunteers (10 males and 8 females), with Fitzpatrick phototypes I-III participated in the study. The test formulations were applied to the backs of the subjects, in the presence or absence of SSR. Five columns (product application areas) were tested per subject: control², and model perfumes with different concentration (5, 15 and 50 ppm) with or without sunscreen ingredients. The test areas were irradiated 1, 2 and 4 hours after the test samples were applied. Phototoxic erythema and pigmentation were graded on a scale of 0 to 4 and were assessed respectively 3 days and 14 days post-application. These phototoxic responses reached maximum when irradiation was performed 2 hours after application. The authors found evidence of erythema and pigmentation in some human volunteers at 5 ppm while these phototoxic effects always occurred at 15 ppm. The authors found that adding 0.5% sunscreens to a model perfume containing 5-MOP at 50 ppm resulted in equivalent phototoxicity to a product containing 5-MOP at 15 ppm, without added sunscreen ingredients.

3.3.2 Recommendations of the European Commission

In 1990, the Scientific Committee on Cosmetology (SCC) adopted an opinion indicating furocoumarins are photomutagenic and photocarcinogenic (SCC, 1990). At that time, the SCC found that based on the available scientific, technical and epidemiological data, it was not possible to conclude that the use of protective UV filters along with 15-60 ppm or more bergapten (5-MOP) content³ would guarantee the safety of sun protection and bronzing products above a minimum level. Key evidence considered by the committee included clear evidence of mutagenicity in bacteria, yeasts and mammalian cells upon exposure to bergapten (5-MOP) in the presence of UVA radiation. This combination was also found to be clastogenic⁴ in mammalian cells in tissue culture. In mice, bergapten (5-MOP) + UVA caused

² No 5-MOP or sunscreen ingredients

³ Effective dose of 5-MOP in suntan products marketed by Bergasol

⁴ A clastogenic substance can cause breaks in chromosomes that result in the gain, loss, or rearrangements of chromosomal segments

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an increased incidence of skin cancer (compared to SSR alone), but there are no adequate studies available in humans. However, the combination of 8-methoxypsoralen (8-MOP) plus UVA was previously found to be clastogenic in human and classified as an IARC group 1 carcinogen (i.e. known human carcinogen). Based on their potential for photomutagenicity and photocarcinogenicity, a limit of 1 ppm was recommended by the Committee as a maximum permitted furocoumarin content for these product types.

Three data submissions were provided to the SCCNFP by industry for additional review of the furocoumarins isopimpinellin (SCCNFP/0761/03) and bergamottin (SCCNFP/0740/03) as well as various furocoumarin-like substances in citrus oils in 2005 (SCCP/0942/05). Photomutagenicity and photocarcinogenicity were the main effects of concern in relation to the use of furocoumarins in cosmetics. The SCCNFP concluded that insufficient data was presented to enable a safety evaluation of the substances with regards to their photomutagenicity or photocarcinogenicity potentials. The Opinion of the SCCNFP on Furocoumarins in Sun Protection and Bronzing Products (SCCNFP/0765/03) stated:

“(...) the data available from in vitro short-term studies, experimental studies in animals, and epidemiological studies on humans on the effect of furocoumarins in sun protection and sun bronzing product do not justify a higher limit than 1 ppm (not to be intentionally added) for furocoumarins in cosmetics. This Opinion should be interpreted in conjunction with the Opinion on CMR substances (SCCNFP/0474/01, final, Adopted 25 September 2001)”

The SCCP (2005) emphasized that in the absence of additional data submission to substantiate consumer safety and justify a higher allowance, the furocoumarin content (irrespective of source) in any finished cosmetic should be restricted to 1 ppm, particularly as consumers may be exposed to sunlight after application of various types of cosmetic products and not just bronzing or sun protection products. The committee noted that in studies with 5-MOP and 8-MOP, photogenotoxic and photomutagenic effects *in vitro* were observed at concentrations below 0.01 and 0.1 ppm, respectively, while *in vivo* studies conducted in mice with 25 ppm 5-MOP in a UVB sunscreen enhanced tumour formation in the presence of UVA irradiation.

The recommendation of the SCCP is supported by the SCCNFP's published opinion on *“Chemical Ingredients in Cosmetic Products Classified as Carcinogenic, Mutagenic or Toxic to Reproduction According to the Chemicals Directive 67/548/EEC”* (SCCNFP/0474/01) which indicates a risk assessment may be performed on a case-by-case basis to establish safety:

“... cosmetic products may contain small amounts of carcinogens, mutagens, or substances toxic to reproduction even if such substances are not intentionally added to the product. In these cases, it will be necessary to perform risk assessment on a case-by-case basis to establish that the product does not pose a threat to the health of the consumer.”

3.3.3 Recommendations of the Cosmetic Ingredient Review (CIR) Expert Panel

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To date, the CIR Expert Panel has conducted several safety assessments on various Citrus-derived ingredients with relevance to furocoumarins: Citrus-derived peel oils, Citrus-fruit derived ingredients, and Citrus peel-derived ingredients (CIR 2021a, 2021b, 2019). The safety assessments were not focused on the toxicity data available for the individual constituents, but rather the citrus-derived ingredients as UVCBs⁵. However, the Panel considered compositional information, particularly the constituents that other recognised scientific expert bodies had previously identified as posing safety concerns.

The primary focus of these safety assessments was on the potential for irritation and sensitization resulting from dermal exposure to citrus-derived ingredients. A particular concern highlighted by the Panel was the phototoxicity potential of constituents such as 5-MOP as well as the potential of other ingredients such as synephrine, limonene, citral and additional monoterpenes to cause skin sensitization or other local adverse effects. The Panel noted an IFRA standard has been issued for *Citrus* oils and other furocoumarin-containing essential oils in order to mitigate the risk of phototoxicity associated with the presence of furocoumarin 5-MOP. The opinion acknowledged that botanical ingredients are complex mixtures with hundreds of constituents and, thus, the use of multiple botanical ingredients in a cosmetic formulation may enhance the final concentration of individual constituents that could increase the risk of local adverse effects. Although, there was generally no evidence of skin irritation or sensitization at the levels relevant to cosmetic use, due to cumulative effects of multiple botanical ingredients, the Panel recommended that the products as a whole should be formulated to be non-irritating and non-sensitizing.

Phototoxicity was observed for several citrus-derived peel oils which are known to contain photoactive agents such as furocoumarins. Phototoxic reactions were observed in response to dermal application of undiluted bitter orange oil, lemon oil (1%), sweet orange oil (1%) and undiluted and diluted expressed lime oil (30%) on human skin. No evidence of phytophotodermatitis was observed in rats after the liberal application of undiluted lemon fruit juice and exposure to natural sunlight. Lemon peel juice, however, caused phototoxic reactions in several rat studies reviewed by the CIR. Human subjects that were exposed to undiluted extracts of orange mesocarp or fruit, and irradiated with UVA did not present any local reactions. No dermal phototoxic responses were observed when exposing human subjects ($n=20$) to a lotion containing *Citrus aurantium bergamia* (bergamot) fruit extract at 0.081525% and subsequently to UVA and UVB. However, strong erythema and infiltration were observed after exposure to pure sweet orange peel and peel extract, with UVA irradiation, in human subjects ($n=2$ with type I skin), but no reactions were induced in a type II skin subject ($n=1$). A number of case reports show the presence of phytophotodermatitis in individuals dermally exposed to various lemon and lime juice preparations (not cosmetic formulations).

The Panel also indicated that citrus-derived peel oils that claimed to be “furocoumarin-free” tended to not produce phototoxic reactions in humans.

⁵ Of unknown or variable composition

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The overarching conclusion of the Panel was that all 80 citrus fruit- and 47 peel-derived ingredients under assessment, are safe for use in cosmetic products, when formulated to be non-irritating and non-sensitizing, provided leave-on products do not contain more than 0.0015% (15 ppm) of furocoumarin 5-MOP. This limit was endorsed in alignment with the IFRA Standard for “*Citrus oils and other furocoumarins containing essential oils*”.

3.3.4 United States National Toxicology Program (NTP)

The NTP first identified the furocoumarin 8-methoxypsoralen (Methoxsalen; 8-MOP) as a human carcinogen in 1985 in the Fourth Annual Report on Carcinogens. The entry was later revised in the Fourteenth edition of the Report on Carcinogens, describing concurrent Ultraviolet A exposure for the therapy of psoriasis (PUVA). The report states “*Methoxsalen (psoralen) with ultraviolet A (UVA) long-wave therapy (PUVA) is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans.*” (NTP, 2016).

The oral toxicity and carcinogenicity of psoralens were studied in an F344/N rat model in 1989 as described in the NTP report “*Toxicology and Carcinogenesis Studies of 8-Methoxypsoralen (CAS No. 298-81-7) in F344/N Rats (Gavage Studies)*” (NTP, 1989). Skin toxicity was measured following oral doses of the substance followed by UVA radiation. Oral dosing of psoralens alone did not promote toxicity to skin or other organs at the doses used in mice (high dose of 5-MOP or 8-MOP 5.8 mmol/kg feed). Skin toxicity was observed with 2.9 and 5.8 mmol/kg feed dosage of both 5-MOP and 8-MOP when mice were subsequently exposed to UVA at 2 J/cm². Skin toxicity was also observed with oral exposure to 0.23 mmol/kg feed of 8-MOP in combination with 48 J/cm² UVA light over exposure to UVA light alone. Animal feed doses were considered to be equivalent to high human doses by the investigators. Thus, these levels are not similar to exposures from cosmetic products, thereby limiting the applicability of the data. The investigators dosed 0.23 mmol/kg feed equivalent to 6 mg/kg body weight/week, 2.9 mmol/kg feed equivalent to 80 mg/kg body weight/week, and 5.8 mmol/kg feed equivalent to 160 mg/kg body weight/week.

The NTP later reviewed the phototoxicity of lemon oil and lime oil in topical cosmetic products (NTP, 1989). Safety data for raw fragrance materials included human, swine, shaved albino guinea pigs and albino hairless mice studies, revealing evidence of phototoxicity of both lemon oil and lime oil in humans and animals. Two components of the oils were associated with phototoxicity: oxypeucedanin and 5-methoxypsoralen. Several furocoumarins were identified in lemon oil and lime oil, including psoralen, 8-methoxypsoralen, 5-methoxypsoralen, 5-geranoxypsoralen, 5,7-dimethoxypsoralen, and 5-(isoamyl-2,3-epoxide) psoralen. The concentrations of furocoumarins varied depending on plant growth conditions. The NTP noted that psoralens have been associated with phototoxicity and photocarcinogenicity in human and animal studies as well as in prokaryotic and eukaryotic test systems. Insufficient data were available at the time of the review to identify the photogenotoxicity, mutagenicity, and/or photocarcinogenicity of several furocoumarins identified in lemon oil and lime oil. The NTP subsequently requested

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additional photogenotoxicity studies be performed for furocoumarins as individual compounds or as complex mixtures.

3.3.5 International Agency for Research on Cancer (IARC). 1986. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Some naturally occurring and synthetic food components, furocoumarins and ultraviolet radiation, Vol 40. Lyon, France: IARC.

Methoxsalen (8-MOP) was first reviewed by IARC in 1980 (Volume 24, IARC monographs) and determined to be a human carcinogen in the presence of ultraviolet A (UVA) radiation due to the ability of furocoumarins to bind to DNA in the presence of UVA (NTP, 1989). IARC evaluated the carcinogenicity of several furocoumarin compounds in Volume 40, noting the available data were generally inadequate to determine dermal or systemic carcinogenicity in humans due to poor study design or limited details in study reports (IARC, 1986a). The table below outlines the availability of data; generally, there was inadequate evidence for carcinogenicity in animals and/or humans and, as such, no evaluation could be made regarding carcinogenicity for several compounds.

Table 1. Summary of IARC Evaluations

Chemical/Exposure	Evidence of human carcinogenicity	Evidence of animal carcinogenicity	Activity in short-term tests
Angelicin	No data	Inadequate	Inadequate
Angelicin + UVA	No data	Limited	Sufficient
5-Methylangelicin	No data	Inadequate	Inadequate
5-Methylangelicin + UVA	No data	Limited	Sufficient
4,4'-Dimethylangelicin	No data	No data	Inadequate
4,4'-Dimethylangelicin + UVA	No data	No data	Limited
4,5'-Dimethylangelicin	No data	Inadequate	Inadequate
4,5'-Dimethylangelicin + UVA	No data	Limited	Sufficient
4,4',6-Trimethylangelicin	No data	No data	Inadequate
4,4',6-Trimethylangelicin + UVA	No data	No data	Inadequate
3-Carbethoxypsoralen	No data	Inadequate	Inadequate
3-Carbethoxypsoralen + UVA	No data	No evidence	Sufficient
5-methoxypsoralen	Inadequate	Inadequate	-
5-methoxypsoralen + UVA	Inadequate	Sufficient	Sufficient
Pyrido[3,4-c]psoralen	No data	No data	Inadequate
Pyrido[3,4-c]psoralen + UVA	No data	Inadequate	Sufficient
7-Methylpyrido[3,4-c]psoralen	No data	No data	Limited
7-Methylpyrido[3,4-c]psoralen + UVA	No data	Inadequate	Sufficient
4,5',8-Trimethylpsoralen	Inadequate	No data	Inadequate

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4,5',8-Trimethylpsoralen + UVA	Inadequate	Inadequate	Sufficient
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4.0 CONCLUSION

Furocoumarins have been associated with adverse health effects in humans, characterized by phototoxicity, photomutagenicity and photocarcinogenicity reactions when combined with exposure to UVA radiation.

These substances are currently restricted on the Hotlist to 1 ppm in sun-tanning products when intentionally added. Naturally occurring sources of furocoumarins as well as products other than sun-tanning products are not subject to the existing Hotlist conditions.

In the EU and other international jurisdictions, furocoumarins are listed as prohibited, except for normal content in natural essences where an allowance of 1 ppm is provided for sun protection and bronzing products which are associated with significant light exposure. If the original intent was to harmonize the regulatory status of furocoumarins with other international jurisdictions, the current placement and phrasing of the entry on the Hotlist do not meet the intended interpretation. A more recent SCCP opinion (2005) recommended that the restriction on furocoumarins (as part of normal content in natural essences) should be extended to all finished cosmetic products, not only to sun protection and bronzing products.

Imperatorin is prohibited at any concentration across all verified jurisdictions. However, no scientific opinions or additional scientific evidence have been found to substantiate its current status or why it is addressed under a separate entry from furocoumarins.

Several recent CIR safety assessments have been published for several citrus fruit- or citrus peel-derived ingredients where the scientific Panel has endorsed a limit of 0.0015% (15 ppm) 5-methoxypsoralen (5-MOP). This limit corresponds to the maximum acceptable concentration of 5-MOP in finished products, according to the IFRA Standard on furocoumarin and furocoumarin-containing essential oils. The recommended limit by CIR is based on the published phototoxic effects of 5-MOP and its established dose-effect relationships. Other international jurisdictions, including the EU, enforce a lower concentration limit of 1 ppm.

Photocarcinogenicity studies performed with 5-MOP in an albino mouse model (Skh1) showed enhanced photocarcinogenic potential even at a low concentration of 5 ppm in the presence of simulated solar radiation. Topically applied 5-MOP (5 ppm) had phototoxic potential in some human subjects, while at 15 ppm all subjects experienced erythema and pigmentation reactions. These key studies did not investigate concentrations lower than 5 ppm and, therefore, the lowest concentration that may result in phototoxicity is unknown and quantitative justification for the current 1 ppm limit (in the EU and Canada) is not apparent based on a review of the available data. As most toxicological studies focus on 5-MOP and 8-MOP, there is limited information on the toxicological characteristics of other furocoumarins.

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Overall, there is insufficient evidence to support a revision to the EU-recommended limit of 1 ppm, which is representative of a trace-level amount. Significant data gaps are apparent, including data for cumulative exposure or combined exposure from multiple products or considerations for pure essential oils. Restricting the levels of furocoumarins to 1 ppm in sun-tanning products *only* is not scientifically supported, because sun exposure may occur following the use of almost any leave-on cosmetic product.

This ingredient review will be assigned to Risk Management Strategies for consideration of further action.

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APPENDIX 1 - Ingredient summary

Table 1. Ingredient Summary details for furocoumarin substances that may be present as naturally-occurring constituents of ingredients used in cosmetic formulations

INCI Name	CAS RN	Synonym(s)
N/A	66-97-7 (PubChem, 2021)	Furocoumarin ; psoralen; 2-Propenoic acid, 3-(6-hydroxy-5-benzofuranyl)-, δ -lactone; 6,7-Furanocoumarin; Ficusin; Furo[2',3':7,6]coumarin; Furo[4',5':6,7]coumarin; Furo(3,2-g)-coumarin; Prosuler; Psoralene; 5-Benzofuranacrylic acid, 6-hydroxy-, δ -lactone; 6-Hydroxy-5-benzofuranacrylic acid β -lactone; Psorline-P; 7H-Furo[3,2-g]chromen-7-one; furano[3,2-g]chromen-2-one; 2H-furo[3,2-g]chromen-2-one; 6-hydroxy-5-benzofuranacrylic acid γ -lactone; 6-hydroxy-5-benzofuranacrylic acid γ -lactone; pyrano[5,6-f]benzofuran-7-one; 7-furo[3,2-g][1]benzopyranone (ChemIDplus, 2021; PubChem, 2021; NCIGlobal, 2021)
N/A	482-44-0 (PubChem, 2021)	Imperatorin ; 8-Isopent-2-enyloxy-6,7-furanocoumarin; 8-Isopentenylloxypsoralene; 5-Benzofuranacrylic acid, 6-hydroxy-7-((3-methyl-2-butenyl)oxy)-, δ -lactone; 5-hydroxy-8-(1,1-dimethylallyl)psoralen; 6-Hydroxy-7-(3-methyl-2-butenyloxy)-5-benzofuranacrylic acid ω -lactone; 8-(3-Methyl-2-butenyloxy)psoralen; 9-(3-Methyl-2-butenyloxy)-7-oxofuro[3,2-g]chromene; 9-(3-methylbut-2-enoxy)-7-furo[3,2-g][1]benzopyranone; 9-(3-Methylbut-2-enyloxy)-7H-furo(3,2-g)chromen-7-one; 9-(3-methylbut-2-enyloxy)furan[3,2-g]chromen-2-one; 9-(3-Methylbut-2-enyloxy)furo[3,2-g]chromen-7-one; 9-[(3-methyl-2-buten-1-yl)oxy]-7H-furo[3,2-g]chromen-7-one; 9-[(3-methylbut-2-en-1-yl)oxy]-2H-furo[3,2-g]chromen-2-one; 7H-Furo[3,2-g][1]benzopyran-7-one, 9-[(3-methyl-2-buten-1-yl)oxy]-; 7H-Furo[3,2-g][1]benzopyran-7-one, 9-[(3-methyl-2-butenyl)oxy]-; 9-(3-methylbut-2-enyloxy)-7H-furo[3,2-g][1]benzopyran-7-one; Ammidin; Marmelide; Marmelosin (ChemIDplus, 2021; PubChem, 2021; NCIGlobal, 2021)

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INCI Name	CAS RN	Synonym(s)
Alloimperatori n	642-05-7 (PubChem, 2021)	Prangenidin ; 7 <i>H</i> -Furo[3,2- <i>g</i>][1]benzopyran-7-one, 9-hydroxy-4-(3-methyl-2-butenyl)-; 5-Benzofuranacrylic acid, 6,7-dihydroxy-4-(3-methyl-2-butenyl)-, δ -lactone; 9-Hydroxy-4-(3-methyl-2-butenyl)-7 <i>H</i> -furo[3,2- <i>g</i>][1]benzopyran-7-one; 9-Hydroxy-4-(3-methyl-2-butenyl)-7 <i>H</i> -furo[3,2- <i>g</i>]chromen-7-one; 9-hydroxy-4-(3-methylbut-2-enyl)furo[3,2- <i>g</i>]chromen-7-one; 9-hydroxy-4-(3-methylbut-2-en-1-yl)-7 <i>H</i> -furo[3,2- <i>g</i>]chromen-7-one; 8-Hydroxy-5-prenylpsoralen (PubChem, 2021)
N/A	523-50-2 (PubChem, 2021)	Isopsoralen ; Angelicin; Angecin; 2 <i>H</i> -Furo[2,3- <i>h</i>]-1-benzopyran-2-one; 2-Propenoic acid, 3-(4-hydroxy-5-benzofuranyl)-, δ -lactone; 3-(4-Hydroxy-5-benzofuranyl)-2-propenoic acid gamma-lactone; Furo[2,3- <i>h</i>]coumarin; Furo[5',4':7,8]coumarin; 2 <i>H</i> -Furo[2,3- <i>H</i>]chromen-2-one; furo[2,3- <i>h</i>]chromen-2-one; 2-Oxo-(2 <i>H</i>)-furo(2,3- <i>h</i>)-1-benzopyran; Isopsoralin; 4-Hydroxy-5-benzofuranacrylic acid gamma-lactone; Furo[5',8]coumarin; furano[2,3- <i>h</i>]chromen-8-one; pyrano[6,5- <i>e</i>]benzofuran-2-one (NCIGlobal, 2021; PubChem, 2021)
N/A	484-20-8 (PubChem, 2021)	5-Methoxypsoralen (5-MOP) ; 8-Demethoxyisimpinellin; 7 <i>H</i> -Furo[3,2- <i>g</i>][1]benzopyran-7-one, 4-methoxy-; 4-Methoxy-7 <i>H</i> -furo(3,2- <i>g</i>)(1)benzopyran-7-one; 5-Methoxy-6,7-furanocoumarin; 5-MOP; Bergaptan; Bergapten; Bergaptene; Geralen; Heraclin; Majudin; 4-methoxy-7-furo[3,2- <i>g</i>][1]benzopyranone; 4-methoxy-7 <i>H</i> -furo[3,2- <i>g</i>][1]benzopyran-7-one; 4-Methoxy-7 <i>H</i> -furo[3,2- <i>g</i>]benzopyran-7-one; 4-Methoxy-7 <i>H</i> -furo[3,2- <i>g</i>]chromen-7-one; 4-Methoxyfuro[3,2- <i>g</i>]benzopyran-7-one; 4-Methoxyfuro[3,2- <i>g</i>]benzopyrane-7-one; 4-methoxyfuro[3,2- <i>g</i>]chromen-7-one; 5-methoxy-2 <i>H</i> -furo[3,2- <i>g</i>]chromen-2-one; 5-methoxyfurano[3,2- <i>g</i>]chromen-2-one; 5-Methoxyfuranocoumarin; 6-Hydroxy-4-methoxy-5-benzofuranacrylic acid, gamma-lactone; 7 <i>H</i> -Furo(3,2- <i>g</i>)(1)benzopyran-7-one, 4-methoxy-; 7 <i>H</i> -Furo[3, 4-methoxy-; O-Methylbergaptol; Psoraderm (NCIGlobal, 2021; PubChem, 2021)

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INCI Name	CAS RN	Synonym(s)
N/A	298-81-7 (PubChem, 2021)	8-Methoxypsoralen (8-MOP) ; 7H-Furo[3,2-g][1]benzopyran-7-one, 9-methoxy-; 5-Benzofuranacrylic acid, 6-hydroxy-7-methoxy-, 8-lactone; 5-Demethoxyisoimipinellin; 8-Methoxy-6,7-furanocoumarin; 8-Methoxypsoralene; 8-MOP; 8-MP; Deltapsoralen; Meladoxen; Meloxine; Methoxsalen; Methoxsalene; Oxsoralen; Oxsoralen-Ultra; Oxsoralen Lotion; Oxypsoralen; Xanthotoxin; Xanthotoxine; 8-methoxy-4',5':6,7-furocoumarin; Ammoidin; Meladinin; Meladinine; Methoxa-Dome; 6-Hydroxy-7-methoxy-5-benzofuranacrylic acid delta-lactone; 7-Furocoumarin; 7H-Furo(3,2-G)(1)benzopyran-7-one, 9-methoxy-; 7H-Furo[3, 9-methoxy-; 8-Methoxy; 8-Methoxy(furano-3'.2':6.7-coumarin); 8-Methoxy-(furano-3'.2':6.7-coumarin); 8-methoxy-[furano-3".2":6.7-coumarin]; 8-Methoxy-2',3',6,7-furocoumarin; 8-methoxy-2",3",6,7-furocoumarin; 8-Methoxy-2',6,7-furocoumarin; 8-Methoxy-4',5',6,7-furocoumarin; 8-methoxy-4",5":6,7-furocoumarin; 8-Methoxy-4',6,7-furocoumarin; 8-Methoxyfuranocoumarin; 9-(methyloxy)-7H-furo[3,2-g]chromen-7-one; 9-methoxy-2h-furo[3,2-g]chromen-2-one; 9-Methoxy-7H-furo(3,2-g)(1)benzopyran-7-one; 9-Methoxy-7H-furo(3,2-g)benzopyran-7-one; 9-Methoxy-7H-furo[3,2-g]chromen-7-one; 9-methoxyfurano[3,2-g]chromen-2-one; 9-Methoxyfuro(3,2-g)chromen-7-one; 9-Methoxyfuro[3,2-g][1]benzopyran-7-one; 9-methoxyfuro[3,2-g]chromen-7-one; 9-Methoxy-furo[3,2-g]chromen-7-one; 9-Methoxypsoralen; Ammodin; Dltasoralen; Geroxalen; Methoxalen; Methoxaten; Methoxy-8-psoralen; Metoxaleno; New-Meladinin; O-methylxanthotoxol; Oxoralen; Proralone-mop; Psoralen-mop; Psoralon-MOP; Puvalen; Puvamet; Ultra Mop; Uvadex; Vitpso; Zanthotoxin (NCIGlobal, 2021; PubChem, 2021)
N/A	482-27-9 (PubChem, 2021)	Isopimpinellin ; 7H-Furo[3,2-g][1]benzopyran-7-one, 4,9-dimethoxy-; 5,8-Dimethoxy-6,7-furanocoumarin; 5,8-Dimethoxypsoralen; 4,9-Dimethoxy-7H-furo[3,2-g][1]benzopyran-7-one; 4,9-Dimethoxy-7H-furo[3,2-g][1]benzopyran-7-one, 9CI; 4,9-Dimethoxy-7H-furo[3,2-g]chromen-7-one; 4,9-Dimethoxy-7-oxofuro[3,2-g]chromene; 4,9-Dimethoxyfuro[3,2-g]benzopyran-7-one; 4,9-dimethoxyfuro[3,2-g]chromen-7-one; 4,9-Dimethoxy-furo[3,2-g]chromen-7-one; 5,8-Dimethoxypsoralene; 5,9-dimethoxy-2H-furo[3,2-g]chromen-2-one; 5,9-dimethoxyfurano[3,2-g]chromen-2-one; 7H-Furo(3,2-g)(1)benzopyran-7-one, 4,9-dimethoxy- (8CI); 7H-Furo(3,2-g)(1)benzopyran-7-one, 4,9-dimethoxy- (8CI)(9CI); 7H-Furo[3, 4,9-dimethoxy-; 7H-Furo[3,2-g][1]benzopyran-7-one,4,9-dimethoxy-; Dimethylpsoralen; 5-Methoxyxanthotoxin; 8-Methoxybergapten; Isoimipinellin (NCIGlobal, 2021; PubChem, 2021)

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INCI Name	CAS RN	Synonym(s)
N/A	482-45-1 (PubChem, 2021)	Isoimperatorin ; 7H-Furo[3,2- <i>g</i>][1]benzopyran-7-one, 4-[(3-methyl-2-butenyl)oxy]-; 4-((3-methylbut-2-en-1-yl)oxy)-7H-furo[3,2- <i>g</i>]chromen-7-one; 4-(3-methylbut-2-en-1-yl)oxy-7H-furo[3,2- <i>g</i>]chromen-7-one; 4-(3-methylbut-2-en-1-yl)oxy-7H-furo[3,2- <i>g</i>]chromen-7-one; 4-[(3-Methyl-2-butenyl)oxy]-7H-furo[3,2- <i>g</i>]chromen-7-one #; 4-[(3-methylbut-2-en-1-yl)oxy]-7H-furo[3,2- <i>g</i>]chromen-7-one; 4-prenyloxypsoralen; 7,4-[(3-methyl-2-butenyl)oxy]-7H-furo[3,2- <i>g</i>]-1-benzopyran-7-one; 7H-Furo(3,2- <i>g</i>)(1)benzopyran-7-one, 4-[(3-methyl-2-butenyl)oxy]-; 7H-Furo[3,2- <i>g</i>][1]benzopyran-7-one, 4-[(3-methyl-2-butenyl)oxy]-; 7H-Furo[3,2- <i>g</i>][1]benzopyran-7-one, 4-[(3-methyl-2-butenyl)oxy]-; Auraptin; Cnidin; Iso Imperatorin; Iso-imperatorin (PubChem, 2021)
N/A	2543-94-4 (PubChem, 2021)	Phellopterin ; 7H-Furo[3,2- <i>g</i>][1]benzopyran-7-one, 4-methoxy-9-[(3-methyl-2-butenyl)oxy]-; 4-methoxy-9-(3-methylbut-2-en-1-yl)oxy-7H-furo[3,2- <i>g</i>]chromen-7-one; Phelloterin; 7H-Furo(3,2- <i>g</i>)(1)benzopyran-7-one, 4-methoxy-9-[(3-methyl-2-butenyl)oxy]-; 4-Methoxy-9-prenyloxypsoralen; 4-methoxy-9-(3-methylbut-2-en-1-yl)oxy-7H-furo[3,2- <i>g</i>][1]benzopyranone; 4-Methoxy-9-[(3-methyl-2-butenyl)oxy]-7H-furo[3,2- <i>g</i>]chromen-7-one (PubChem, 2021)
N/A	7380-40-7 (PubChem, 2021)	Bergamottin ; Bergamotine; Bergaptin; 5-Geranyloxypsoralen; 7H-Furo[3,2- <i>g</i>][1]benzopyran-7-one, 4-[[[(2E)-3,7-dimethyl-2,6-octadienyl]oxy]-]; 7H-Furo[3,2- <i>g</i>][1]benzopyran-7-one, 4-[[[(2E)-3,7-dimethyl-2,6-octadien-1-yl]oxy]-]; (E)-4-(3,7-dimethylocta-2,6-dienyloxy)-7H-furo[3,2- <i>g</i>]chromen-7-one; 4-[[[(2E)-3,7-dimethyl-2,6-octadienyl]oxy]-7H-furo[3,2- <i>g</i>]chromen-7-one; 4-[[[(2E)-3,7-dimethylocta-2,6-dienoxy]furo[3,2- <i>g</i>]chromen-7-one; 4-[[[(2E)-3,7-dimethylocta-2,6-dien-1-yl]oxy]-7H-furo[3,2- <i>g</i>][1]benzopyran-7-one; 4-[[[(2E)-3,7-Dimethylocta-2,6-dien-1-yl]oxy]-7H-furo[3,2- <i>g</i>]chromen-7-one; 5-Geranyloxypsoralen; 7H-Furo(3,2- <i>g</i>)(1)benzopyran-7-one, 4-[(3,7-dimethyl-2,6-octadienyl)oxy]-, (E)-; Bergamotin; Bergaptol geranyl ether; Bergomottin (NCIGlobal, 2021; PubChem, 2021)

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INCI Name	CAS RN	Synonym(s)
N/A	7437-55-0 (PubChem, 2021)	8-Geranyloxypsoralen ; Xanthotoxol geranyl ether; 7H-Furo[3,2-g][1]benzopyran-7-one, 9-[[[(2E)-3,7-dimethyl-2,6-octadien-1-yl]oxy]-; (E)-9-((3,7-Dimethyl-2,6-octadienyl)oxy)-7H-furo(3,2-g)(1)benzopyran-7-one; 7H-Furo(3,2-g)(1)benzopyran-7-one, 9-((3,7-dimethyl-2,6-octadienyl)oxy)-; 7H-Furo(3,2-g)(1)benzopyran-7-one, 9-((3,7-dimethyl-2,6-octadienyl)oxy)-, (E)-; 8-geranopsoralen; 8-Geranoxypsoralen; 8-geranoxy-psoralen; 8-Geranyloxy psoralen; 9-((2E)-3,7-dimethylocta-2,6-dienyloxy)furano[3,2-g]chromen-2-one; 9-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-7H-furo[3,2-g]chromen-7-one; 9-[(2E)-3,7-dimethylocta-2,6-dienoxy]furo[3,2-g]chromen-7-one; 9-[(3,7-Dimethyl-2,6-octadienyl)oxy]-7H-furo[3,2-g][1]benzopyran-7-one; 9-[[[(2E)-3,7-dimethylocta-2,6-dien-1-yl]oxy]-2H-furo[3,2-g]chromen-2-one; 9-Geranyloxypsoralen (PubChem, 2021)
N/A	3902-71-4 (PubChem, 2021)	Trioxsalen ; 5-Benzofuranacrylic acid, 6-hydroxy- β ,2,7-trimethyl-, δ -lactone; 2,5,9-Trimethylfuro[3,2-g]chromen-7-one; Trioxysalen; Trisoralen; TMP; Trimethylpsoralen; 7H-Furo[3,2-g][1]benzopyran-7-one, 2,5,9-trimethyl-; 4,5',8'-Trimethylpsoralen; 4,5',8'-Trimethylpsoralene; Trioxisaleno; Trioxysalene; Trioxysalenum; TRIOXSALIN; Teijin compound 1 hydrochloride; antipsoriatic; Trioxalen; Trixalen; LACTONE; 2',8-Trimethylpsoralen; 2,5,9-Trimethyl-7H-furo[3,2-g]chromen-7-one; 2,5,9-trimethylfuro[3,2-g]chromen-7-one; 2,5,9-Trimethylfuro[3,2-g]benzopyran-7-one; 2,5,9-Trimethyl-7H-furo(3,2-g)(1)benzopyran-7-one; 7H-Furo(3,2-g)(1)benzopyran-7-one, 2,5,9-trimethyl-; 2,5,9-Trimethylpsoralen; 7H-Furo[3,2,5,9-trimethyl-; 2,5,9-trimethyl-7-furo[3,2-g][1]benzopyranone; 2,5,9-Trimethyl-7H-furo[3,2-g]chromen-7-one #; 7-Oxo-2,5,9-Trimethyl-7H-furo(3,2-g)(1)benzopyron; 4,5',8'-Trimethylpsoralen; 4,7,9-trimethylfurano[3,2-g]chromen-2-one; 4,7,9-trimethyl-2H-furo[3,2-g]chromen-2-one; 4,8,5'-Trimethylpsoralen; 6-Hydroxy-beta,2,7-trimethyl-5-benzofuranacrylic acid gamma-lactone; 6-hydroxy-beta,2,7-trimethyl-5-benzofuranacrylic acid, delta-lactone; BENZOFURANACRYLIC ACID,2,7-TRIMETHYL-; 5-Benzofuranacrylic acid,2,7-trimethyl-, .delta.-lactone; 5-Benzofuranacrylic acid, 6-hydroxy-.beta.,2,7-trimethyl-, .delta.-lactone; 2,9-Trimethyl-7H-furo[3,2-g][1]benzopyran-7-one; 2',4,8-Trimethylpsoralen; 4,8-Trimethylpsoralen; 4,8-Trimethylpsoralene (NCIGlobal, 2021; PubChem, 2021)

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INCI Name	CAS RN	Synonym(s)
N/A	737-52-0 (PubChem, 2021)	(±)-Oxypeucedanin ; 7H-Furo[3,2-g][1]benzopyran-7-one, 4-[(3,3-dimethyl-2-oxiranyl)methoxy]-; (RS)-Oxypeucedanin; 5-Epoxyisopentenylloxypsoralene; 4-[(3,3-dimethyloxiran-2-yl)methoxy]furo[3,2-g]chromen-7-one; Oxypeucadanin; 7H-Furo[3,2-g][1]benzopyran-7-one, 4-[(3,3-dimethyloxiranyl)methoxy]-, (S)-; PHOSPHORUS METAL, 99.999%, RED; 4-[(3,3-Dimethyloxiran-2-yl)methoxy]-7H-furo[3,2-g]chromen-7-one; 7H-Furo(3,2-g)(1)benzopyran-7-one, 4-[(3,3-dimethyloxiranyl)methoxy]-; 7H-Furo[3,2-g][1]benzopyran-7-one, 4-[(3,3-dimethyl-2-oxiranyl)methoxy]- (PubChem, 2021)
N/A	2643-85-8 (PubChem, 2021)	(+)-Oxypeucedanin hydrate ; Oxypeucedanin hydrate; Hydroxypeucedanin hydrate; Prangol; Prangolarin hydrate; (R)-oxypeucedanin hydrate; 4-(2,3-Dihydroxy-3-methylbutoxy)-7H-furo[3,2-g][1]benzopyran-7-one; 4-[(2R)-2,3-dihydroxy-3-methylbutoxy]furo[3,2-g]chromen-7-one; 7H-Furo(3,2-g)(1)benzopyran-7-one, 4-(2,3-dihydroxy-3-methylbutoxy)-, (R)-; 7H-FURO(3,2-g)(1)BENZOPYRAN-7-ONE, 4-(2,3-DIHYDROXY-3-METHYLBUTOXY)-, (R)-(+)-; Aviprin; Oxypeucedaninhydrate; Prawgol (PubChem, 2021)
N/A	26091-79-2 (PubChem, 2021)	Byakangelicol ; Biacangelicol; 7H-Furo[3,2-g][1]benzopyran-7-one, 9-[(2R)-3,3-dimethyloxiranyl]methoxy]-4-methoxy-; (R)-9-[(3,3-Dimethyl-2-oxiranyl)methoxy]-4-methoxyfuro(3,2-g)chromen-7-one; 7H-Furo(3,2-g)(1)benzopyran-7-one, 9-[(3,3-dimethyloxiranyl)methoxy]-4-methoxy-, (R)-; 9-[(3,3-Dimethyl-2-oxiranyl)methoxy]-4-methoxy-7H-furo[3,2-g]chromen-7-one #; 9-[(2R)-3,3-dimethyloxiran-2-yl]methoxy]-4-methoxyfuro[3,2-g]chromen-7-one (PubChem, 2021)
N/A	482-25-7 (PubChem, 2021)	(+)-Byakangelicin ; Biacangelicin; Bjacangelicin; Bjakangelicin; Byankagelicine; (R)-9-(2,3-Dihydroxy-3-methylbutoxy)-4-methoxy-7H-furo(3,2-g)(1)benzopyran-7-one; (R)-9-(2,3-dihydroxy-3-methylbutoxy)-4-methoxy-7H-furo[3,2-g]chromen-7-one; 7H-Furo(3,2-g)(1)benzopyran-7-one, 9-(2,3-dihydroxy-3-methylbutoxy)-4-methoxy-, (R)-; 7H-Furo[3,2-g][1]benzopyran-7-one, 9-[(2R)-2,3-dihydroxy-3-methylbutoxy]-4-methoxy-; 9-(2,3-Dihydroxy-3-methylbutoxy)-4-methoxy-7H-furo(3,2-g)(1)benzopyran-7-one; 9-[(2R)-2,3-dihydroxy-3-methyl-butoxy]-4-methoxy-furo[3,2-g]chromen-7-one; Byacangelicin; Byak-angelicin; Byakangelicine (PubChem, 2021)

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INCI Name	CAS RN	Synonym(s)
N/A	2880-49-1 (PubChem, 2021)	Heraclenin ; (+)-Heraclenin; 9-[[[(2R)-3,3-dimethyloxiran-2-yl]methoxy]furo[3,2-g]chromen-7-one; Prengenine; 7H-Furo(3,2-g)(1)benzopyran-7-one, 9-[(3,3-dimethyloxiranyl)methoxy]-, (R)-; 7H-FURO(3,2-g)(1)BENZOPYRAN-7-ONE, 9-(2,3-EPOXY-3-METHYLBUTOXY)-, (R)-(+)-; 7H-Furo[3,2-g][1]benzopyran-7-one, 9-[[[(2R)-3,3-dimethyloxianyl]methoxy]- (PubChem, 2021)
N/A	206978-14-5 (PubChem, 2021)	Epoxybergamottin ; Epoxybergamottin; 4-[(E)-5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-enoxy]furo[3,2-g]chromen-7-one; 6',7'-Epoxybergamottin (PubChem, 2021)
N/A	85878-62-2 (PubChem, 2021)	Pyrido[3,4-c]psoralen ; 5H-Furo[3',2':6,7]chromeno[3,4-c]pyridin-5-one; 5H-Furo(3',2':6,7)(1)benzopyrano(3,4-c)pyridin-5-one; Pyrido(3,4-c)furo(3,2-g)coumarin; 9H-Furo(3',2':6,7)(1)benzopyrano(3,4-c)pyridin-9-one (PubChem, 2021)
N/A	85878-63-3 (PubChem, 2021)	7-Methylpyrido[3,4-c]psoralen ; Pyrido(3,4-c)-7-methylpsoralen; 5H-Furo(3',2':6,7)(1)benzopyrano(3,4-c)pyridin-5-one, 7-methyl; 11-Methyl-9H-furo(3',2':6,7)(1)benzopyrano(3,4-c)pyridin-9-one; 9H-Furo(3',2':6,7)(1)benzopyrano(3,4-c)pyridin-9-one, 11-methyl-; 7-methylpyridopsoralen (PubChem, 2021)
N/A	20073-24-9 (PubChem, 2021)	3-Carbethoxypsoralen ; 3-Ethoxycarbonylpsoralen; Ethyl 3-psoralencarboxylate; ethyl 7-oxo-7h-furo[3,2-g][1]benzopyran-6-carboxylate; ethyl 7-oxo-7H-furo[3,2-g]chromene-6-carboxylate; ethyl 7-oxofuro[3,2-g]chromene-6-carboxylate; ethyl 7-oxo-7H-furo(3,2-g)(1)benzopyran-6-carboxylate; 7H-Furo(3,2-g)(1)benzopyran-6-carboxylic acid, 7-oxo-, ethyl ester; 7-Oxo-7H-furo(3,2-g)(1)benzopyran-6-carboxylic acid ethyl ester(PubChem, 2021)
N/A	22975-76-4 (PubChem, 2021)	4,4'-Dimethylangelicin ; 4,4'-Dimethylisopsoralen; 4,9-Dimethyl-2H-furo(2,3-h)-1-benzopyran-2-one; 2H-Furo(2,3-h)-1-benzopyran-2-one, 4,9-dimethyl- (8CI,9CI); 2H-Furo(2,3-h)(1)benzopyran-2-one, 4,9-dimethyl- (PubChem, 2021)

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INCI Name	CAS RN	Synonym(s)
N/A	4063-41-6 (PubChem, 2021)	4,5'-Dimethylangelicin ; 4,8-Dimethylisopsoralen; 2H-Furo(2,3-h)(1)benzopyran-2-one, 4,8-dimethyl-; 4,8-Dimethyl-2H-furo[2,3-h]chromen-2-one; 2H-Furo[2,3-h][1]benzopyran-2-one, 4,8-dimethyl-; 4,8-dimethylfuro[2,3-h]chromen-2-one; 4',4-Dimethylangelicin; 5-Benzofuranacrylic acid, 4-hydroxy-beta,2-dimethyl-, delta-lactone; 4,8-Dimethyl-2H-furo[2,3-H]chromen-2-one; 5-Benzofuranacrylic acid, 4-hydroxy-.beta.,2-dimethyl-, .delta.-lactone; 2H-Furo(2,3-h)(1)benzopyran-2-one, 4,8-dimethyl; 4,8-Dimethyl-2H-furo(2,3-h)(1)benzopyran-2-one (PubChem, 2021)
N/A	73459-03-7 (PubChem, 2021)	5-Methylangelicin ; 5-Methylisopsoralen; 5-Methyl-2H-furo(2,3-h)-1-benzopyran-2-one; 2H-Furo[2,3-h]-1-benzopyran-2-one, 5-methyl-; 4-Hydroxy-6-methyl-5-benzofuranacrylic acid gamma-lactone(PubChem, 2021)
N/A	90370-29-9 (PubChem, 2021)	4,4',6-Trimethylangelicin ; 4,6,4'-Trimethylangelicin; 4,6,9-trimethylfuro[2,3-h]chromen-2-one; 4,6,9-Trimethyl-2H-furo(2,3-h)-1-benzopyran-2-one; 4-Hydroxy-beta,3,7-trimethyl-5-benzofuranacrylic acid delta-lactone; 4,6,9-Trimethyl-2H-furo(2,3-h)(1)benzopyran-2-one; 2H-Furo(2,3-h)-1-benzopyran-2-one, 4,6,9-trimethyl- (PubChem, 2021)

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APPENDIX 2 - Regulatory status of the ingredient(s) in Canada

Table 2. Comparison of Regulatory Status of Furocoumarins in Certain Jurisdictions

	Canada ¹	USA ²	European Union ^{3,10}	Other Jurisdictions ⁴⁻⁹
Status	Restricted	Not restricted	Prohibited except for normal content in natural essences used. Annex II/358	Switzerland, ASEAN, New Zealand, MERCOSUR, EEC: Prohibited except for normal content in natural essences used.
Max.	1 mg/kg (1 ppm)	-	Furocoumarin content must not exceed 1 mg/kg	Switzerland: - Restricted to 1 mg/kg total furocoumarin content in leave-on products and products with potential exposure to sunlight - Fragrance products such as eau de cologne, eau de parfum, eau de toilette, are exempt from the application of this limit ASEAN, New Zealand, MERCOSUR, EEC: - Subject to the same restrictions set out by EU in Annex II/358 of

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	Canada ¹	USA ²	European Union ^{3,10}	Other Jurisdictions ⁴⁻⁹
				Cosmetics Regulation (EC) No. 1223/2009
Product Type	Sun tanning products	-	Sun protection and in bronzing products	Leave-on products and products with potential for direct exposure to sunlight.
Product Form	-	-	-	-
Label Requirements	-	-	-	-
Other	-	-	-	-

¹HC, 2022; ²US FDA, 2023; ³EU-Annex II, 2021; ⁴FDHA, 2017; ⁵EEC, 2011; ⁶ASEAN, 2023; ⁷MERCOSUR-N° 62/14, 2014; ⁸Japan, 2000; ⁹New Zealand, 2017, ¹⁰Norway, Iceland, and Liechtenstein have the same cosmetic regulations as the EU for this ingredient.

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Table 3. Comparison of Regulatory Status of Imperatorin in Certain Jurisdictions

	Canada ¹	USA ²	European Union ^{3,10}	Other Jurisdictions ⁴⁻⁹
Status	Prohibited	Not restricted	Prohibited Annex II/34	Switzerland, EEC, ASEAN, New Zealand, MERCOSUR: Prohibited
Max.	-	-	-	-
Product Type	-	-	-	-
Product Form	-	-	-	-
Label Requirements	-	-	-	-

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	Canada ¹	USA ²	European Union ^{3,10}	Other Jurisdictions ⁴⁻⁹
Other	-	-	-	-

¹HC, 2022; ²US FDA, 2023; ³EU-Annex II, 2021; ⁴FDHA, 2017; ⁵EEC, 2011, ⁶ASEAN, 2023; ⁷MERCOSUR-N° 62/14, 2014; ⁸Japan, 2000; ⁹New Zealand, 2017, ¹⁰Norway, Iceland, and Liechtenstein have the same cosmetic regulations as the EU for this ingredient.

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APPENDIX 3 – Status of Ingredient in Other Cosmetic Lists or Databases

Table 4. Active cosmetic notifications and product categories for furocoumarin-containing fragrance ingredients (extracts) as identified by IFRA (2020), in products notified since January 1st, 2018 to July 25, 2023:

[Redacted for confidentiality]

Table 5. Active cosmetic notifications and product categories for essential oils identified by IFRA (2020) to contain small amounts of phototoxic furocoumarins:

[Redacted for confidentiality]

Return to Section [2.2 Status of Ingredients in Other Cosmetic Databases](#).