



EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL
Directorate C - Public Health and Risk Assessment
C7 - Risk assessment

SCIENTIFIC COMMITTEE ON CONSUMER PRODUCTS

SCCP

Opinion on

Furocoumarins in cosmetic products

Adopted by the SCCP
during the 6th plenary of 13 December 2005

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1. BACKGROUND

Commission Directive 95/34/EC July 10, 1995 adopted an amendment to Annex II, Annex to Cosmetic Directive under reference number 358 as follows: “Furocoumarins (e.g. trioxysalan, 8-methoxypsoralen, 5-methoxypsoralen) except for normal content in natural essences used. In sun protection and in bronzing products, furocoumarins shall be below 1 mg/kg.”

The technical adaptation was based on an opinion adopted by the Scientific Committee on Cosmetology (SCC) in 1990. Furocoumarins are recognized to be photomutagenic and photocarcinogenic. International Agency for Research on cancer (IARC) has classified 5-MOP and 8-MOP plus ultraviolet radiation in group 2A (probably carcinogenic to humans) and in group 1 (carcinogenic to human), respectively.

The Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP) adopted an “Initial List of Perfumery Materials which must not form part of Cosmetic Products except subject to the restrictions and conditions laid down” (SCCNFP/0392/00, final, adopted by the SCCNFP during the 18th Plenary meeting of 25 September 2001). The opinion is based on information submitted as ‘monographs’ (synopses) on behalf of industry. On the basis of the available information and assessment of the cutaneous toxicity of the substances tabulated in its opinion, it is the recommendation of the SCCNFP that these substances may be used as ingredients in cosmetic products only under the conditions and restrictions specified in the table attached in its opinion.

This opinion under entry nr 6 mentions that the following 11 essential oils: *Angelica root oil* (*Angelica archangelica* L.) CAS n° 8015-64-3; *Bergamot oil* CAS n° 8007-75-8; *Grapefruit oil, expressed* (*Citrus paradisi* Macf.) CAS n° 8016-20-4; *Lemon oil* CAS n° 8008-56-8; *Lemon oil, cold pressed, California type* CAS n° 8008-56-8; *Lemon oil, cold pressed, desert type* CAS n° 8008-56-8; *Lime oil, cold pressed, Mexican* CAS n° 8008-26-2; *Lime oil, expressed* CAS n° 8008-26-2; *Lime oil expressed rectified* CAS n° 8008-26-2; *Orange peel oil, bitter* (*Citrus aurantium* L.) CAS n° 68916-04-1; *Rue oil* (*Ruta graveolens* L.) CAS n° 8014-29-7 “may be used in cosmetic products, provided that the total concentration of furocoumarin-like substances in the finished cosmetic product does not exceed 1 ppm.”

These plant extracts are often used as ingredients in fragrances and cosmetic products.

Submission I from European Flavour & Fragrance Association (EFFA) was submitted to the SCCNFP in November 2002.

Submission II was received in August 2003

The SCCNFP adopted during the 26th plenary meeting December 2003 an opinion concerning Furocoumarins in sun protection and bronzing products (SCCNFP/0765/03). This opinion states that the provided data “do not justify a higher limit than 1 ppm (not to be intentionally added) for furocoumarins in cosmetics”. The SCCNFP also stated that the opinion should be interpreted in conjunction with the opinion on CMR substances (SCCNFP/0474/01, final, adopted 25 September 2001).

At the same meeting the SCCNFP also adopted an opinion on furocoumarin Isopimpinellin (SCCNFP/0761/03) stating “that there is incomplete information on photo-mutagenicity and on

photo-clastogenicity of isopimpinellin to enable a safety evaluation in order to provide an update of the “Initial List of Fragrance”” for entry n° 6.

At the same meeting the SCCNFP also adopted an opinion on the furocoumarin Bergamottin (SCCNFP/0740/03) stating “*Photo-mutagenicity and photo-carcinogenicity are the main effects of concern in relation to the use of furocoumarins in cosmetics. The data submitted by ECHA on bergamottin is not adequate for evaluation of the safety of the substance in relation to photo-mutagenicity and photo-carcinogenicity.*”

Submission III was sent to the Commission in April 2005 by ECHA.

2. TERMS OF REFERENCE

1. *Is the SCCP of the opinion that the limitation to below 1 ppm of furocoumarins should be extended to all finished cosmetic products and not only cover sun protection and bronzing products?*
2. *Does the SCCP recommend any restrictions with regard to the use of the 11 plants extracts, which in the SCCNFP opinion (SCCNFP/0392/00) are known to contain furocoumarins when they are used as ingredients as such in cosmetics and not as ingredients in fragrances?*

3. OPINION

The following documents were submitted to support the terms of references:

- * Saita T, Fujito H and Mori M (2004) Screening of furocoumarin derivatives in citrus fruits by enzyme-linked immunosorbent assay. Biol Pharmacol Bull 27: 974-977.
- * Frérot E and Decorzant E (2004) Quantification of total furocoumarins in citrus oils by HPLC coupled with UV, fluorescence and mass detection. J Agr. Food Chem. 52: 6879-6886.
- * IFRA/RIFM Furocoumarins Fact Sheet: Furocoumarins in essential oils. (Angelicin, bergamottin, 5-methoxypsoralen, psoralen)

- 3.1. Screening of furocoumarin derivatives in citrus fruits by enzyme-linked immunosorbent assay. Saita et al (2004) Biol Pharmacol Bull 27: 974-977

This paper describes an enzyme-linked immunosorbent assay for screening of furocoumarin derivatives as cytochrome P450 3A4 inhibitor in citrus fruits. The antibody used in this assay was produced by immunizing rabbits with 6',7'-dihydroxybergamottin conjugated with serum albumin. The assay revealed that this antibody could detect both 6',7'-dihydroxybergamottin and bergamottin, detection limits 800 pg/ml and 4 ng/ml. The specificity testing of the antibody, determined by the cross reactivity with other types of furocoumarin derivatives, revealed 17.2%, 0.28 % and <0.06% (not detectable) cross reaction respectively with bergamottin, 5-methoxypsoralen and 8-methoxypsoralen for 50% replacement of β -Gal activity. Thus the antibody was

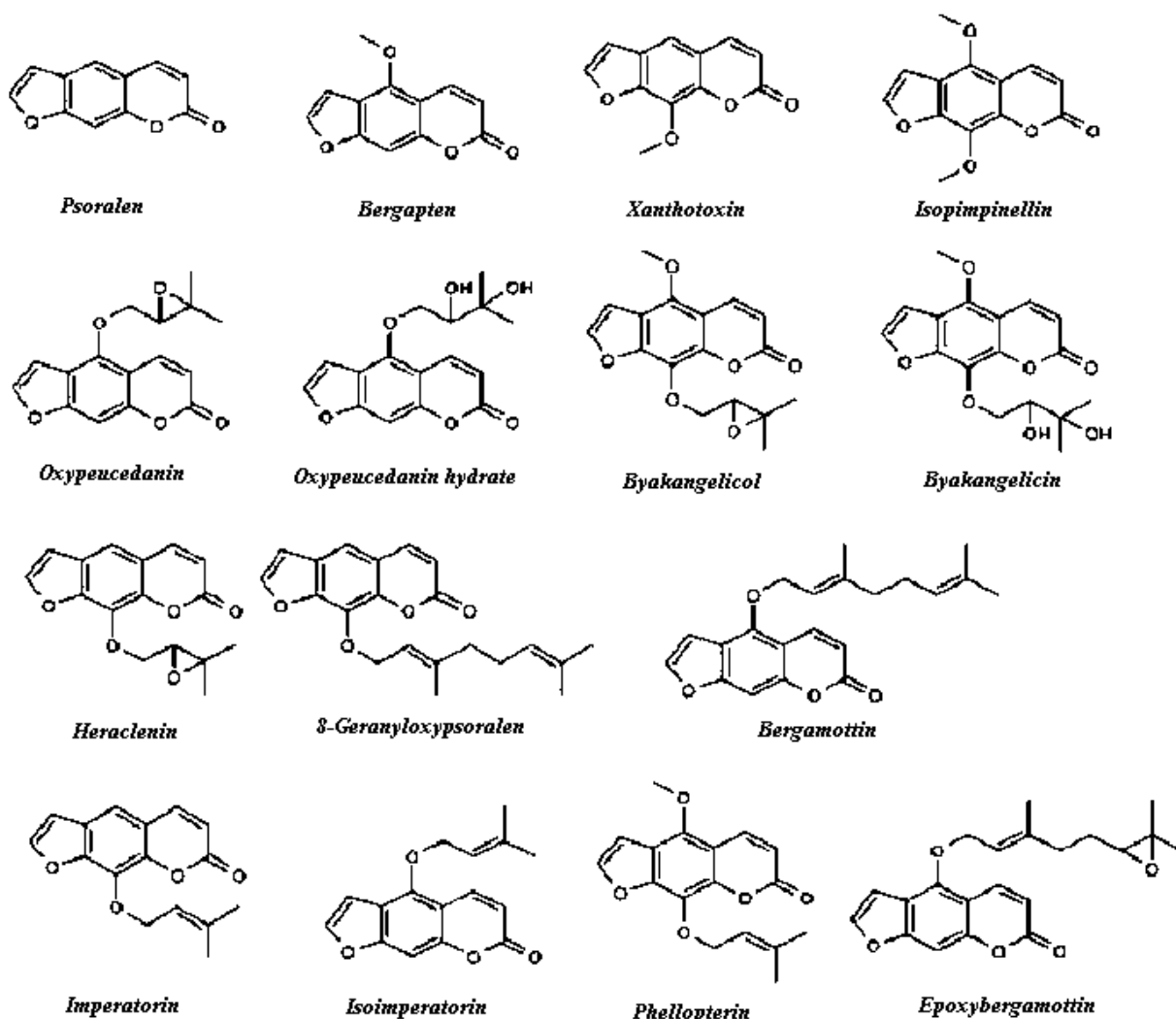
considered to be specific for furocoumarins containing geranyloxy side chain as in bergamottin and 6',7'-dihydroxybergamottin, the inhibitors of P450 3A4 inhibitor in citrus fruits.

- 3.2. Quantification of total furocoumarins in citrus oils by HPLC coupled with UV, fluorescence, and mass detection. Frérot and Decorzán (2004) *J Agr. Food Chem.* 52: 6879-6886

In this study, an analytical method employing a combination of two high performance liquid chromatography (HPLC) methods and detections by UV diode array, fluorescence and atmospheric pressure chemical ionisation (APCI)-mass spectrometry (MS) was developed for the detection and quantification of 15 furocoumarins (see below). Quantification by UV, fluorescence, or MS was compared in terms of linearity and limit of detection. The method would theoretically allow for the quantification of these 15 furocoumarins at 0.1 ppm level in the sample injected in HPLC. However, some interference was observed when 6 different citrus oils (see below) were analysed employing diode array detection. This problem could be solved by the use of other detection systems, in addition to diode array detection. The authors concluded that the method could be implemented in quality control laboratories. The authors also noted that cold-pressed citrus oils generally contain a high amount of total furocoumarins and would have to be distilled prior to their use in cosmetic products to fall below the permitted level of 1 ppm.

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Furocoumarins analysed in the above study are:



Citrus oils analysed in the above study: Bergamot oil, lemon oil, grapefruit oil, mandarin oil, tangerine oil and bitter orange oil

3.3. IFRA/RIFM Fact Sheet: Furocoumarins in essential oils, Submission Number 3

The Fact Sheet describes the chemical names, CAS No. EINECS No., molecular formula and molecular weight of some furocoumarins. The EU regulation concerning furocoumarins in cosmetic products is also described in the Fact Sheet. Further, it is stated that the amounts of furocoumarins in plant extracts may vary in a wide range. So far only alkoxyfurocoumarins, having alkyl groups of 11 carbons or less, have been identified, but it is completely plausible that other furocoumarins exist in natural essences, which have so far escaped detection. However, reliable methods are available for only the major furocoumarins (Ferrot and Decorzant, 2004). The results of some analyses of these are described in Table 1. The variations shown in Table 1 clearly indicate that there is no single “marker” furocoumarin that can be used to allow

estimation of total furocoumarin levels. It is also mentioned in the Fact Sheet that “it seems that not all furocoumarins have equivalent biological properties”

4. DISCUSSION

The data provided in Submission III has shown that there are many furocoumarin-like substances present in citrus oils. Some of these can be identified and quantified by the newly developed methods. Several furocoumarins have been recognised as phototoxic and SCCNFP has evaluated consumer safety by the use of cosmetic products containing furocoumarins, as already described in the ‘Background’ to this opinion. The data provided, so far, has not ruled out the photo-toxicity of any of the known furocoumarins. The consumer is exposed to sunlight after application of various types of cosmetic products, not only after the application of bronzing and sun protection products. According to earlier SCCNFP Opinions (SCCNFP/0392/00, SCCNFP/0765/03), the total concentration of furocoumarin-like substances should not exceed 1 ppm in the finished cosmetic product.

In the absence of any additional new data demonstrating the safety of any of the furocoumarin-like substances, the SCCP reemphasise that total concentrations of furocoumarins exceeding 1 ppm in any finished cosmetic product will be of concern with regard to consumer safety.

5. CONCLUSION

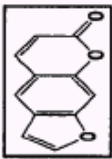
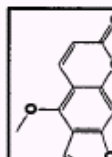
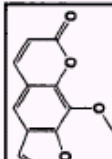
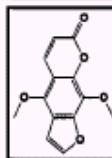
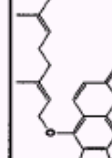

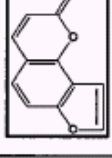
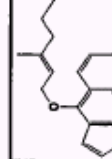
The data provided so far has not ruled out the photo-toxicity of any furocoumarin. No new data is provided in Submission III to substantiate consumer safety when using cosmetic products containing furocoumarins.

As the consumer is exposed to sunlight after using various types of cosmetic products, not only bronzing or sun protection products, the SCCP reemphasise that total concentrations of furocoumarins exceeding 1 ppm in any finished cosmetic product will be of concern with regard to consumer safety.

The Opinion concerns the content of furocoumarins in cosmetic formulations, irrespective of the source of these substances.

This Opinion should be interpreted together with the opinion on CMR substances (SCCNFP/0474/01, Final).

IFRA **RIFM**
Furocoumarins – Fact Sheet
Table 1: Summary of furocoumarin analysis in citrus oils

	FUROCOUMARIN									
	PSORALEN	BERGAPTEN (5-MOP)	XANTHOTOXIN (8-MOP)	ISOPIMPINELLIN	BERGAMOTTIN	OXYPEUCEDANIN	ANGELICIN	EPOXY-BERGAMOTTIN		
Essential Oil										
Angelica root oil	up to 112 ppm	up to 78 ppm	not detected	not detected	not detected	?	230 ppm	?		
Bergamot oil	0-26 ppm*	up to 2300 ppm (0.23%)	not detected	not detected	up to 2.22%	not detected	not detected	?		
Grapefruit oil	not detected	up to 1900 ppm (0.19%)	not detected	< 5 ppm	up to 1100 ppm (0.11%)	not detected	not detected	1126 ppm		
Lemon oil, cold pressed	0-3 ppm*	up to 275 ppm	not detected	0-18 ppm*	up to 5412 ppm (0.54%)	up to 8224 ppm (0.82%)	not detected	?		
Lime oil, cold pressed	< 5 ppm	up to 2200 ppm (0.22%)	< 5 ppm	2000 (0.2%)	2.5%	1200 ppm (0.12%)	not detected	?		
Mandarin oil	not detected	0-3 ppm*	not detected	not detected	0-10 ppm*	not detected	not detected	?		
Orange oil bitter	70 ppm	350 ppm (0.035%)	not detected	not detected	5 ppm	not detected	not detected	820 ppm ⁽¹⁾		
Rue oil	150 ppm	180 ppm	320 ppm	200 ppm	not detected	?	430 ppm	?		
Tagetes oil	110 ppm	not detected	not detected	not detected	not detected	?	not detected	?		

All values reported were measured by the fragrance industry unless noted. Furocoumarin peaks were identified by comparing the retention time and the UV-spectrum in the sample solution with that of the standard solution.

* Qualitative determination was performed using the retention time of the reference (the amount was too low for a UV-spectrum)

⁽¹⁾ McHale and Sheridan, 1989. The oxygen heterocyclic compounds of citrus peel oils. Proceedings of the 11th International Congress of Essential Oils, Delhi, India, 12-16 November.

6. MINORITY OPINION

Not applicable

7. REFERENCES

- * Furocoumarins in essential oils. Fact sheets (Angelicin, Bergamottin, 5-Methoxypsoralen, Psoralen).
- * Frérot E and Decorzant E (2004) Quantification of Total Furocoumarins in Citrus Oils by HPLC Coupled with UV, Fluorescence, and Mass Detection. *J. Agric. Food Chem.* 2004, 52, 6879-6886.
- * Saita T, Fujito H and Mori M (2004) Screening of Furanocoumarin Derivatives in Citrus Fruits by Enzyme-Linked Immunosorbent Assay. *Biol. Pharm. Bull.* 27(7) 974-977 (2004).
- * Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers concerning an initial list of perfumery materials which must not form part of cosmetic products except subject to the restrictions and conditions laid down. Adopted by the SCCNFP during the 18th Plenary meeting of 25 September 2001. Doc. n° SCCNFP 0392/00
- * Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers concerning chemical ingredients in cosmetic products classified as carcinogenic, mutagenic or toxic to reproduction according to the chemicals Directive 67/548/EEC. Adopted by the SCCNFP during the 18th Plenary meeting of 25 September 2001. Doc. n° SCCNFP/0474/01
- * Opinion of the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers concerning furocoumarins in sun protection and bronzing products. Adopted by the SCCNFP during the 26th plenary meeting of 9 December 2003. Doc. n° SCCNFP/0765/03

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