

THE SCIENTIFIC COMMITTEE ON COSMETIC PRODUCTS AND NON-FOOD PRODUCTS
INTENDED FOR CONSUMERS

OPINION

CONCERNING

FRAGRANCE ALLERGY IN CONSUMERS

A REVIEW OF THE PROBLEM

**ANALYSIS OF THE NEED FOR APPROPRIATE CONSUMER INFORMATION AND
IDENTIFICATION OF CONSUMER ALLERGENS**

**Adopted by the SCCNFP
during the plenary session of 8 December 1999**

Executive summary

1. Terms of Reference

1.1 Context of the question

Under the current Community legislation, fragrance ingredients as all ingredients which are part of cosmetic products, fall under the scope of the Cosmetics Directive 76/768/EEC of July 1976 and are submitted to all specified provisions. In relation with the labelling of the ingredients, the Article 6 of the Directive provides a specific provision for fragrance ingredients which states that “perfume and aromatic compositions and their raw materials shall be referred to by the word ‘perfume’ or ‘flavour’”. This general wording substitutes for the detailed list of fragrance ingredients.

Independently from the existing legal provisions, the fragrance industry is self-regulated through the Code of Practice of the International Fragrance Association (IFRA). IFRA issues recommendations for the safe use of fragrance ingredients, which are published in the IFRA Code of Practice and its guidelines. The most important reason for quantitative restrictions is skin sensitisation.

1.2 Request to the SCCNFP

In response to a question from a Member state and members of the European parliament, the SCCNFP has been asked by DG Enterprise to respond to the following mandate in relation to the safety of fragrance ingredients:

- It is proposed that all known fragrance allergens are labelled on cosmetics if used in the products. Does the SCCNFP agree to this proposal ? If so :
 - Which chemicals fall under this classification ?
 - Is there a maximum concentration of each chemical permissible without the requirement for labelling ?
- Does the SCCNFP agree to the inclusion of all IFRA restricted materials in the Annex III (List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down) ?
Are the permitted levels recommended by IFRA suitable for use in the Cosmetics Directive 76/768/EEC ?
- Does the SCCNFP agree that all materials that IFRA recommend should not be used as fragrance compounds are included in Annex II (List of substances which must not form part of the composition of cosmetic products) ?

- Restrictions are proposed for the 3 most common fragrance allergens (cinnamic aldehyde, isoeugenol, hydroxycitronellal). Does the SCCNFP agree to restriction on the use of common fragrance allergens (Annex III listing)? If so :
 - Which fragrance materials should be subject to restrictions?
 - What are the conditions for restrictions (maximum concentration, fields of applications, etc) ?

1.3 Strategy of the SCCNFP

The SCCNFP has considered that this mandate can be usefully divided into two sections (Interim position on Fragrance allergy SCCNF/0202/99 adopted at the SCCNFP session of 23. June 99):

- I. Identification of those fragrance ingredients, which are of concern as allergens for the consumer. Recommendations on informing the consumer of the presence of important allergens to permit the consumer with a known fragrance allergy a means to avoid contact with an allergen. An opinion as to whether such identification can be related to concentrations present in a product when elicitation levels are known.
- II. An opinion on the adoption of industry prohibited substances into Annex 2 and adoption of industry restricted substances into Annex 3. Considerations as to whether the concentration limits or other restrictions suggested by industry can be supported or need to be changed if there is such inclusion in Annex 3. Whether there are additional substances which should be subject to inclusion in an Annex.

This opinion relates to the first section and consists of :

- a critical review of the problem of fragrance allergy in consumers;
- identification of those fragrance ingredients which are well-recognised as consumer allergens;
- an opinion as to whether such identification can be related to concentrations present in a product when elicitation levels are known.

Allergy to natural ingredients will be analysed separately.

2. Opinion of the SCCNFP

It is the opinion of the SCCNFP that:

- Fragrance ingredients have to be considered an important cause of contact allergy.
- Based on criteria restricted to dermatological data reflecting the clinical experience, it has been possible to identify 24 fragrance ingredients, which correspond to the most frequently

recognised allergens.

Thirteen of these have been reported more frequently, these are well-recognised contact allergens in consumers and are thus of most concern, eleven others are less well documented.

List A: Fragrance chemicals, which according to existing knowledge, are most frequently reported and well-recognised consumer allergens:

Common name	CAS no	Common name	CAS no
Amyl cinnamal	122-40-7	Amylcinnamyl alcohol	101-85-9
Benzyl alcohol	100-51-6	Benzyl salicylate	118-58-1
Cinnamyl alcohol	104-54-1	Cinnamal	104-55-2
Citral	5392-40-5	Coumarin	91-64-5
Eugenol	97-53-0	Geraniol	106-24-1
Hydroxycitronellal	107-75-5	Hydroxymethylpentyl-	31906-04-4
Isoeugenol	97-54-1	cyclohexenecarboxaldehyde	

List B: Fragrance chemicals, which are less frequently reported and thus less documented as consumer allergens. These are:

Common name	CAS no	Common name	CAS no
Anisyl alcohol	105-13-5	Benzyl benzoate	120-51-4
Benzyl cinnamate	103-41-3	Citronellol	106-22-9
Farnesol	4602-84-0	Hexyl cinnamaldehyde	101-86-0
Lilial	80-54-6	d-Limonene	5989-27-5
Linalool	78-70-6	Methyl heptine carbonate	111-12-6
3-Methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-butene-2-one			127-51-5

- There are at the present not sufficient scientific data to allow for determination of dose-response relationships and thresholds for these allergens.

Further, SCCNFP is of the opinion that information should be provided to consumers about the known presence in cosmetic products of fragrance ingredients with a well-recognised potential to cause contact allergy.

Information regarding these fragrance chemicals should be given to consumers if deliberately added to a fragrance formulation either in the form of a chemical or as an identified constituent of an ingredient.

In the future other fragrance chemicals may be included (or excluded) depending on the epidemiological and safety data available.

This is required to improve the protection of the consumer by ensuring that the correct diagnosis of contact allergy to well-recognised fragrance allergens can be made without undue

delay and by providing information that will help the consumer avoid specific substances that they may not tolerate.

Natural materials, such as oak moss, will according to the interim position statement given by the SCCNFP be considered in a separate document (SCCNFP/0202/99).

In the DG Enterprise's request the term "labelling" of cosmetic products with respect to fragrance ingredient is used. This term belongs to the sector of risk management which is beyond the remit of the SCCNFP. It is up to the legislator to consider the best way to provide the information to the consumers.

Full opinion

1. Introduction

1.1 Background

In recent years there has been a scientific debate on the safety of fragrance (perfumery) ingredients. Dermatologists have highlighted the risk of contact allergy from fragrance ingredients (9,25,64,65) and actions to prevent the disease have been requested (1,2,63).

1.2 Terms of Reference

1.2.1 Context of the question

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Independently from the existing legal provisions, the fragrance industry is self-regulated through the Code of Practice of the International Fragrance Association (IFRA) (68). IFRA issues recommendations for the safe use of fragrance ingredients, which are published in the IFRA Code of Practice and its guidelines. The most important reason for quantitative restrictions is skin sensitisation (53, 54). Restrictions in use are recommended for 28 fragrance ingredients with sensitising potential (1995) (53).

1.2.2 Request to the SCCNFP

In response to a question from a Member state and members of the European parliament the SCCNFP has been asked by DG Enterprise to respond to the following mandate in relation to the safety of fragrance ingredients:

- It is proposed that all known fragrance allergens are labelled on cosmetics if used in the products. Does the SCCNFP agree to this proposal ? If so :
 - Which chemicals fall under this classification ?
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III (List of substances which cosmetic products must not contain except subject to restrictions and conditions laid down) ?

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Taking into account the importance and enormity of the mandate, the first section has been considered initially and is the subject of this opinion. It consists of :

- a critical review of the problem of fragrance allergy in consumers;
- identification of those fragrance ingredients which are well-recognised as consumer allergens;
- an opinion as to whether such identification can be related to concentrations present in a product when elicitation levels are known.

Allergy to natural ingredients will be analysed separately.

2. Critical review of the problem of fragrance allergy for the consumer

The following is a response to the first section of the mandate regarding identification of fragrance ingredients well recognised as consumer allergens.

2.1 Definitions of terms

2.1.1 Fragrances

A fragrance ingredient is defined by the International Fragrance Association (IFRA) as any basic substance used in the manufacture of fragrance materials for its odorous, odour-enhancing or blending properties. Fragrance ingredients may be obtained by chemical synthesis from synthetic, fossil or natural raw materials or by physical operations from natural sources. The class comprises aroma chemicals, essential oils, natural extracts, distillates and isolates, oleoresins etc.

A fragrance compound is a blend of fragrance ingredients, representing a specific fragrance formula.

A fragrance material is defined as fragrance ingredient or a fragrance formula (68).

2.1.2 Contact allergy to fragrances

Contact allergy is a type IV immunological reaction caused by low-molecular weight substances that come in close contact with the skin (3). The clinical manifestation of contact allergy is eczema, which is an inflammatory skin disease characterised by erythema, induration and in some cases vesicles. At a later stage scaling and fissures may develop. In case of contact allergy to fragrance ingredients the face, axillae or hands will often be affected (4,5,6), while generalised eczema is rare. Contact eczema may be a significant burden to the individual because of itch, changed appearances, discomfort and functional limitations. Medical consultations, treatment with corticosteroids and in some individuals sick-leave is a consequence.

Contact allergy is diagnosed by patch testing, where the patient under investigation is re-exposed to suspected allergens under controlled circumstances. International recommendations and standardisation for the patch test method, most common allergens and recording of results exist (7).

More than 2000 fragrance ingredients are available to the perfumer for compounding a fragrance formula, that may consist of 10 to 300 or more different ingredients. For this reason

a mixture of 7 fragrance chemicals and one natural extract is used for diagnosing fragrance contact allergy (table 1). This mixture is called the Fragrance Mix and is included in the standard patch test tray containing the most common allergens in Europe.

Table 1: Ingredients of the Fragrance Mix.

alfa-amyl cinnamic aldehyde (= amyl cinnamal)	1%
cinnamic alcohol (=cinnamyl alcohol)	1%
cinnamic aldehyde (=cinnamal)	1%
eugenol	1%
geraniol	1%
hydroxycitronellal	1%
isoeugenol	1%
oak moss (a natural extract)	1%
sorbitan sesquioleate (added as an emulsifier)	5%

2.2 Frequency of fragrance allergy – as measured by the Fragrance Mix

2.2.1 - in eczema patients

In two multicentre studies performed in Europe, 7.5-8.3% (8,9) of tested eczema patients were allergic to fragrances as determined by patch testing with the Fragrance Mix. In comparison contact allergy to preservatives like formaldehyde and Kathon CG* has been found in 2.6% and 3.0% respectively of tested patients on an European basis (10). Both these preservatives are restricted in the Cosmetic Directive as contact allergens and covered by the duty of ingredient labelling.

The frequency of fragrance contact allergy and the use of cosmetics vary between different countries as shown in table 2. (11).

In several studies an increase of fragrance contact allergy has been reported as measured by reactions to the Fragrance Mix (12-16).

In a German multicentre study it was found that an average of 10.2% of more than 36.000 patients tested reacted to the Fragrance Mix in the period of 1990-95 (17). It was argued that this figure could be regarded as representative for central Europe (17). A variation between different regions of Germany was found (17) and also a variation over years showing an increasing trend from 7.4% in 1992 to 10.3% Fragrance Mix positive patients in 1996 (12).

*: methylchloroisothiazolinone (and) methylisothiazolinone

Table 2: Frequency of fragrance allergy in consecutively tested eczema patients detected by the Fragrance Mix. Studies including data from 1990 and on.

Clinic	Country	Year	No. tested	% positive
Multicentre (17) - (12) - (12)	Germany	1990-95	36.552	10.2%
		1992	6.700	7.4%
		1996	9.600	10.3%
Multicentre (16)	USA	1992-94	3.509	11.4%
		1994-96	3.082	14.0%
Multicentre (57)	Netherlands	1991	677	9.0%
Multicentre (14)	Denmark	1985/86	1232	4.1%
		1997/98	1267	9.9%
Bologna (58)	Italy	1991/92	1.802	5.8%
Lisbon (59)	Portugal	1990-96	4.318	8.7%
Malmö (60)	Sweden	1992 males only	149	10.6%
Multicentre (18)	Italy	1984-88*	1518	6.0%
		1989-93	947	5.4%
London (19)	England	1980-96*	25.545	8.5% (females) 6.7% (males)

*: The test concentration of the Fragrance Mix was reduced from 16% to 8% in 1985 in Italy and from 1984 in London

In one dermatological clinic in Denmark a statistically significantly rising trend of fragrance allergy for women, as measured by reactions to the Fragrance Mix, was found over more than a decade (13). A result that recently has been confirmed by the Danish Contact Dermatitis Group, who has repeated an investigation done in 1985/86 (14). The study was performed again in 1997/98 in the same clinics using the same methods and for the same 6 months period as 12 years before. Results are presented in Figure 1. It is seen that a significant increase in fragrance allergy has occurred and that fragrance allergy is the most common cause of contact allergy, next to nickel (fig 1), which is in agreement with other investigations (12,15,16). The

increase in fragrance allergy affected all age groups also children of 0-18 years, where an increase from 2.1% to 5.8% was found (14).

Figure 1. Patch test results from 1985/86 compared with 1997/98.

Data from the Danish Contact Dermatitis Group

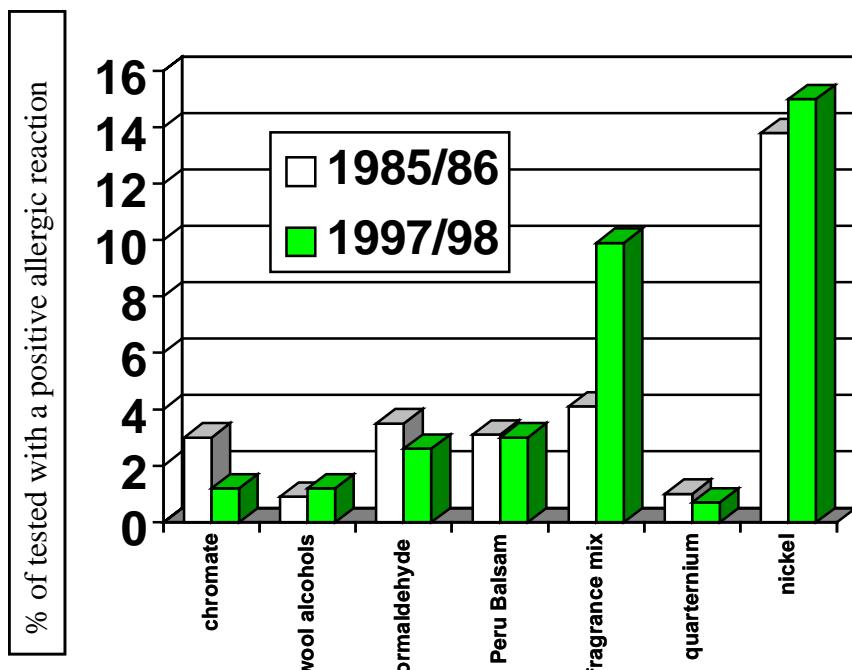


Figure 1. 1232 eczema patients were included in the study in 1985/86 and 1267 in 1997/98 (14). The sex distribution was similar in the two periods. Fragrance Mix was tested in 8% petrolatum in both periods. Quarternium -15 and formaldehyde: preservatives used in cosmetics.

The North American Contact Dermatitis Group has also recently provided results indicating an increase in fragrance allergy. They found that in 1992/94, 11.4% of 3509 patients were positive to Fragrance Mix and in 1994/96, a significant rise ($p=0.002$) to 14.3% of 3082 patients had occurred (16). In comparison the frequency of nickel allergy in this time period remained unchanged at 14.3%.

In other countries, such as Italy (1984-93), and UK (1980-96), no significant changes have been reported over years (18,19). Still fragrance ingredients were one of the most frequent causes of contact allergy in these countries (table 2).

2.2.2 -In population groups

Investigations of contact allergy in the general population are difficult to perform and for this reason few studies exist (cf. table 3). A Swedish study of hand eczema in an industrial city

showed that among 1087 individuals recruited from the general population with symptoms of present or previous hand eczema 5.8% were positive to the Fragrance Mix (20). In Denmark Fragrance Mix sensitivity was found in 1.1% (0.3-2.1%) of 567 persons drawn as a sample from the general Danish population, only nickel sensitivity was more prevalent (21). In Italy female eczema patients with hand eczema due to contact with detergents were patch tested. 3.1% of 1100 women reacted to the Fragrance Mix (22). A control group of 619 female patients with no eczema disease were also patch tested, 1.3% were positive to the Fragrance Mix (22). Among Danish school children, 14-15 years of age, fragrance contact allergy was detected in 1.8% by patch testing with the Fragrance Mix (23). A study of 85 American student nurses showed that 15 (17.6%) had a positive reaction to the Fragrance Mix, 12 of the individuals also had a positive history of contact dermatitis (24). In this study the concentration of Fragrance Mix was 16% as opposed to the currently recommended 8% and the study included only young females which both may contribute to the high prevalence of fragrance sensitivity found.

**Table 3: Results from patch testing with the Fragrance Mix
in different population based groups.**

Country	Population	Year	No. tested	% positive
Italy (22)	Dermatological patients. -females without eczema	1988 ?	619	1.3%
Denmark (21)	population sample adults, 15-69 years	1990-91	567	1.1%
Denmark (23)	school children 14-15 years old	1995/96	717	1.8%
USA (24)	student nurses, females	1980	85	17.6%*
Sweden (20)	population sample adults, 20-65 years reporting hand eczema	1983-84	1087	5.8%*

*testing performed with Fragrance Mix 16%. The current standard is Fragrance Mix 8%.

2.3 The role of cosmetic products in fragrance contact allergy.

2.3.1 Personal awareness

Two out of three patients with fragrance contact allergy are aware that they cannot tolerate fragranced products on their skin before the diagnosis is made (25,26). Most of them are also able to name specific product categories that started their skin problems (26). In an epidemiological study fragranced deodorants, colognes and lotions alone or in combination were significantly more often given as the primary cause of skin problems in fragrance allergic eczema patients compared with two control groups, one drawn as a sample from the general population and the other a group of eczema patients without fragrance contact allergy (26). The same 3 product categories have the most intense contact with the skin and contain the highest amount of perfume concentrate (27).

2.3.2 Provocation of allergic contact eczema by fragrance formulas from commercial products.

A. Patch tests studies

The 10 most sold fine fragrance brands on the European market were shown by patch testing to be able to provoke contact allergy in 6.9% of 335 consecutive female eczema patients (table 4). For comparison 8.1% of the females reacted to the diagnostic test, the Fragrance Mix, which means that the fine fragrances, that are commercially available consumer products intended for skin contact, were equally potent provokers of contact allergy as the diagnostic test for fragrance allergy (28).

Fragrance formulas from other marketed consumer products: toilet soaps, shampoos, lotions, deodorants, and after shaves have also been shown to provoke allergic contact eczema in eczema patients when used for patch testing (29-31) (table 4).

Table 4. Fragrance formulas from cosmetic products used for patch testing

	Patch test concentration	Number of patients tested	Result % positive	Ref.
perfumes from the 4 most common brands of toilet soap	5%-2.5% in pet.	1943	4%	29
perfume from an after shave lotion	3% in pet.	1823	3.6%	30
10 best selling fine fragrances	undiluted	335 (females only)	6.9%	28
perfumes from lower price cosmetics: 9 from wash-off products 8 from stay-on products				31
	5% in pet.	498	4.2%	
	5% in pet.	497	3.2%	

(pet. means petrolatum)

B. Use test studies

•Methodology

In a use test the normal contact with the allergen is simulated. Either a solution of the allergen or a product containing the allergen is applied openly and repeatedly to normal skin in subjects

sensitized to the substance under study. Usually 2-3 open applications are made a day on normal skin, either the upper arm or the cubital fossa, for a minimum of 7 days (7).

•Results from testing with single allergens

The fragrance allergens cinnamal and isoeugenol are some of the most common causes of fragrance contact allergy (27). They have been used as model substances in studies elucidating the risk of contact eczema from exposure to single fragrance allergens in cosmetic products (32,33). The allergens were tested openly in concentrations that could occur in consumer products either as the maximal or usual concentration according to Fragrance industry (34,35). 12/19 (63%) of subjects sensitised to isoeugenol developed eczema to an 0.2% isoeugenol solution in ethanol (33), which at the time of study was the maximal permitted concentration according to IFRA guideline (34). 13/18 (72%) of subjects sensitized to cinnamal developed eczema to a solution of 0.8% cinnamal in ethanol (32), which was the maximum used in perfumes according to industry (35). There is no limit to the use concentrations of cinnamal in IFRA guideline. Healthy control groups performed similar usage tests and none reacted (32,33).

Fragrance industry has studied hydroxycitronellal in usage tests performed by healthy individuals, who have been sensitised to hydroxycitronellal experimentally (36). It was found that none of 41 subjects reacted to a soap-bar or a lotion containing 0.03-0.05% hydroxycitronellal used for several months. When 31 of these subjects proceeded to use a cologne containing 0.05% and later 1% hydroxycitronellal a total of 4 subjects reacted (36). No documentation exist, that testing in experimentally sensitised individuals can predict the risk of contact eczema in subject sensitised by everyday exposure to cosmetic products.

• Results from testing with commercial products

A fine fragrance, containing 6 of the allergens from the Fragrance Mix, was used for patch testing in consecutive female eczema patients (28). 5/83 (6%) of the patients had a positive allergic reaction. All 83 patients also applied the fine fragrance openly to healthy skin 3 times a day for 7 days. 3 of the 5 patients, who had a positive patch test to the fine fragrance, developed an eczematous reaction on the skin from the open application of the fine fragrance. None of those with a negative patch test developed eczema in the usage test (28).

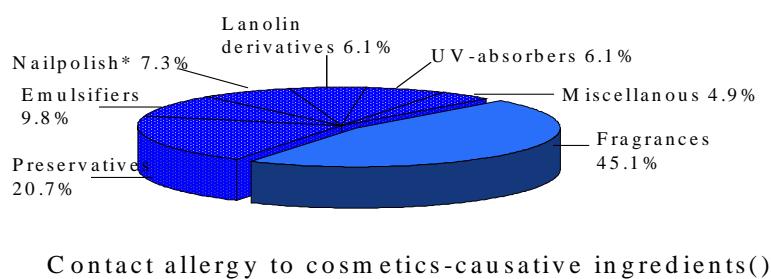
A group of 14 Fragrance Mix positive patients identified one or two deodorants each that within the past year had caused axillary dermatitis (37). The patients performed a 7 days use test with the relevant deodorants on normal axillary skin. Eczema was provoked within 7 days

in 60% of the cases. No controls were included. The deodorants were chemically analysed by gas chromatography mass spectrometry, and were all, except one, found to contain one or more of the allergens from the diagnostic tests, the Fragrance Mix (37).

2.3.3 The relative importance of fragrance ingredients in contact allergy to cosmetic products.

Fragrance ingredients account for 30-45% of the allergic reactions to cosmetics in eczema patients and is the most frequent cause of contact allergy to cosmetic products followed by preservatives (4,38,40). The results of a Dutch study is given in fig 2. It is seen that 45.1% of allergic reactions to ingredients of cosmetics were caused by fragrance ingredients. The results were based on the reviewing of 1781 patients seen in a period of 6 years (1981-86) in a private practice in a medium sized town in the Netherlands (38).

Figure 2:



Contact allergy to cosmetics-causative ingredients()

*: Toluenesulphonamide formaldehyde resin

2.4 Exposure to fragrance allergens in cosmetic products

2.4.1 General exposure

Exposure to nearly 400 fragrance substances used in major commercial products marketed around the world was studied. The results from fine fragrances, household products and soaps were published in 1989 (41). The 25 most frequently detected fragrance substances with a concentration exceeding 1% in the product were listed. Three of these were constituents of the diagnostic test the Fragrance Mix, that is:

Geraniol, which was found in 43% of the fine fragrance products in an average concentration of 3.2%.

Eugenol, which was found in 26% of the products in an average concentration of 2.0% and

Hydroxycitronellal, which was in 21% of the products in an average concentration of 3.0% (41).

Since 1987 The IFRA guideline has restricted the use of hydroxycitronellal to 1% in consumer products. Among the 25 most frequently found fragrance substances in fine fragrances (41) several other substances have been reported as allergens in cosmetics or toiletries (27).

In a series of studies more than 100 cosmetic products purchased on the European retail market have been analysed by gas chromatography-mass spectrometry for their contents of well-known fragrance allergens (28,31,37,42,43,44). Some of these results can be seen in table 5. One or more of the allergens from the diagnostic test, The Fragrance Mix, was found in 15%-100% of the examined cosmetic products depending on its type (table 5). The concentrations covered a large range, but the fine fragrances, generally had the highest amount of the examined fragrance allergens. The content of allergens in these products as well as in other products have been demonstrated to be sufficiently high to provoke eczema in sensitised individuals (cf. section 2.3.2). Cases, where the restrictions of the IFRA guideline were not respected are indicated for two substances, hydroxycitronellal and isoeugenol, in table 5.

A general finding was that 3 to 4 of the allergens from the Fragrance Mixture was found in the same cosmetic product (28,31,37). This increases the risk of provoking allergic contact eczema, as exposure to combinations of fragrance allergens have a synergistic effect on the inflammation and extent of eczematous reactions provoked in subjects sensitised to the fragrances in question (45). The effect of allergen combination on the induction of contact allergy is unknown.

Table 5: Detection of fragrance allergens from the diagnostic test, the Fragrance Mix, in cosmetic products by gas chromatography -mass spectrometry.

	Natural ingredient based perfumes, n=22 (42) in no (%) of products		Other natural ingredient based cosmetics, n= 20 (42) in % Concentration of products		Women's best-selling fine fragrances,n=10 (28) in % Concentration of products		Deodorants on the European market,n=73 (43) in % Concentration of products	
		% (w/v)		% (w/v)		% (w/v)		% (w/v)
a-amylcinnamal	8 (36%)	0.19-3.0	1(5%)	0.082	3(30%)	0.0-0.69	22(31%)	0.0001-0.062
cinnamyl alcohol	3 (14%)	0.089-2.1	1(5%)	0.004	6(60%)	0.03-0.79	27(39%)	0.0006-0.12
cinnamal	0		1(5%)	0.013	0		12(17%)	0.0001-0.04
eugenol	8 (36%)	0.035-2.3	1(5%)	0.019	9(90%)	0.04-0.89	40(57%)	0.0001-0.24
geraniol	14 (64%)	1.191§	1(5%)	0.016	9(90%)	0.08-0.48	53(76%)	0.0001-0.12
hydroxycitronellal	5 (23%)	0.135-6.04*	0		9(90%)	0.25-1.2*	35(50%)	0.0001-0.10
isoeugenol	2 (5%)	0.027,0.14	1(5%)	0.013	7(70%)	0.05-0.34*	20(29%)	0.0001-0.05
Number of products with one or more of the allergens	82%		15%		100%		NG	

Of the substances in this table only hydroxycitronellal and isoeugenol are quantitatively restricted in the IFRA guideline. The asterix * means that the recommendations of the IFRA guideline at the time of study was exceeded. 6% hydroxycitronellal was found in one product (42). 5% hydroxycitronellal have been reported to induce sensitisation in 36% of healthy volunteers (36).

§: quantitative analysis only possible for 1 product due to interferenc

2.4.2 Cosmetic products from fragrance allergic individuals

Cosmetic products identified as the cause of contact eczema in fragrance sensitised individuals have generally been shown to contain the fragrance allergens in question (37,44). It has also been demonstrated that there may be a quantitative difference between products that cause contact allergic reactions and those which do not. This is exemplified by hydroxycitronellal: its concentration on average was 5 times higher in cosmetics inducing positive patch tests in hydroxycitronellal-sensitised individuals, when compared with cosmetics tested in hydroxycitronellal negative patients (44). In accordance the average concentration of Fragrance Mix allergens was found to be 1.3-8.6 times higher in deodorants causing axillary eczema in a one week usage test performed by Fragrance Mix sensitive individuals than in deodorants negative after one week (37).

3. Information to the consumer regarding fragrance ingredients

3.1 Exposure information

3.1.1 In prevention of contact allergy to fragrance ingredients

Appropriate diagnostic procedures and patients information are cornerstones in secondary prevention of contact allergy (62). Lack of information on the ingredients of cosmetic products seriously interferes with the adequate diagnosis of patients with cosmetic allergy. In addition even when the offending allergens can be identified, such patients cannot be given proper advice about which products to avoid and which can be used without risking recurrence of dermatitis (1,2).

The Fragrance Mixture identifies 50-80% of cases with perfume allergy (28,50). It means that there are patients where the correct diagnosis cannot be made as the diagnostic test is negative, but no information is available of the content of other fragrance allergens in the products used by the patient. It has been the policy of the fragrance industry not to disclose the fragrance formula for many years (54). In the most recent edition of the International Fragrance Association (IFRA)'s Code of practice fragrance manufacturers are required to collaborate with dermatologists to discover the causative agents of clinical dermatitis in individual patients¹. However, the correspondence with industry delays the investigations of the patient's disease. Testing with coded fractions of the perfumes in question is the alternative to ingredient information. In two published cases it took 9 months to 2½ years to reach a final diagnosis, that could have been made in one week if relevant exposure information had been present

¹ It is also stated that fragrance manufacturers will respond to requests for information about fragrance formulations issued by customers or governmental bodies.

(51,52). Such delays in the diagnosis of contact allergy may affect the prognosis of the patient's disease and is a burden for the patient.

Fragrance ingredients are widely used. If the diagnosis of fragrance contact allergy fails to be made it will mean a risk of continuous exposure to the allergen(s) and recurrent or chronic eczema. It may also cause occupational problems for the patient as fragrance formulas are used in industrial products and also as preservatives or degreasing agents (66).

Once the diagnosis of contact allergy is made the patient is informed about the cause of his disease and advised to avoid further contact with the specified allergens. In case of contact allergy to fragrance ingredients no information can be provided to the consumer that makes it possible to avoid fragranced cosmetics that do not contain the offending allergen.

Further it has been a concern that fragrance industry does not receive feedback about their use of fragrance allergens and thus cannot take sufficient measure to improve consumer protection, if necessary (67).

3.1.2 Dermatological expert opinions

The European Society of Contact Dermatitis and the European Environmental and Contact Dermatitis Research Group have called attention to the need for a more useful identification of fragrance ingredients in products than the statement: "contains perfume" as presently required in the Cosmetics Directive (25,56). The American Academy of Dermatology recently sent a similar request to The Food and Drug Administration (63). The members of these organisations are mainly clinical working dermatologists that in their daily work see patients with side effects from exposure to fragrances. Full information (declaration) of fragrance ingredients has been mentioned as the optimal solution (56), however since a fragrance formula may consist of hundreds of ingredients it may not in practice be possible to supply this information. Instead it has been suggested that ingredients known to be allergens should be identified by the manufacturers (56).

3.2 Identification of fragrance ingredients recognised as consumer allergens.

3.2.1 Existing criteria for classification of contact allergens

The criteria for classification of sensitising substances in the European Union (Annex VI of Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances) consider that positive data from appropriate patch testing are sufficient to classify a substances as a skin sensitisier (contact allergen). Normally data from more than one dermatological clinic are required.

The criteria of the World Health Organisation (WHO) are similar in this respect (61) and regard sufficient evidence to classify a substance as a significant contact allergen to be epidemiological studies and/or studies in consecutive skin tested patients conducted in accordance with well established principles which demonstrate an association between exposure and the clinical evaluation of dermatitis/contact urticaria, including positive skin tests. Data from more than one patient in more than one independent centre are required.

In addition both the EU and WHO criteria consider positive results from animal tests to be sufficient evidence on its own to classify a substance as a skin sensitiser (contact allergen).

3.2.2 Criteria for selection of fragrance ingredients recognised as contact allergens in consumers.

The criteria for selection is restricted to dermatological data reflecting the clinical experience of fragrance allergens in accordance with the WHO/EU criteria. Results from animal sensitisation tests are thus not taken into consideration.

The following criteria have been applied:

- Positive patch test data from more than one patient in more than one independent centre should be present.
- The patch test should be conducted according to well-established principles.
- Relationship to clinical contact eczema should be established preferably by an exposure assessment.

However as data about fragrance ingredients in cosmetic products are not available, the following criteria are also used:

- a patient history of clinical contact reactions to fragrance ingredients/cosmetic products or
- a clinical presentation of disease in accordance with contact allergy to fragrance ingredients/cosmetic products.

3.2.3 Fragrance ingredients identified as contact allergens

Fragrance chemicals have been considered, which have been reported as contact allergens in cosmetics or toiletries according to a review paper (27). Natural materials, such as oak moss, have not been considered in the present document, as they constitute a complex group of compounds. They will be reviewed separately as stated in the interim position on Fragrance allergy SCCNFP/0202/99.

In table 6a and 6b twenty-four fragrance chemicals are listed which, based on dermatological data reflecting the clinical experience, correspond to the most recognised contact allergens.

The fragrance chemicals mentioned in table 6a meet the above criteria of selection (3.2.2), but have been more frequently reported than the allergens in table 6b, and thus according to existing knowledge of most concern.

Table 6a: Fragrance chemicals most frequently reported as contact allergens.

Ref *	Common name	CAS registry number	Comments
1	Amyl cinnamal	122-40-7	Ingredient of the Fragrance Mix
2	Amylcinnamyl alcohol	101-85-9	May crossreact with amył cinnamal (Ref.1)
3	Benzyl alcohol	100-51-6	
4	Benzyl salicylate	118-58-1	
5	Cinnamyl alcohol	104-54-1	Ingredient of the Fragrance Mix
6	Cinnamal	104-55-2	Ingredient of the Fragrance Mix
7	Citral	5392-40-5	
8	Coumarin	91-64-5	
9	Eugenol	97-53-0	Ingredient of the Fragrance Mix
10	Geraniol	106-24-1	Ingredient of the Fragrance Mix
11	Hydroxycitronellal	107-75-5	Ingredient of the Fragrance Mix
12	Hydroxymethyl-pentylcyclo-hexenecarboxaldehyde	31906-04-4	
13	Isoeugenol	97-54-1	Ingredient of the Fragrance Mix

Fragrance chemicals mentioned in table 6b also meet the criteria of selection (3.2.2), but less documentation exist than for the ingredients mentioned in table 6a or other reservations exist as in the case of d-limonene.

Table 6b: Fragrance chemicals reported less frequently as contact allergens

Ref *	Common name	CAS registry number	Comments
14	Anisyl alcohol	105-13-5	
15	Benzyl benzoate	120-51-4	
16	Benzyl cinnamate	103-41-3	
17	Citronellol	106-22-9	
18	Farnesol	4602-84-0	
19	Hexyl cinnamaldehyde	101-86-0	used as positive control substance in animal sensitization tests
20	Lilial	80-54-6	=2-(4-tert-Butyl benzyl)propion aldehyde
21	d-Limonene	5989-27-5	oxidation products are strong sensitizers. Mostly reported as an occupational allergen.
22	Linalool	78-70-6	
23	Methyl heptine carbonate	111-12-6	
24	3-Methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one	127-51-5	Synonym: γ -methylionone

(* refers to the number in the appendix)

3.3 Dose-response relationships in fragrance allergy

The risk of induction as well as provocation of contact allergy depends on a range of factors one of which is the concentration of allergen in the product. The product type and the individual composition of products will affect the concentration of allergen necessary to induce/provoke a reaction (46,47). In addition individual factors such as skin condition and the frequency of usage will be important (46). Few fragrance allergens have been investigated as regards to the no-effect level of provocation under experimental conditions (32,33,36,48). A great variation was found in sensitivity between individual patients (32,33) and none of the experiments take all the above mentioned factors into account. Therefore there is not sufficient scientific data to determine concentration levels of no concern for all fragrance allergic patients.

4. Summary

- Contact allergy is a type IV immunological reaction, which if due to fragrance ingredients, may cause facial, axillary and/or hand eczema and can be a compounding factor for other eczematous conditions. This is a burden to the individual because of discomfort, functional limitations, altered appearance, medical treatment and in some cases sick-leave.
- About 8% of eczema patients on a European basis are sensitised to fragrance ingredients. From studies performed on sectors of the population it can be estimated that the frequency of contact allergy to fragrance ingredients in the general population in Europe is 1-2%. A rising trend of fragrance allergy among eczema patients has been demonstrated in some clinics in Europe.
- Most individuals with contact allergy to fragrance ingredients are aware that they cannot tolerate fragranced products on their skin and are able to specifically name product categories that initiated their disease. In this context colognes, deodorants and lotions are named significantly more often by fragrance allergic eczema patients than by patients without fragrance contact allergy.
- Commercially available fragrance formulas are potent provokers of allergic contact dermatitis under patch test as well as simulated use conditions. Amongst individuals with eczema referred to dermatology clinics fragrance ingredients account for 30-45% of allergic reactions to cosmetic products and are thus the most frequent cause of cosmetic allergy. Well-known fragrance allergens are found in 15%-100% of cosmetic products and most often in combinations of 3 to 4 in the same product. It has been demonstrated by two model allergens, cinnamal and isoeugenol, that concentrations, which have been used by fragrance industry, will provoke contact eczema in 2 out of 3 individuals sensitised to the allergen in question.
- The fragrance industry is self-regulated. Recommendations for the safe use of fragrance ingredients are issued by the International Fragrance Association (IFRA) and published as a code of practice. The main focus has been on experimental evidence of sensitisation in healthy human volunteers, which means that secondary prevention of clinical disease in sensitised consumers is not considered in the code of practice.
- Appropriate diagnostic procedures and patient information are cornerstones in secondary prevention of contact allergy. The current standard diagnostic procedure detects only 50-80% of cases of contact allergy to fragrance ingredients.

No information about fragrance ingredients in cosmetic products is provided, which means that:

- an adequate diagnosis of fragrance contact allergy cannot be made in a significant proportion of cases without undue delay.
- consumers with known fragrance ingredient allergy have no information about the presence of specific fragrance allergens in cosmetic products, which they may not tolerate.
- industry does not receive feedback about their use of fragrance allergens and cannot take measures to improve consumer protection, if necessary.

The European Society of Contact Dermatitis and the European Environmental and Contact Dermatitis Research Group have called attention to the need for a more useful identification of fragrance ingredients in products than the statement: 'contains parfum' as presently required in the Cosmetics Directive. The American Academy of Dermatology recently sent a similar request to the Food and Drug Administration.

- The European Union as well as the World Health Organization (WHO) have defined general criteria to classify substances as skin sensitizers (contact allergens). On this basis a selection of fragrance ingredients recognised as contact allergens has been made. The selection is mainly based on dermatological data reflecting the clinical experience, without considering animal sensitisation tests. 24 fragrance chemicals have been identified: 13 of these have been reported more frequently, these are well-recognised contact allergens in consumers and are thus of most concern (Table 6a), 11 others are less well documented (Table 6b).
- There are insufficient scientific data available at the present time to determine dose-response relationships in contact allergy to these fragrance ingredients.

5. Opinion of the SCCNFP

In order to answer to the questions asked by DG Enterprise concerning the safety of fragrance ingredients the SCCNFP has decided to divide its mandate into two sections as indicated previously.

The opinion given here is related to the first section and includes the review of the fragrance ingredient allergy problem in consumers, the identification of fragrance chemicals well-recognised as consumer allergens, the scientific assessment of dose response relationships and thresholds in fragrance allergy, and finally the need for appropriate consumer information.

It is the opinion of the SCCNFP that:

- Fragrance ingredients have to be considered an important cause of contact allergy.
- Based on criteria restricted to dermatological data reflecting the clinical experience, it has been possible to identify 24 fragrance ingredients, which correspond to the most frequently

recognised allergens. Thirteen of these have been reported more frequently, these are well-recognised contact allergens in consumers and are thus of most concern, eleven others are less well documented.

List A: Fragrance chemicals, which according to existing knowledge, are most frequently reported and well-recognised consumer allergens:

Common name	CAS no	Common name	CAS no
Amyl cinnamal	122-40-7	Amylcinnamyl alcohol	101-85-9
Benzyl alcohol	100-51-6	Benzyl salicylate	118-58-1
Cinnamyl alcohol	104-54-1	Cinnamal	104-55-2
Citral	5392-40-5	Coumarin	91-64-5
Eugenol	97-53-0	Geraniol	106-24-1
Hydroxycitronellal	107-75-5	Hydroxymethylpentyl-	31906-04-4
Isoeugenol	97-54-1	cyclohexenecarboxaldehyde	

List B: Fragrance chemicals, which are less frequently reported and thus less documented as consumer allergens:

Common name	CAS no	Common name	CAS no
Anisyl alcohol	105-13-5	Benzyl benzoate	120-51-4
Benzyl cinnamate	103-41-3	Citronellol	106-22-9
Farnesol	4602-84-0	Hexyl cinnamaldehyde	101-86-0
Lilial	80-54-6	d-Limonene	5989-27-5
Linalool	78-70-6	Methyl heptine carbonate	111-12-6
3-Methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one			127-51-5

- There are at the present not sufficient scientific data to allow for determination of dose-response relationships and thresholds for these allergens.

Further, SCCNFP is of the opinion that information should be provided to consumers about the known presence in cosmetic products of fragrance ingredients with a well-recognised potential to cause contact allergy.

Information regarding these fragrance chemicals should be given to consumers if deliberately added to a fragrance formulation either in the form of a chemical or as an identified constituent of an ingredient.

In the future other fragrance chemicals may be included (or excluded) depending on the epidemiological and safety data available.

This is required to improve the protection of the consumer by ensuring that the correct diagnosis of contact allergy to well-recognised fragrance allergens can be made without undue

delay and by providing information that will help the consumer to avoid specific substances that they may not tolerate.

Natural materials, such as oak moss, will according to the interim position statement given by the SCCNFP be considered in a separate document (SCCNFP/0202/99).

In the DG Enterprise's request the term "labelling" of cosmetic products with respect to fragrance ingredient is used. This term belongs to the sector of risk management which is beyond the remit of the SCCNFP. It is up to the legislator to consider the best way to provide the information to the consumers.

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FRAGRANCE ALLERGY IN CONSUMERS

Appendix

Background information on fragrance chemicals, which have been identified as contact allergens in consumers

Fragrance chemicals most frequently reported as contact allergens

Ref n° *	Common name	cas no	comment
1	Amyl cinnamal	122-40-7	Ingredient of the Fragrance mix
2	Amylcinnamyl alcohol	101-85-9	May cross react with amył cinnamal (Ref no 1)
3	Benzyl alcohol	100-51-6	
4	Benzyl salicylate	118-58-1	
5	Cinnamyl alcohol	104-54-1	Ingredient of the Fragrance mix
6	Cinnamal	104-55-2	Ingredient of the Fragrance mix
7	Citral	5392-40-5	
8	Coumarin	91-64-5	
9	Eugenol	97-53-0	Ingredient of the Fragrance mix
10	Geraniol	106-24-1	Ingredient of the Fragrance mix
11	Hydroxycitronellal	107-75-5	Ingredient of the Fragrance mix
12	Hydroxymethyl-pentylcyclo-hexenecarboxaldehyde	31906-04-4	
13	Isoeugenol	97-54-1	Ingredient of the Fragrance mix

* Ref n° refers to the number of the short review presented on the following pages.

Fragrance chemicals less frequently reported as contact allergens

Ref no*	Common name	Cas. Number	Comments
14	Anisyl alcohol	105-13-5	
15	Benzyl benzoate	120-51-4	
16	Benzyl cinnamate	103-41-3	
17	Citronellol	106-22-9	
18	Farnesol	4602-84-0	
19	Hexyl cinnamaldehyde	101-86-0	positive control substance in animal sensitisation tests.
20	Lilial	80-54-6	2-(4-tert-butylbenzyl)propion-aldehyde
21	d-Limonene	5989-27-5	Oxidation products are strong sensitisers. Mostly reported as an occupational allergen.
22	Linalool	78-70-6	
23	Methyl heptine carbonate	111-12-6	
24	3-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one	127-51-5	= γ -Methylionone

*: Ref no refers to the number of the short review presented on the following pages

Background documentation

Common name Chemical name	Amyl cinnamal 2-benzylideneheptanal	Ref n° 1
Synonyms	α -amyl cinnamic aldehyde	
Cas. no	122-40-7	
Einecs	204-541-5	
Data	<p>Amyl cinnamal is one of 8 constituent of the fragrance mix that is used for diagnosing contact allergy to fragrances.</p> <p>General eczema patient population:</p> <ul style="list-style-type: none"> In an European multicentre study a total of 1072 patients were patch tested in 9 different centres. 5/1072 (0.47%) had a positive reaction to amyl cinnamal 1% in pet (1). <p>Subgroups of patients:</p> <ul style="list-style-type: none"> 176 patients suspect of fragrance sensitivity were patch tested with selected fragrance substances. 167 of these were tested with amyl cinnamal 5% and 5 patients (3 %) gave an allergic reaction (2). 713 patients with cutaneous reactions to cosmetic products were identified. In 578 cases sensitization were observed. In 2 subjects amyl cinnamal was one of the causative ingredients as judged by patch testing (3). Among 156 patients with pure contact allergy to cosmetic products, amyl cinnamal was one of the causative ingredient in 2 (1.3%) of the cases (4). The causative ingredients were identified in 119 patients with contact allergy to cosmetic products. 1/119 (0.8%) were allergic to amyl cinnamal, patch tested in 5% in pet. (5). 13 patients sensitive to α-amyl cinnamal were identified over 3 years, 10 of these were also sensitive to α-amyl cinnamic alcohol (6). 179 patients suspected of cosmetic allergy were patch tested with 16 fragrance materials among these amyl cinnamal 10% in pet. 7 cases (3.9%) were found positive to α-amyl cinnamal (7). <p>As part of the fragrance mix:</p> <ul style="list-style-type: none"> In an European multicentre study involving 6 countries, 78 patients who were positive to one or the other of two different fragrance mixes, one contained amyl cinnamal. The 78 patients were tested with the individual constituents of the mixes. 2/78 (2.6%) were positive to amylcinnamal 2% (8). The frequency of contact allergy to amyl cinnamal in patients positive to the fragrance mix, is reported in a range of studies from different countries: 1.9 % of the fragrance mix reactions were due to amyl cinnamal in Italy (9), 2.3% in Denmark (10) and 2,5% in France (11). <p>Test concentration:</p> <ul style="list-style-type: none"> Test concentration: 1% cinnamyl alcohol is the standard concentration used in routine testing, however 2% in pet may be used according to De Groot et al (12)and 5% in pet gave no irritant reactions when tested in 100 control individuals (24). 	
Summary	Amyl cinnamal is a wellknown allergen as part of the diagnostic test, the fragrance mix. It accounts for 2%-3% of the reactions to the fragrance mix and has been identified as a cause of allergic reactions in persons with eczema from cosmetic products.	

Common name	Amylcinnamyl alcohol	Ref n° 2
Chemical name	2-pentyl-3-phenylprop-2-en-1-ol	
Synonyms	α -amyl cinnamic alcohol	
Cas. no	101-85-9	
Einecs	202-982-8	
Data	<p>Patient subgroups</p> <ul style="list-style-type: none"> • 8 patients with contact allergy to ethylenediamine and the perfume in mycolog cream were patch tested with the ingredients of the perfume (14). α-amyl cinnamyl alcohol 5% in pet were found to be strongly positive in 5/8 cases. α-amyl cinnamyl alcohol was present in the cream in 0.001%. Reactions to other fragrance ingredients, but less frequently, were also found (14). • 20 perfume allergic patients were tested with several screening series of fragrances. 15 were allergic due to perfumes in cosmetics. 2/20 reacted with a positive reaction to α-amyl cinnamyl alcohol 5% in petrolatum. (15). • 11 patients sensitive to α-amyl cinnamic alcohol were identified over 3 years, 10 of these were also sensitive to α-amyl cinnamic aldehyde. Some of the patients primarily sensitized by the perfume in a medicament. Test concentration according to authors way below an irritant level (6). • 179 patients suspected of cosmetic allergy were patch tested with 16 fragrance materials among these α-amyl cinnamyl alcohol 20% in pet. 7 cases (3.9%) were found positive to α-amyl cinnamyl alcohol . Test concentrations were chosen based on existing recommendations or a pilot study involving 60 eczema patients. Test concentrations were chosen deliberately high, but non irritant, to avoid false negative reaction (7) • 460 patients were considered to have contact allergy related to cosmetics. 80 patients were positive to the fragrance mix and by testing with ingredients of the mix and other fragrances 3 cases of allergic reactions to amyl cinnamyl alcohol were identified. Test concentrations unknown (16). <p>Test concentrations:</p> <ul style="list-style-type: none"> • Amyl cinnamyl alcohol 2% in pet is recommended for patch testing according to De Groot (12). Higher concentrations have been used in a number of studies (7, 15). 	
Summary	<p>Five single cases reported of contact allergy to amyl cinnamyl alcohol and allergic reactions by patch testing <u>were found</u> in 7/179-2/20 (4-10%) of patients with contact eczema from cosmetics.</p> <p>Amyl cinnamyl alcohol probably cross reacts with amylicinnamal.</p>	

Common name Chemical name	Benzyl alcohol (INCI) Benzyl alcohol	Ref n° 3	
Synonyms			
Cas. No	100-51-6		
Einecs	202-859-9		
Data	<p>General eczema patient population:</p> <ul style="list-style-type: none"> •0.5% of tested patients in Japan gave a positive reaction to benzyl alcohol 5%. Number of included patients unknown (17). <p>Subgroups of patients:</p> <ul style="list-style-type: none"> •20 perfume allergic patients were tested with several screening series of fragrances. 15 were allergic due to perfumes in cosmetics. Benzyl alcohol 5% gave a positive reaction in 3/20 patients (15). •176 patients suspect of fragrance sensitivity were patch tested with selected fragrance substances. 167 of these were tested with benzyl alcohol 5% and 2 patients (1.2 %) gave an allergic reaction (2). •182 patients suspected of contact allergy to cosmetics were patch tested with a series of 22 fragrance substances. 3 (1.6%) of the patients had a positive patch test reaction to benzyl alcohol 10% which was also found in 10/79 cosmetic products sent for analysis by the patients or their physicians. Benzyl alcohol 10% was negative in a pilot study for irritant reactions in 81 eczema patients (18). •1.3% (2/156) of patients with contact allergy to cosmetic products were sensitized to benzyl alcohol (4). •713 patients with cutaneous reactions to cosmetic products were identified. In 578 cases sensitization were observed. In 3 subjects benzyl alcohol was one of the causative ingredients as judged by patch testing (3). •242 randomly selected patients with proven contact allergy from different origin were tested with 7 perfume components. 4(1.6%) had a positive patch test to benzyl alcohol (19). <p>Case reports:</p> <ul style="list-style-type: none"> •A 46 year old man with atopic eczema were allergic to the perfume of a preparation used. Benzyl alcohol was found to be the causative ingredient by patch testing with 5% in pet and found in the perfume in a high concentration (13). •2 cases of contact allergy to a perfume and an after shave lotion were reported together with contact allergy to benzyl alcohol, patch tested in 1 % in pet (20) <p>Other studies:</p> <ul style="list-style-type: none"> •Occurs in minor amounts in balsam of Peru, which is used as a screening agent for fragrance contact allergy (21). Benzyl alcohol is also used as a preservative. <p>Test concentrations:</p> <ul style="list-style-type: none"> •Benzyl alcohol 5% is recommended (12). Benzyl alcohol 10% was negative in 20 eczema patients and 61 patients with cosmetic eczema, when tested for irritancy (18). 		
Summary	Benzyl alcohol is found in several studies as a cause of allergic reactions in 1.2-15% (2-4 cases in each study) of patients with eczema from cosmetic products.		

Common name Chemical name	Benzyl salicylate (INCI) Benzyl-o-hydroxybenzoate	Ref n° 4
Synonyms		
Cas. No	118-58-1	
Einecs	204-262-9	
Data	<p>General eczema patient population:</p> <ul style="list-style-type: none"> • 2.3% of tested patients in Japan gave a positive reaction to benzyl salicylate 2%. Number of included patients unknown (17). • 1943 consecutive eczema patients were examined with regard to sensitivity to perfumes from toilet soap and detergents. 78 patients (4%) showed positive reactions to perfumes and in 75% of the cases the reaction was found to be associated with sensitivity to benzyl salicylate patch tested in 2% pet. Benzyl salicylate was present in the positive perfumes (22). • 241 patients were tested with a perfume screening series. 6 (2.5%) had a positive reaction to benzyl salicylate 2% in pet (23). <p>Subgroups of patients:</p> <ul style="list-style-type: none"> • 20 perfume allergic patients were tested with several screening series of fragrances. 15 were allergic due to perfumes in cosmetics. Benzyl salicylate 2% gave a positive reaction in 2/20 patients (15). • 176 patients suspect of fragrance sensitivity were patch tested with selected fragrance substances. 167 of these were tested with benzyl salicylate 5 and 2%. 8 and 5 patients (4.8%-3%) reacted with an allergic reaction, respectively. Benzyl salicylate was a more common cause of positive patch test reactions in Japan than in Europe and US (2). • 713 patients with cutaneous reactions to cosmetic products were identified. In 578 cases sensitization were observed. In 1 subject benzyl salicylate was one of the causative ingredients as judged by patch testing (3). <p>Test concentrations:</p> <ul style="list-style-type: none"> • Benzyl salicylate 1% is recommended for patch testing (24). 	
Summary	Benzyl salicylate is as a cause of allergic reactions in 0.2-10% of patients with eczema from cosmetic products and in one study accounted for 75% of reactions to commercial perfumes.	

Common name Chemical name	Cinnamyl alcohol [INCI] Cinnamic alcohol	Ref n° 5	
Synonyms			
Cas. no	104-54-1		
Einecs	203-212-3		
Data	<p>Cinnamyl alcohol is one of 8 constituent of the fragrance mix, that is used for diagnosing contact allergy to fragrances.</p> <p>General eczema patient population:</p> <ul style="list-style-type: none"> • In an European multicentre study a total of 1072 patients were patch tested in 9 different centres. 6/1072 (0.56%) had a positive reaction to cinnamyl alcohol 1% (1). <p>Subgroups of patients:</p> <ul style="list-style-type: none"> • 20 perfume allergic patients were tested with several screening series of fragrances. Cinnamyl alcohol 5% gave a positive reaction in 15/20 (75%) patients. 50 control patients were tested with the fragrance allergens and were negative (15). • 713 patients with cutaneous reactions to cosmetic products were identified. In 578 cases sensitization were observed. In 17 subjects cinnamyl alcohol was one of the causative ingredients as judged by patch testing. This constituted 10% of fragrance ingredients causing cutaneous reactions (3). • Among 156 patients with pure contact allergy to cosmetic products, cinnamyl alcohol was one of the causative ingredient in 6 (3.8%) of the cases (4). • The causative ingredients were identified in 119 patients with contact allergy to cosmetic products. 2/119 (1.7%) were allergic to cinnamyl alcohol, patch tested in 5% in pet. (5). • 176 patients suspect of fragrance sensitivity were patch tested with selected fragrance substances. 167 of these were tested with cinnamyl alcohol 5% in lanolin and 11(6.6%) had an allergic reaction (2). <p>As part of the fragrance mix:</p> <ul style="list-style-type: none"> • In an European multicentre study involving 6 countries, 78 patients were positive to one or the other of two different fragrance mixes, both containing cinnamyl alcohol. The patients were tested with the individual constituents of the mixes. 5/78 (6.4%) were positive to cinnamyl alcohol 1% (8). • The frequency of contact allergy to cinnamyl alcohol in patients positive to the fragrance mix, is reported in a range of studies from different countries: 9.3% of the fragrance mix reactions were due to cinnamyl alcohol in Italy (9), 10.8% in Denmark (10), 8% in Hungary (25) , 5.5% in Germany (26) and 14% in France (11). <p>Other:</p> <ul style="list-style-type: none"> • Cinnamyl alcohol is restricted in the IFRA guideline to a maximum use concentration of 0.8%. In a children's toy perfume cinnamyl alcohol has been found in a concentration of 3.7% (27). • Cinnamyl alcohol has induced sensitization in 2.7% (4/150) healthy volunteers at exposure to a 4% concentration (28). <p>Test concentration:</p> <ul style="list-style-type: none"> • Test concentration: 1% cinnamyl alcohol is the standard concentration used in routine testing, however 2% in pet may be used according to De Groot et al (12) and 5% in pet gave no irritant reactions when tested in 100 control individuals (24). 		

Summary	Cinnamyl alcohol is a well-known allergen as part of the diagnostic test, the fragrance mix. It accounts for 5-14% of the reactions to the fragrance mix. In addition it has been shown to be a cause of allergic reactions by patch test in 1.7%-75% of patients with eczema from cosmetic products.
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Common name Chemical name	Cinnamal [INCI] Cinnamaldehyde; 3-phenyl-2-propenal	Ref n° 6
Synonyms	Cinnamic aldehyde	
Cas. no	104-55-2	
Einecs	203-213-9	
Data	<p>Cinnamal is one of 8 constituent of the fragrance mix, that is used for diagnosing contact allergy to fragrances.</p> <p>General eczema patient populations:</p> <ul style="list-style-type: none"> • In an European multicentre study a total of 1072 patients were patch tested in 9 different centres. 10/1072 (0.9%) had a positive reaction to cinnamal 1% (1). • Cinnamal is a part of the North American Standard patch test series, that is used for testing all eczema patients. In 1985-89 3.1% of 3964 patients and in 1994/96 2.4% of 3112 patients were positive to cinnamal 1% (10). 85% of these cases were of current definite, probable or possible relevance (46). <p>Subgroups of patients:</p> <ul style="list-style-type: none"> • 20 perfume allergic patients were tested with several screening series of fragrances. Cinnamal 1% gave a positive reaction in 6/20 (30%) patients (15). • 182 patients suspected of contact allergy to cosmetics were patch tested with a series of 22 fragrance substances. 3.7% of the patients had a positive patch test reaction to cinnamal 0.5%. Cinnamal was found in 8/79 cosmetic products sent in for analysis by the patients or their physicians (18). • 713 patients with cutaneous reactions to cosmetic products were identified. In 578 cases sensitization were observed. In 6 subjects cinnamal was one of the causative ingredients as judged by patch testing (3). • 176 patients suspect of fragrance sensitivity were patch tested with selected fragrance substances. 167 of these were tested with cinnamal 1% in pet and 24 (14.4%) gave an allergic reaction (2). <p>As part of the fragrance mix:</p> <ul style="list-style-type: none"> • In an European multicentre study involving 6 countries, 78 patients positive to one or the other of two different fragrance mixes, both containing cinnamal, were tested with the individual constituents of the mixes. 10/78 (12.8%) were positive to cinnamal 1% (8). • The frequency of contact allergy to cinnamal in patients positive to the fragrance mix, is reported in a range of studies from different countries: 5.5% of the fragrance mix reactions were due to cinnamal in Italy (9), 16.9% in Denmark (10), 24% in Hungary (25), 21% in Germany (26) and 36% in France (11). <p>Others:</p> <ul style="list-style-type: none"> • Cinnamal has actively sensitized 8%-44% of healthy volunteers using different concentrations and experimental methods (29). According to the IFRA guideline, cinnamal must only be used in conjunction with substances preventing sensitization, but no restrictions is made on the concentrations. <p>Test concentrations: 1% cinnamal is the standard concentration used in routine testing (12). Higher concentrations may give irritant reactions (23).</p>	
Summary	Cinnamal is a well proven allergen as part of the diagnostic test, the fragrance mix. It accounts for 5-36% of the reactions to the fragrance mix. It gives reactions in 2-3% of consecutively patch tested patients, most of which are of relevance. In addition it has been shown to be a cause of allergic reactions by patch test in 1%-30% patients with eczema from cosmetic products in several studies.	

Common name	Citral	Ref n° 7
Chemical name	3,7-dimethyl-2,6-octadien-1-al, mix of cis and trans isomers	
Cas. no	5392-40-5	
Einecs	226-394-6	
Data	<p>General eczema patient population:</p> <ul style="list-style-type: none"> •228 patients were tested by the North American Contact Dermatitis Research Group in 1973/74 with citral 1% in pet. 1.7% had a positive patch test reaction to citral (30). •2455 eczema patients were patch tested with two separate mixes: one standard fragrance mix and a new mix containing dihydrocoumarine and citral instead of oak moss and amyl cinnamic aldehyde. 6.7% of the patients reacted to the new mix. 78 patients positive to either of the mixes were patch tested with the individual ingredients. Isoeugenol gave most reactions and next citral 2% in pet that gave reactions in 13 individuals, 16.7% of those positive to the mix (8). •19/1855, (1.0%) consecutively patch tested eczema patients in a European multicentre study gave a positive reaction to Citral tested in 2% (31-personal communication). <p>Subgroups of patients:</p> <ul style="list-style-type: none"> •182 patients suspected of contact allergy to cosmetics were patch tested with a series of 22 fragrance substances. 2.6% of the patients had a positive patch test reaction to citral 2% in pet. Citral was found in 4/79 cosmetic products sent in for analysis by the patients or their physicians (18). <p>Occupational setting:</p> <ul style="list-style-type: none"> •4 bakers with hand eczema were patch tested with fragrance/flavours. One reacted with a positive reaction to citral 0.5% in pet. Relevance unknown (32). <p>Other data:</p> <ul style="list-style-type: none"> •Citral from different sources and in different concentrations have been studied by the Human Maximization Test. In all tests citral induced sensitization in 12%-64% of human volunteers, 3/25-16/25 (33). Citral was also studied in the repeated insult patch procedure at 4-8% and sensitized 48% of a panel of 40 human volunteers (33). According to IFRA guideline citral must only be used in conjunction with substances preventing sensitization, but no restrictions are made on the use concentrations. <p>Test concentrations:</p> <ul style="list-style-type: none"> •2% in petrolatum is the recommended concentration (12). 	
Summary	Citral is a cause of allergic reactions in about 1% of consecutive patch tested patients. It was the most frequent cause of reactions to a new diagnostic test for fragrance contact allergy and proved to cause contact allergic reactions in 2.6% of patients with eczema from cosmetic products.	

Common name Chemical name	Coumarin (INCI) 1-benzopyran-2-one; cis-o-coumarinic acid lactone	Ref n° 8
Synonyms	occurs naturally in tonka beans and other plants.	
Cas. no	91-64-5	
Einecs	202-086-7	
Data	<p>General eczema patient population:</p> <ul style="list-style-type: none"> • 241 consecutive patients were patch tested with coumarin 5%. 2 (0.8%) had a positive reaction (23). • 14.000 consecutive eczema patients were patch tested with coumarin 5 % in pet or for a short period 8% in pet. 58 (0.4%) showed a positive reaction. 20/58 cases were not identified by other markers of perfume allergy and would have been missed if coumarin had not been patch tested (34). <p>Subgroups of patients:</p> <ul style="list-style-type: none"> • 20 perfume allergic patients were tested with several screening series of fragrances. 15 had dermatitis related to the use of a cosmetic product. Coumarin 5% gave a positive reaction in 2/20 (10%) patients (15). • 176 patients suspect of fragrance sensitivity were patch tested with selected fragrance substances. 167 of these were tested with coumarin 5% and 2 patients (1.2%) reacted with an allergic reaction (2). • 182 patients suspected of contact allergy to cosmetics were patch tested with a series of 22 fragrance substances. 6.8% of the patients had a positive patch test reaction to coumarin 8% in pet. Coumarin was found in 16/79 (20.3%) cosmetic products sent in for analysis by the patients or their physicians. The concentration of 8% coumarin was tested in a total of 54 controls and no reactions were found (18). • 713 patients with cutaneous reactions to cosmetic products were identified. In 578 cases sensitization were observed. In 4 subjects coumarin was one of the causative ingredients as judged by patch testing (3). • The causative ingredients were identified in 119 patients with contact allergy to cosmetic products. 1/119 (0.8%) were allergic to coumarin patch tested in 5% in pet. (5). • A group of 242 randomly selected eczema patients were patch tested with perfume components. 9 (3.7%) were positive to coumarin 5.8% at patch testing (19). <p>Case reports:</p> <ul style="list-style-type: none"> • A women developed severe eczema from using a perfumed lotion. Patch testing showed a strong reaction to coumarin 0.5% in pet and the diluent, which was constituents of the perfume formulation of the lotion (35). • A women developed severe eczema from a perfume. She was positive at patch testing to the perfume. By chemical fractionation it was established that coumarin was the causative ingredient. It was contained in a concentration of 0.23% in the perfume (36). <p>Test concentrations:</p> <ul style="list-style-type: none"> • Coumarin 5% is the recommended patch test concentration (12). 	
Summary	Coumarin is a cause of allergic reactions in about 0.4-0.8% of consecutive patch tested patients. 1/3 of these cases is not detected by the fragrance mix. Coumarin has caused contact allergic reactions in 0.8-10% of patients with eczema from cosmetic products	

Common name Chemical name	Eugenol (INCI) Eugenol	Ref n° 9
Synonyms		
Cas. no	97-53-0	
Einecs	202-589-1	
Data	<p>Eugenol is one of 8 constituent of the fragrance mix, that is used for diagnosing contact allergy to fragrances.</p> <p>Consecutive patients:</p> <ul style="list-style-type: none"> • In an European multicentre study a total of 1072 patients were patch tested in 9 different centres. 13/1072 (1.2%) had a positive reaction to eugenol 1% (1). <p>Subgroups of patients:</p> <ul style="list-style-type: none"> • 20 perfume allergic patients were tested with several screening series of fragrances. Eugenol 2% gave a positive reaction in 4/20 (20%) patients (15). • 713 patients with cutaneous reactions to cosmetic products were identified. In 578 cases sensitization were observed. In 4 subjects eugenol was one of the causative ingredients as judged by patch testing (3). • Among 156 patients with pure contact allergy to cosmetic products, eugenol was one of the causative ingredient in 11 (7.1%) of the cases (4). • 176 patients suspect of fragrance sensitivity were patch tested with selected fragrance substances. 167 of these were tested with eugenol 5% and 13 patients (7.8 %) gave an allergic reaction (2). <p>As part of the fragrance mix:</p> <ul style="list-style-type: none"> • In an European multicentre study involving 6 countries, 78 patients positive to one or the other of two different fragrance mixes, both containing eugenol, were tested with the individual constituents of the mixes. 8/78 (10.3%) were positive to eugenol 2% (8). • The frequency of contact allergy to eugenol in patients positive to the fragrance mix, is reported in a range of studies from different countries: 16.7% of the fragrance mix reactions were due to eugenol in Italy (9), 12.2% in Denmark (10), 4% in Hungary (25), 6.8% in Germany (26) and 22% in France (11). <p>Test concentrations:</p> <ul style="list-style-type: none"> • 1% eugenol is the standard concentration used in routine testing, however 2% have been used for a number of years and is recommended by De Groot (12). In a study 5% eugenol in pet was tested in 100 healthy volunteers and gave no reactions (24) 	
Summary	Eugenol is a well known contact allergen. Many investigations have been performed. It is the cause of sensitization in 1.2% of consecutive eczema patients and accounts for 4%-16% of reactions to the fragrance mix. Eugenol has caused contact allergic reactions in 0.7-20% of patients with eczema from cosmetic products	

Common name Chemical name	Geraniol (INCI)	Ref n° 10
Synonyms		
Cas. no	106-24-1	
Einecs	203-377-1	
Data	<p>Geraniol is one of 8 constituent of the fragrance mix, that is used for diagnosing contact allergy to fragrances.</p> <p>Consecutive patients:</p> <ul style="list-style-type: none"> In an European multicentre study a total of 1072 patients were patch tested in 9 different centres. 4/1072 (0.4%) had a positive reaction to geraniol 1% (1). <p>Subgroups of patients:</p> <ul style="list-style-type: none"> 20 perfume allergic patients were tested with several screening series of fragrances. Geraniol 5% gave a positive reaction in 6/20 (30%) patients (15). 182 patients suspected of contact allergy to cosmetics were patch tested with a series of 22 fragrance substances. 1.6% of the patients had a positive patch test reaction to geraniol 1%. Geraniol was found in 4/79 cosmetic products sent for analysis by the patients or their physicians (18). 713 patients with cutaneous reactions to cosmetic products were identified. In 578 cases sensitization were observed. In 8 subjects geraniol was one of the causative ingredients as judged by patch testing (3). Geraniol caused contact allergy in 2/156 (1.2%) patients suffering from contact allergy to cosmetic products (4). 176 patients suspect of fragrance sensitivity were patch tested with selected fragrance substances. 167 of these were tested with geraniol 5% and 5 patients (3.0%) gave an allergic reaction (2). <p>As part of the fragrance mix:</p> <ul style="list-style-type: none"> In an European multicentre study involving 6 countries, 78 patients positive to one or the other of two different fragrance mixes, both containing geraniol, were tested with the individual constituents of the mixes. 4/78 (5.1%) were positive to geraniol 1% (8). The frequency of contact allergy to geraniol in patients positive to the fragrance mix, is reported in a range of studies from different countries: 7.4% of the fragrance mix reactions were due to geraniol in Italy (9), 3.3 % in Denmark (10), 4% in Hungary (25), 6.8% in Germany (26) and 22% in France (11). <p>Test concentration:</p> <ul style="list-style-type: none"> 1% geraniol is the standard concentration used in routine testing (12), however 2% have been used for a number of years and is recommended by De Groot (12). In a study 5% geraniol in pet was tested in 100 healthy volunteers and gave no irritant reactions (24). 	
Summary	<p>Geraniol is a well-known contact allergen as an ingredient in the diagnostic test, the fragrance mix. It is a cause of sensitization in 0.4% of consecutive eczema patients and accounts 3%-7% of reactions to the fragrance mix.</p> <p>Geraniol has caused contact allergic reactions in 1.2-30% of patients with eczema from cosmetic products</p>	

Common name	Hydroxycitronellal	Ref n° 11
Chemical name	7-Hydroxycitronellal	
Synonyms	Laurine	
Cas. No	107-75-5	
Einecs	203-518-7	
D Data	<p>Hydroxycitronellal is one of 8 constituent of the fragrance mix, which is used for diagnosing contact allergy to fragrances.</p> <p>General eczema patients population:</p> <ul style="list-style-type: none"> In an European multicentre study a total of 1072 patients were patch tested in 9 different centres. 8/1072 (0.75%) had a positive reaction to Hydroxycitronellal 1% (1). <p>Subgroups of patients:</p> <ul style="list-style-type: none"> 20 perfume allergic patients were tested with several screening series of fragrances. Hydroxycitronellal 4% gave a positive reaction in 9/20 (45%) of the patients (15). 182 patients suspected of contact allergy to cosmetics were patch tested with a series of 22 fragrance substances. 19/182 (10.5%) of the patients had a positive patch test reaction to hydroxycitronellal 10%. Hydroxycitronellal was found in 47/79 (59%) of cosmetic products sent in for analysis by the patients or their physicians (18). 713 patients with cutaneous reactions to cosmetic products were identified. In 578 cases sensitization were observed. In 11 subjects hydroxycitronellal was one of the causative ingredients as judged by patch testing (3). 156 patients with contact allergy to cosmetic products were identified. Hydroxycitronellal was one of the causative ingredients in 6 cases (3.8%), as determined by patch testing (4). 23 cosmetic products, which had caused contact allergic reactions in 11 patients with perfume allergy, were subjected to chemical analysis. The products of all patients sensitive to hydroxycitronellal, n=6, was found to contain the substance. The content of hydroxycitronellal was at average 5 times higher in cosmetics from hydroxycitronellal sensitive patients compared with hydroxycitronellal negative patients (37) 176 patients suspect of fragrance sensitivity were patch tested with selected fragrance substances. 167 of these were tested with hydroxycitronellal 4% and 23 patients (13.8%) reacted with an allergic reaction (2). <p>As part of the Fragrance mix:</p> <ul style="list-style-type: none"> In an European multicentre study involving 6 countries, 78 patients positive to one or the other of two different fragrance mixes, both containing hydroxycitronellal, were tested with the individual constituents of the mixes. 7/78 (9%) were positive to hydroxycitronellal 5% (8). The frequency of contact allergy to hydroxycitronellal in patients positive to the fragrance mix, is reported in a range of studies from different countries: 16% of the fragrance mix reactions were due to hydroxycitronellal in Italy (9), 7.4 % in Denmark (10), 10% in Hungary (25) 6.2% in Germany (26) and 5% in France (11). <p>Others:</p> <ul style="list-style-type: none"> Hydroxycitronellal is restricted in the IFRA guideline to 1% in consumer products due to its sensitizing properties. 5% hydroxycitronellal has been found to cause sensitization in 36% of healthy volunteers (38). <p>Test concentration:</p> <ul style="list-style-type: none"> 1% hydroxycitronellal is the standard concentration used in routine testing, however 2% have been used for a number of years and is recommended by De Groot (12). In a study 5% hydroxycitronellal in pet was tested in 100 healthy volunteers and gave no irritant reactions (24) 	
Summary	Hydroxycitronellal is a well known contact allergen as ingredient in the diagnostic test, the fragrance mix. It is a cause of sensitization in 0.75% of consecutive eczema patients and accounts 6%-16% of reactions to the fragrance mix. Hydroxycitronellal has caused contact allergic reactions in 10%-45% of patients with eczema from cosmetic products	

Common name Chemical name	Hydroxymethyl-pentylcyclo-hexenecarboxaldehyde 4-(4-Hydroxy-4-methylpentyl)cyclohex-3-enecarbaldehyde	Ref n° 12
Synonyms	Lyral	
Cas. No	31906-04-4	
Einecs	250-863-4	
Data	<p>General eczema patient population:</p> <ul style="list-style-type: none"> • 106 patients were tested with Lyral 5% and 1% in petrolatum as part of a screening study for fragrance contact allergy. 3 (2.8%) had a positive patch test reaction to Lyral 5% and 1 (0.9%) to Lyral 1%. Clinical relevance was not firmly established, but may have been present in 2 patients (1). • 1855 eczema patients were tested with a screenings series of 11 fragrance allergens among these Lyral 5% in pet. 50/1855 (2.7%) were positive at patch testing to Lyral. Judged by history 2/3 Lyral positive cases were either definitively or probably relevant. In 4 cases of Lyral allergy an extended exposure evaluation was performed. Lyral was identified in one or more cosmetic products, that had caused contact dermatitis (41). <p>Subgroups of patients:</p> <ul style="list-style-type: none"> • The causative ingredients were identified in 75 patients with contact allergy to cosmetic products. One patient was allergic to Lyral which was present in a deodorant cream, patch test concentration unknown (42). <p>Case-reports:</p> <ul style="list-style-type: none"> • A 28 year old man developed allergic contact dermatitis to two separate underarm deodorants. By patch testing with fractions of the perfumes from the products it was established that Lyral was responsible for the reaction to both products. An additional fragrance allergen, acetyl cedrene, was found in one of the two deodorants (43). • A 20 year-old woman presented with a 5-months history of severe dermatitis in both axillae, related to the use of her underarm deodorant of a particular brand. Testing with Standard series was negative, including the Fragrance mix. Subsequent patch testing with the ingredients of her deodorant showed that she was allergic to Lyral, tested in 10% in pet, contained in the fragrance compound in the deodorant (59). <p>Test concentration:</p> <ul style="list-style-type: none"> • Lyral 10% in pet has been reported to be non-irritant under patch test conditions (12) 	
Summary	Lyral was a cause of allergic reactions in about 2.8% of consecutive patch tested patients. 2/3 of the cases <u>were</u> relevant. In addition three relevant cases of contact allergy to Lyral from cosmetic products are established.	

Common name Chemical name	Isoeugenol Isoeugenol	Ref n° 13	
Synonyms			
Cas. No	97-54-1		
Einecs	202-590-7		
Data	<p>Isoeugenol is one of 8 constituent of the fragrance mix, that is used for diagnosing contact allergy to fragrances.</p> <p>General eczema patients population:</p> <ul style="list-style-type: none"> • In an European multicentre study a total of 1072 patients were patch tested in 9 different centres. 20/1072 (1.86%) had a positive reaction to Isoeugenol 1% (1). <p>Subgroups of patients:</p> <ul style="list-style-type: none"> • 20 perfume allergic patients were tested with several screening series of fragrances. Isoeugenol 2% gave a positive reaction in 5/20 (25%) of the patients (15). • 713 patients with cutaneous reactions to cosmetic products were identified. In 578 cases sensitisation were observed. In 10 subjects isoegenol was one of the causative ingredients as judged by patch testing (3). • 156 patients with contact allergy to cosmetic products were identified. Isoeugenol was one of the causative ingredients in 16 cases (10.3%), as determined by patch testing (4). <p>As part of the fragrance mix:</p> <ul style="list-style-type: none"> • In an European multicentre study involving 6 countries, 78 patients positive to one or the other of two different fragrance mixes, both containing isoegenol, were tested with the individual constituents of the mixes. 16/78 (20,5%) were positive to isoegenol 2%, which was the most frequent allergen (8). • The frequency of contact allergy to isoegenol in patients positive to the fragrance mix, is reported in a range of studies from different countries: 22% of the fragrance mix reactions were due to Isoeugenol in Italy (9), 18.5 % in Denmark (10), 6% in Hungary (25), 16.6% in Germany (26) and 17% in France (11). <p>Others:</p> <ul style="list-style-type: none"> • Isoeugenol was restricted in the IFRA guideline to 0.2% until May 1998, where the concentration was lowered to 0.02%. Isoeugenol has been found to cause sensitisation in 12-36% of healthy volunteers (39,40). <p>Test concentrations:</p> <ul style="list-style-type: none"> • 1% isoegenol is the standard concentration used in routine testing , however 2% have been used for a number of years (12). In a study 5% isoegenol in pet was tested in 100 healthy volunteers and gave no irritant reactions (24) 		
Conclusion	Isoeugenol is a well-known contact allergen as ingredient in the diagnostic test, the fragrance mix. It is a cause of sensitisation in 1.9% of consecutive eczema patients and accounts for 6%-22% of reactions to the fragrance mix. Isoeugenol has caused contact allergic reactions in 2-25% of patients with eczema from cosmetic products		

Common name	Anisyl alcohol	Ref n° 14
Chemical name	4-methoxybenzyl alcohol	
Synonyms		
Cas. No	105-13-5	
Einecs	203-273-6	
Data	<p>Subgroups of patients</p> <ul style="list-style-type: none"> • 176 patients suspect of fragrance sensitivity were patch tested with selected fragrance substances. 167 of these were tested with anisyl alcohol 5% in pet and 3 (1.6%) reacted with an allergic reaction (2). • 20 perfume allergic patients were tested with several screening series of fragrances. 15 were allergic due to perfumes in cosmetics. Anisyl alcohol 5% in pet. gave a positive reaction in 4/20 (20%)(15). <p>Test concentration:</p> <ul style="list-style-type: none"> • 5% anisyl alcohol has been reported to be a non-irritant patch test concentration (12) 	
Conclusion	Two studies reported with contact allergy to anisyl alcohol among patients with cosmetic eczema. 3 and 4 cases were documented (1.6-20%).	

Common name Chemical name	Benzyl benzoate (INCI) Benzyl benzoate	Ref n° 15
Synonyms		
Cas. no	120-51-4	
Einecs	204-402-9	
Data	<p>Consecutive patients:</p> <ul style="list-style-type: none"> • 335 and 284 patients were tested by the North American Contact Dermatitis Research Group in 1979/80 with benzyl benzoate 2% in pet. 1% of the 284 had a positive patch test reaction to benzyl benzoate and none of the 335 patients (30). • 241 patients were tested with a perfume screening series. 1 (0.4%) had a positive reaction to benzyl benzoate 2% in pet (23). <p>Subgroups of patients:</p> <ul style="list-style-type: none"> • 20 perfume allergic patients were tested with several screening series of fragrances. 15 were allergic due to perfumes in cosmetics. Benzyl benzoate 5% gave a positive reaction in 1/20 patients (15). • 713 patients with cutaneous reactions to cosmetic products were identified. In 578 cases sensitization were observed. In 1 subject benzyl benzoate was one of the causative ingredients as judged by patch testing (3). • Benzoyl benzoate is one of the main components of Peru Balsam, which is used as a screening agent for fragrance contact allergy (24). 103 cases with contact allergy to Peru balsam was tested with known ingredients. 12 (12%) were positive to Benzoyl benzoate tested 5% in pet. (44). <p>Other studies:</p> <ul style="list-style-type: none"> • Occurs in fairly large amounts in a number of blossom concretes and absolutes as tuberose and hyacinth (45). <p>Test concentrations:</p> <ul style="list-style-type: none"> • Benzyl benzoate 5% in pet is the recommended patch test concentration according to De Groot (12). 	
Summary	Benzyl benzoate is positive in several studies, but only a single case are reported in each except for patients sensitive to Peru balsam	

Common name Chemical name	Benzyl cinnamate (INCI) Benzyl 3-phenyl-2-propenoate	Ref n° 16
Synonyms	Cinnamein	
Cas. No	103-41-3	
Einecs	203-109-3	
Data	<p>Subgroups of patients:</p> <ul style="list-style-type: none"> • 182 patients suspected of contact allergy to cosmetics were patch tested with a series of 22 fragrance substances. 6 (3.2%) of the patients had a positive patch test reaction to benzylcinnamate 8%. No Benzylcinnamate was found in 79 cosmetic products sent in for analysis by the patients or their physicians (18). • Benzyl cinnamate is a component of balsam of Peru (21), which is used as a screening agent for fragrance contact allergy. 103 cases with contact allergy to Peru balsam was tested with known ingredients. 19 (18%) were positive to Benzyl cinnamate tested 5% in pet. (44). <p>Test concentrations:</p> <ul style="list-style-type: none"> • Benzyl cinnamate 5% is recommended for patch testing according to De Groot (12) 	
Summary	Benzyl cinnamate positive in one study of patients with contact allergy to cosmetic products and in a high proportion of patients with contact allergy to Peru balsam.	

Common name Chemical name	Citronellol (INCI) 3,7-Dimethyl-6-octenol	Ref n° 17
Synonyms		
Cas. no	106-22-9	
Einecs	203-375-0	
Data	<p>General eczema patient population:</p> <ul style="list-style-type: none"> • 100 patients were tested with citronellol 5% and 1% in petrolatum as part of a screening study for fragrance contact allergy. 1 (1%) had a positive patch test reaction to citronellol 1%, but none to 5%. The patient was without a history of fragrance sensitivity (1) <p>Subgroups of patients:</p> <ul style="list-style-type: none"> • 20 perfume allergic patients were tested with several screening series of fragrances. 15 had dermatitis related to cosmetic products. Citronellol 5% gave a positive reaction in 7/20 (35%) patients (15). • The causative ingredients were identified in 75 patients with contact allergy to cosmetic products. 1 patient was allergic to citronellol, concentration unknown, present in a lotion (42). • The causative ingredients were identified in 119 patients with contact allergy to cosmetic products. 2/119 (1.7%) were allergic to citronellol, patch tested in 2% in pet. (5). <p>Test concentrations:</p> <ul style="list-style-type: none"> • Citronellol 1-2% in petrolatum is the recommended patch test concentration (12). 	
Summary	One case of contact allergy to citronellol of uncertain relevance found by testing consecutive patients. Two studies of eczema patients with cosmetic eczema show more than one case each of patch test reactions to citronellol.	

Common name	Farnesol (INCI)	Ref n° 18
Chemical name	3,7,11 trimethyldodeca-2,6,10 trienol	
Synonyms		
Cas. no	4602-84-0	
Einecs	225-004-1	
Data	<p>General eczema patients population:</p> <ul style="list-style-type: none"> • 466 patients were patch tested by the Japanese society of contact dermatitis. Farnesol 2%, 5% and 10% was used. 1.1% of the patients reacted positively to farnesol 10% or 5% and 0.2% to farnesol 2% (17). <p>Subgroups of patients:</p> <ul style="list-style-type: none"> • 182 patients suspected of contact allergy to cosmetics were patch tested with a series of 22 fragrance substances. 2 (1.1%) of the patients had a positive patch test reaction to farnesol 4% in pet. Farnesol was not found in any of 79 cosmetic products sent in for analysis by the patients or their physicians. The patch test concentration of Farnesol 4% was based on a negative result in testing 20 control eczema patients (18) • 111 patients were tested with farnesol 1% in lanolin. 8 cases of sensitization to farnesol <u>were</u> found. 6 of the 8 also reacted to the balsam of Peru (47). <p>Case Reports:</p> <ul style="list-style-type: none"> • A women with an axillary dermatitis due to a deodorant tested positive to farnesol 5% in pet, probably used as preservative in the deodorant (47). <p>Other:</p> <ul style="list-style-type: none"> • Farnesol has been mentioned as a constituent of Peru Balsam (18,21). • 1/230 Patients with contact allergy to Peru balsam reacted also to Farnesol (44). • Restricted in IFRA –guideline: Farnesol should be at least 96% pure. The recommendation is based on a private communication that farnesol containing impurities caused sensitization while preparations of at least 96% purity did not. <p>Test concentrations:</p> <ul style="list-style-type: none"> • Farnesol 4% is the recommended patch test concentration (12). 	
Summary	One study of eczema patients with cosmetic eczema shows two cases of contact allergy to farnesol. Additional cases in Peru balsam positive patients are found.	

Common name Chemical name	Hexyl cinnamaldehyde α -hexyl cinnamaldehyde	Ref n° 19
Synonyms		
Cas. No	101-86-0	
Einecs	202-983-3	
Data	<p>Subgroups of patients:</p> <ul style="list-style-type: none"> • 20 perfume allergic patients were tested with several screening series of fragrances. Hexylcinnamal 2% was positive in one patient (15). • Ingredients responsible for allergy to cosmetics were determined in 119 patients suffering from cosmetic-related contact dermatitis. One was allergic to hexylcinnamic aldehyde 5% (5). • 179 patients suspected of cosmetic allergy were patch tested with a series of 16 fragrance substances. 7/179 (3.9%) had a positive patch test to hexyl cinnamic aldehyde 10% (7). <p>Other information:</p> <ul style="list-style-type: none"> • Hexyl cinnamic aldehyde is a positive control substance in the OECD guideline for animal sensitization tests (48) • Hexylcinnamic aldehyde 2% is the recommended patch test concentration according to De Groot (12) 	
Summary	Two studies with one case and one study with 7 cases of contact allergy to hexyl cinnamic aldehyde <u>were</u> found among patients with eczema from cosmetic products.	

Common name	Ref n° 20
Chemical name	2-(4-tert-Butylbenzyl)propionaldehyde (Lilial) 2-(4-tert-Butylbenzyl)propionaldehyde;4-(1,1-Dimethylethyl)- α -methylbenzenepropanal; p-tert-Butyl- α -methylhydrocinnamaldehyde
Synonyms	Lilial , Lilestral
Cas. No	80-54-6
Einecs	201-289-8
Data	<p>General eczema patient population: •3/685 (0.44) consecutive, Japanese patients with eczema had an allergic reaction to lilial 10% (17).</p> <p>Subgroups of patients:</p> <ul style="list-style-type: none"> •176 patients suspect of fragrance sensitivity were patch tested with selected fragrance substances. 167 of these were tested with lilial 5% and 2 patients (1.2%) reacted with an allergic reaction (2). •179 patients suspected of cosmetic allergy were patch tested with a series of 16 fragrance substances. 5/179 (2.8%) had a positive patch test to lilial 20%. However some of these may have been false positive reactions due to the excited skin syndrome (7). <p>Case reports:</p> <ul style="list-style-type: none"> • A young man developed axillary dermatitis after using a new roll-on antiperspirant. He was patch test positive to the deodorant and the perfume from the deodorant. Fractionation and subsequent patch testing of the perfume showed that the offending allergen was lilial (49). <p>Test concentrations:</p> <ul style="list-style-type: none"> •Patch tests were performed with 0%, 2%,5% and 10% lilial in 685 patients with contact dermatitis. Only one irritant reaction was found to each concentration and 10% lilial was recommended for patch testing (17). De Groot recommends 1% lilial for patch testing (12)
Summary	Two cases of contact allergy to <u>Lilial</u> were found in a study of 176 eczema patients with cosmetic eczema and a case with contact allergy to lilial from a deodorant. More cases found but these may have been false positive.

Common name Chemical name	d-Limonene (R)- <i>p</i> -Mentha-1,8-diene	Ref n° 21
Synonyms		
Cas. no	5989-27-5	
Einecs	227-813-5	
Data	<p>General eczema patient population:</p> <ul style="list-style-type: none"> Oxidised d-limonen were tested on consecutive patients. Two batches were used one oxidised for 10 weeks and one for 20 weeks. Patients were tested in both Stockholm and Leuven. 4/153 (2.6%) and 2/216 (0.9%) were positive to the first batch of d-limonen, test concentration 3% in the two participating clinic. 8/413 (1.9%) and 14/953 (1.6%) reacted to the second batch at a 3% concentration. Many of the limonene positive cases reacted to markers of fragrance contact allergy, such as the fragrance mix, Peru balsam and colophony (50). 2/88 (2.3%) of patch tested patients reacted to oxidised limonene in 2% concentration. Probable relevance was documented in one case of a mechanic using a d-limonen hand cleanser (51) <p>Subgroups of patients:</p> <ul style="list-style-type: none"> 179 patients suspected of cosmetic allergy were patch tested with a series of 16 fragrance substances. 2/179 (1.1%) had a positive patch test to d-limonene 10%. (7). <p>Occupational setting:</p> <ul style="list-style-type: none"> 2/105 (1.9%) car mechanics were allergic to d-limonene 5% in pet at patch testing (52) <p>Other information:</p> <ul style="list-style-type: none"> d-limonene is apart from being a fragrance substance also used to degrease metal and for hand cleansing in industry. Air-oxidation of d-limonene is essential for its sensitizing effects. Some of the oxidation products of d-limonene has been demonstrated to be potent sensitizers in animal assays (53). IFRA-guideline recommends that d-limonene and natural products containing substantial amount of it, should only be used when the level of peroxides is kept to the lowest practical level, for instance by adding antioxidants at the time of production (IFRA guideline, dec 95). The addition of the antioxidant butylated hydroxytoluene (BTH) prevent autoxidation of d-limonene for periods depending on the purity of d-limonene and room temperature (54). d-Limonene is classified, labelled and warned as a sensitizer under the EU Dangerous Substances and Preparations Directive due to its ability to form allergenic oxidation products. 	
Summary	Oxidisation products of d-limonene are strong allergens. A number of cases of contact allergy from occupational exposures to d-limonene is reported. The frequency of contact allergy to oxidised limonene is 1-2% in consecutive eczema patients. The relationship between contact allergy to oxidised d-limonene and fragrances in cosmetic products need to be further examined.	

Common name Chemical name	Linalool (INCI) Linalool	Ref n° 22
Synonyms		
Cas. no	78-70-6	
Einecs	201-134-4	
Data	<p>Subgroups of patients:</p> <ul style="list-style-type: none"> • 75 patients with contact allergy to cosmetic products were identified among 1781 patients tested . 3 patients gave an allergic reaction to Linalool, which was present in a shampoo, hair lotion and a shaving foam (42). • The causative ingredients were identified in 119 patients with contact allergy to cosmetic products. One patient was allergic to linalool, patch tested in 10% in pet. (5). <p>Case-reports:</p> <ul style="list-style-type: none"> • A 52 year old man developed contact allergy to his after-shave. Linalool and hydroxycitronallal present in the after-shave was determined as the causative ingredient by patch testing (55). <p>Test concentrations:</p> <p>Linalool 30% may be used for patch testing according to De Groot (12)</p>	
Summary	One study with one case and one study with 3 cases of contact allergy to linalool <u>were</u> found among patients with eczema from cosmetic products.	

Common name Chemical name	Methyl heptine carbonate Methyl oct-2-ynoate	Ref n° 23
Synonyms		
Cas. no	111-12-6	
Einecs	203-836-6	
Data	<p>Subgroups of patients:</p> <ul style="list-style-type: none"> • 182 patients suspected of contact allergy to cosmetics were patch tested with a series of 22 fragrance substances. 2 patients (1.1%) had a positive patch test to methylheptine carbonate 0.5%. The test concentration was based on a pilot study where 1/34 patients with contact dermatitis to cosmetics had a positive reaction to 0.5% methyl heptine carbonate (18). Methylheptine carbonate was detected in 3/79 cosmetic products brought in by the patients (18). • 278 patients were tested by the North American Contact Dermatitis Research Group with methylheptine carbonate 1%, as part of a screening series for fragrance contact sensitivity. 1/278 (0.4%) reacted (30). <p>Occupational setting:</p> <ul style="list-style-type: none"> • 4 bakers with hand eczema were patch tested with fragrances/flavours. One reacted with a one plus reaction to methyl heptine carbonate 0.5% in pet. Relevance unknown (32). <p>Case-reports:</p> <ul style="list-style-type: none"> • A 19 year old woman developed contact dermatitis after having worked for 3 years with mixing fragrances in a fragrance laboratory. She regularly worked with methyl octine carbonate and occasionally with methyl heptine carbonate. She was positive at patch testing to each of these tested separately at 1% in pet (56). • A 32 year old barber developed hand eczema. Patch testing showed an allergic reaction to an after shave. Further patch testing with a fragrance series showed positive reactions to: Methyl heptine carbonate 0.5% pet, hydroxycitronellal 10% in pet and cinnamic alcohol 5% in pet. All three fragrance materials were shown to be present in the after shave by chemical analysis (57). <p>Other data:</p> <p>Methyl heptine carbonate is restricted to 0.01% in consumer products (IFRA guideline), due to a strong sensitizing potential. This is based on a private communication to IFRA.</p> <p>Test concentration:</p> <ul style="list-style-type: none"> • Methyl heptine carbonate 0.5% is recommended for patch testing according to De Groot (12) 	
Summary	Single cases <u>were</u> reported. Is a strong sensitizer according to IFRA.	

	Ref n° 24
Common name	3-Methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one
Chemical name	3-Methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one
Synonyms	γ -methylionone
Cas. No	127-51-5
Einecs	204-846-3
Data	<p>Subgroups of patients:</p> <ul style="list-style-type: none"> • 179 patients suspected of cosmetic allergy were patch tested with a series of 16 fragrance substances. 2/179 (1.1%) had a positive patch test to γ-methylionone 10% (7). • The causative ingredients were identified in 75 patients with contact allergy to cosmetic products. 1 patient was allergic to γ-methylionone , concentration unknown. Its presence was detected in a rouge (42). • The causative ingredients were identified in 119 patients with contact allergy to cosmetic products. 1/119 (0.8%) was allergic to γ-methylionone, patch tested in 5% in pet. (5). <p>Case-reports:</p> <ul style="list-style-type: none"> • 86 year old women developed a rash from using a cologne. Patch testing with the cologne gave a strong positive reaction. 18 components from the cologne were tested and reactions were found to ionones, one of these was γ-methylionone (58). <p>Test concentration:</p> <ul style="list-style-type: none"> • γ-Methylionone 10% in pet is recommended for patch testing according to De Groot (12).
Summary	One study with two cases and two studies of 1 case of contact allergy to γ -methylionone <u>were found</u> among patients with eczema from cosmetic products.

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