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 amyl 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	Oxidization 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 Ref n° 1 2-benzylideneheptanal
Synonyms	α-amyl cinnamic aldehyde
Cas. no	122-40-7
Einecs	204-541-5
Data	Amyl cinnamal is one of 8 constituent of the fragrance mix that is used for diagnosing contact allergy to fragrances. **General eczema patient population:** •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). **Subgroups of patients:** •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). **As part of the fragrance mix:** •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). **Test concentration**: •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 Chemical name	Amylcinnamyl alcohol Ref n° 2 2-pentyl-3-phenylprop-2-en-1-ol
Synonyms	α-amyl cinnamic alcohol
Cas. no	101-85-9
Einecs	202-982-8
Data	**Patient subgroups** • 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 deliberatly 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). **Test concentrations**: •Amyl cinnamyl alcohol 2% in pet is recommended for patch testing according to De Groot (12). Higher concetrations have been used in a number of studies (7, 15).
Summary	Five single cases reported of contact allergy to amyl cinnamyl alcohol and allergic reactions by patch testing were found in 7/179-2/20 (4-10%) of patients with contact eczema from cosmetics. Amyl cinnamyl alcohol probably cross reacts with amyl cinnamal.

Common name Chemical name	Benzyl alcohol (INCI) Ref n° 3 Benzyl alcohol
Synonyms	
Cas. No	100-51-6
Einecs	202-859-9
Data	**General eczema patient population:** •0.5% of tested patients in Japan gave a positive reaction to benzyl alcohol 5%. Number of included patients unknown (17). **Subgroups of patients:** •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 81eczema 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). **Case reports:** •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) **Other studies**: •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. **Test concentrations**: •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) Ref n° 4 Benzyl-o-hydroxybenzoate
Synonyms	
Cas. No	118-58-1
Einecs	204-262-9
Data	**General eczema patient population:** •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). **Subgroups of patients:** •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). **Test concentrations**: •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] Ref n° 5 Cinnamic alcohol
Synonyms	
Cas. no	104-54-1
Einecs	203-212-3
Data	Cinnamyl alcohol is one of 8 constituent of the fragrance mix, that is used for diagnosing contact allergy to fragrances. **General eczema patient population:** •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). **Subgroups of patients:** •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). **As part of the fragrance mix:** •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). **Other:** •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). **Test concentration**: •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.

Common name Chemical name	Cinnamal [INCI] Ref n° 6 Cinnamaldehyde; 3-phenyl-2-propenal
Synonyms	Cinnamic aldehyde
Cas. no	104-55-2
Einecs	203-213-9
Data	Cinnamal is one of 8 constituent of the fragrance mix, that is used for diagnosing contact allergy to fragrances. **General eczema patient populations:** •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). **Subgroups of patients:** •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). **As part of the fragrance mix:** •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). **Others:** •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. **Test concentrations:** 1% cinnamal is the standard concentration used in routine testing (12). Higher concentrations may give irritant reactions (23).
Summary	Cinnmal 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 Chemical name	Citral Ref n° 7 3,7-dimethyl-2,6-octadien-1-al, mix of cis and trans isomers
Cas. no	5392-40-5
Einecs	226-394-6
Data	**General eczema patient population:** •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). **Subgroups of patients:** •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). **Occupational setting:** •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). **Other data:** •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 is made on the use concentrations. **Test concentrations**: •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) Ref n° 8 1-benzopyran-2-one;cis-o-coumarinic acid lactone
Synonyms	occurs naturally in tonka beans and other plants.
Cas. no	91-64-5
Einecs	202-086-7
Data	**General eczema patient population:** •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). **Subgroups of patients:** •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). **Case reports:** •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). **Test concentrations:** •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) Ref n° 9 Eugenol
Synonyms	
Cas. no	97-53-0
Einecs	202-589-1
Data	Eugenol is one of 8 constituent of the fragrance mix, that is used for diagnosing contact allergy to fragrances. **Consecutive patients:** •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). **Subgroups of patients:** •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). **As part of the fragrance mix:** •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). **Test concentrations:** •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	Geraniol is one of 8 constituent of the fragrance mix, that is used for diagnosing contact allergy to fragrances. **Consecutive patients:** •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). **Subgroups of patients:** •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). **As part of the fragrance mix:** •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). **Test concentration**: •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	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. Geraniol has caused contact allergic reactions in 1.2-30% of patients with eczema from cosmetic products

Common name Chemical name	Hydroxycitronellal Ref n° 11 7-Hydroxycitronellal
Synonyms	Laurine
Cas. No	107-75-5
Einecs	203-518-7
D Data	Hydroxycitronellal is one of 8 constituent of the fragrance mix, which is used for diagnosing contact allergy to fragrances. **General eczema patients population:** •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). **Subgroups of patients:** •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). **As part of the Fragrance mix:** •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). **Others:** •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 voluenteers (38). **Test concentration**: •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 voluenteers 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 Ref n° 12 4-(4-Hydroxy-4-methylpentyl)cyclohex-3-enecarbaldehyde
Synonyms	Lyral
Cas. No	31906-04-4
Einecs	250-863-4
Data	**General eczema patient population:** •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). **Subgroups of patients**: • 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). **Case-reports:** • 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). **Test concentration**: •Lyral 10% in pet has ben 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 were relevant. In addition three relevant cases of contact allergy to Lyral from cosmetic products are established.

Common name Chemical name	Isoeugenol Ref n° 13 Isoeugenol
Synonyms	
Cas. No	97-54-1
Einecs	202-590-7
Data	Isoeugenol is one of 8 constituent of the fragrance mix, that is used for diagnosing contact allergy to fragrances. **General eczema patients population:** •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). **Subgroups of patients:** •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 isoeugenol 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). **As part of the fragrance mix:** •In an European multicentre study involving 6 countries, 78 patients positive to one or the other of two different fragrance mixes, both containing isoeugenol, were tested with the individual constituents of the mixes. 16/78 (20,5%) were positive to isoeugenol 2%, which was the most frequent allergen (8). •The frequency of contact allergy to isoeugenol 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). **Others:** •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). **Test concentrations**: •1% isoeugenol is the standard concentration used in routine testing , however 2% have been used for a number of years (12). In a study 5% isoeugenol 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 Chemical name	Anisyl alcohol Ref n° 14 4-methoxybenzyl alcohol
Synonyms	
Cas. No	105-13-5
Einecs	203-273-6
Data	**Subgroups of patients** •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). **Test concentration**: • 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%).

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Common name Chemical name	Benzyl benzoate (INCI) Ref n° 15 Benzyl benzoate
Synonyms	
Cas. no	120-51-4
Einecs	204-402-9
Data	**Consecutive patients:** •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). **Subgroups of patients:** •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). **Other studies:** •Occurs in fairly large amounts in a number of blossom concretes and absolutes as tuberose and hyacinth (45). **Test concentrations**: •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) Ref n° 16 Benzyl 3-phenyl-2-propenoate
Synonyms	Cinnamein
Cas. No	103-41-3
Einecs	203-109-3
Data	**Subgroups of patients:** •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). **Test concentrations:** •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) Ref n° 17 3,7-Dimethyl-6-octenol
Synonyms	
Cas. no	106-22-9
Einecs	203-375-0
Data	**General eczema patient population:** • 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) **Subgroups of patients:** • 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). **Test concentrations**: •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 Chemical name	Farnesol (INCI) Ref n° 18 3,7,11 trimethyldodeca-2,6,10 trienol
Synonyms	
Cas. no	4602-84-0
Einecs	225-004-1
Data	**General eczema patients population:** • 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). **Subgroups of patients:** •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 were found. 6 of the 8 also reacted to the balsam of Peru (47). **Case Reports:** • 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). **Other:** •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. **Test concentrations**: •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 Ref n° 19 α-hexyl cinnamaldehyde
Synonyms	
Cas. No	101-86-0
Einecs	202-983-3
Data	**Subgroups of patients:** •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). **Other information**: • Hexyl cinnamic aldehyde is a positive control substance in the OECD guideline for animal sensitization tests (48) **Test concentration**: •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 were found among patients with eczema from cosmetic products.

	Ref n° 20
Common name Chemical name	2-(4-tert-Butylbenzyl)propionaldehyde (Lilial) 2-(4-tert-Butylbenzyl)propionaldehyde;4-(1,1-Dimethylethyl)-a-methylbenzenepropanal; p-tert-Butyl-a-methylhydrocinnamaldehyde
Synonyms	Lilial , Lilestral
Cas. No	80-54-6
Einecs	201-289-8
Data	**General eczema patient population:** •3/685 (0.44) consecutive, Japanese patients with eczema had an allergic reaction to lilial 10% (17). **Subgroups of patients:** •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). **Case reports:** • 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). **Test concentrations:** •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 Lilial 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 Ref n° 21 (R)-*p*-Mentha-1,8-diene
Synonyms	
Cas. no	5989-27-5
Einecs	227-813-5
Data	**General eczema patient population**: • 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) **Subgroups of patients:** •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). **Occupational setting**: •2/105 (1.9%) car mechanics were allergic to d-limonene 5% in pet at patch testing (52) **Other information:** • 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 autooxidation 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 oxidisation 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) Ref n° 22 Linalool
Synonyms	
Cas. no	78-70-6
Einecs	201-134-4
Data	**Subgroups of patients:** • 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). **Case-reports:** • 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). **Test concentrations:** Linalool 30% may be used for patch testing according to De Groot (12)
Summary	One study with one case and one study with 3 cases of contact allergy to linalool were found among patients with eczema from cosmetic products.

Common name Chemical name	Methyl heptine carbonate Ref n° 23 Methyl oct-2-ynoate
Synonyms	
Cas. no	111-12-6
Einecs	203-836-6
Data	**Subgroups of patients:** •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 were 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). **Occupational setting:** • 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). **Case-reports:** •A 19 year old women 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). **Other data:** 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. **Test concentration:** •Methyl heptine carbonate 0.5% is recommended for patch testing according to De Groot (12)
Summary	Single cases were reported. Is a strong sensitizer according to IFRA.

Common name Chemical name	Ref n° 24 3-Methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one 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	**Subgroups of patients:** •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). **Case-reports:** • 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). **Test concentration**: • 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 were found among patients with eczema from cosmetic products.