

Categorization of fragrance contact allergens for prioritization of preventive measures: clinical and experimental data and consideration of structure–activity relationships*

Wolfgang Uter^{1,†}, Jeanne D. Johansen^{2,†}, Anna Börje³, Ann-Therese Karlberg³, Carola Lidén⁴, Suresh Rastogi⁵, David Roberts⁶ and Ian R. White⁷

¹Department of Medical Informatics, Biometry and Epidemiology, University of Erlangen/Nürnberg, 91054 Erlangen Germany, ²Department of Dermato-Allergology, National Allergy Research Centre, Gentofte Hospital, University of Copenhagen, 2900 Hellerup, Denmark, ³Department of Chemistry and Molecular Biology, University of Gothenburg, 41137 Gothenburg, Sweden, ⁴Institute of Environmental Medicine, Karolinska Institutet, 17177 Stockholm, Sweden, ⁵Member of the SCCS, Copenhagen, Denmark, ⁶Liverpool John Moores University, Liverpool, Merseyside L3 5UZ, UK, and ⁷Department of Cutaneous Allergy, St John's Institute of Dermatology, St Thomas' Hospital, London SE1 7EH, UK

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Summary

Contact allergy to fragrances is still relatively common, affecting ~16% of patients patch tested for suspected allergic contact dermatitis, considering all current screening allergens. The objective of the review is to systematically retrieve, evaluate and classify evidence on contact allergy to fragrances, in order to arrive at recommendations for targeting of primary and secondary prevention. Besides published evidence on contact allergy in humans, animal data (local lymph node assay), annual use volumes and structure–activity relationships (SARs) were considered for an algorithmic categorization of substances as contact allergens. A total of 54 individual chemicals and 28 natural extracts (essential oils) can be categorized as established contact allergens in humans, including all 26 substances previously identified as contact allergens (SCCNFP/0017/98). Twelve of the 54 individual chemicals are considered to be of special concern, owing to the high absolute number of reported cases of contact allergy (> 100). Additionally, 18 single substances and one natural mixture are categorized as established contact allergens in animals. SARs, combined with limited human evidence, contributed to the categorization of a further 26 substances as likely contact allergens. In conclusion, the presence of 127 single fragrance substances and natural mixtures should, owing to their skin sensitizing properties, be disclosed, for example on the label. As an additional preventive measure, the maximum use concentration of 11 substances of special concern should be limited to 100 ppm. The substance hydroxyisohexyl 3-cyclohexene carboxaldehyde and the two ingredients chloroatranol and atranol in the natural extracts *Evernia prunastri* and *Evernia furfuracea* should not be present in cosmetic products.

Key words: Directive 76/768/ECC; fragrance allergens; labelling; SCCS; scientific opinion.

Correspondence: Wolfgang Uter, Department of Medical Informatics, Biometry and Epidemiology, University of Erlangen/Nürnberg, Erlangen, Germany. Tel: +49 9131 8522750; Fax: +49 9131 8522721. E-mail: wolfgang.uter@imbe.med.uni-erlangen.de

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[†]Shared first authorship.

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Fragrance substances are organic compounds with characteristic, usually pleasant, odours. They are ubiquitously used in perfumes and other perfumed cosmetic products, but also in detergents, fabric softeners, and other household products. Fragrance substances are also used in aromatherapy, and may be present in herbal products, and used as topical medicaments for their antiseptic properties, or for their scent.

Allergic contact dermatitis resulting from fragrance ingredients is most often caused by cosmetic products, and usually involves the face and/or hands. It may affect fitness for work and the quality of life of the individual. Thus, prevention of contact sensitization to fragrances is an important objective of public health risk management measures.

Ingredient information is the basis of prevention of allergic contact dermatitis, as knowledge about the allergens to which a patient has been exposed is crucial for including the right substances in the patch test, and for subsequent information on avoidance of re-exposure. Originally, the labelling rules in the Cosmetics Directive 76/768/EEC stipulated that perfume and aromatic compositions and their raw materials should be referred to by the word 'perfume' or 'aroma', rather than being labelled individually. This was changed following an opinion from the Scientific Committee on Non-Food Products intended for Consumers (SCCNFP) of the European Commission in 1999 (1), whereby 26 fragrance allergens were identified for which information should be provided to consumers concerning their presence in cosmetic products. This was implemented in the Cosmetics Directive in 2005, and has been shown to be important in the clinical management of patients who are allergic to fragrances.

However, much new evidence concerning fragrance allergy has been published since the 1999 opinion. Therefore, the list of recognized fragrance allergens of which the consumer needs to be made aware was again reviewed by the Scientific Committee on Consumer Safety of the European Commission (SCCS), taking into account clinical (human) and animal data, as well as aspects of the reaction chemistry of the molecules concerned. The present article presents the results of this systematic process, aiming at identifying those substances and natural mixtures that the consumer needs to be made aware of. Furthermore, those allergens causing a considerable number of cases of sensitization, for which a limitation of use concentrations is advisable, were identified. Subsequent reviews will focus on (i) exposure, dose–response relationships, and derivation of a 'safe threshold', and (ii) (bio-)activation of fragrance substances into (stronger) sensitizers.

Clinical Aspects of Contact Allergy to Fragrance Ingredients

Spectrum of reactions

Adverse reactions to fragrances in perfumes and in fragranced cosmetic products include allergic contact dermatitis, irritant contact dermatitis, photosensitivity, immediate contact reactions (contact urticaria), and pigmented contact dermatitis. Airborne and connubial contact dermatitis occur. The present review focuses not only on allergic contact dermatitis, but also on contact allergy (sensitization) to fragrance substances as a precondition of allergic contact dermatitis.

Perfumes and deodorants are the most frequent sources of sensitization to and allergic contact dermatitis caused by fragrance ingredients in women, whereas aftershave products and deodorants are most often responsible in men (2). Thereafter, eczema may appear or be worsened by contact with other fragranced products, such as cosmetics, toiletries, household products, industrial substances, and flavourings. Different anatomical sites of contact dermatitis observed in fragrance-allergic patients reflect the above exposures. Fragrance allergy may be a relevant problem in patients with hand eczema, as perfumes are present in consumer or occupationally used products to which their hands are exposed (3–5). The most common contact allergies in patients with hand eczema are those to metals, Fragrance Mix I (FM I), *Myroxylon pereirae*, and colophonium (6). Bilateral axillary dermatitis may be caused by perfume in deodorants and, if the reaction has been severe, it may spread down the arms and to other areas of the body (7). In individuals who consulted a dermatologist, a history of such first-time symptoms was significantly related to the later diagnosis of perfume allergy (8). Facial eczema is an important manifestation of fragrance allergy resulting from the use of cosmetic products (9). In men, aftershave products can cause an eczematous eruption of the beard area and the adjacent part of the neck (7), and men who wet shave rather than dry shave have been shown to have an approximately three-fold increased risk of being fragrance-allergic (10).

Many more people complain about intolerance to or rashes caused by perfumes or perfumed products than are shown to be allergic by testing (8). This may be attributable to irritant effects or inadequate diagnostic procedures. Moreover, fragrances may cause dose-related contact urticaria of the non-immunological type (irritant contact urticaria). Cinnamal, cinnamic alcohol and *M. pereirae* are well-recognized causes of contact urticaria, but other substances, including menthol, vanillin, and benzaldehyde, have also been reported (11). The reactions

to *M. pereirae* may be attributable to cinnamates (12). A relationship with delayed contact hypersensitivity was suggested (13), but no significant difference was found between a fragrance-allergic group and a control group in the frequency of immediate reactions to fragrance ingredients (11), in keeping with a non-immunological basis for the reactions seen.

Clinical epidemiology of fragrance allergy

A fragrance formula may consist of up to 300, or even more, different ingredients. The CosIng database, which is an indicative, but not exhaustive, list of cosmetics ingredients, lists > 2500 ingredients used for perfuming or as odour 'masking' agents [http://ec.europa.eu/consumers/cosmetics/cosing/ (last accessed 1 October 2012)]. A mixture of seven fragrance chemicals and one natural extract, which have been identified as major fragrance allergens in the past (14), has been used for several decades for diagnosing contact allergy to fragrance ingredients: amyl cinnamal (α -amyl cinnamal), cinnamyl alcohol (cinnamic alcohol), cinnamal (cinnamic aldehyde), eugenol, geraniol, hydroxycitronellal, isoeugenol, oak moss absolute (a natural extract; INCI *Evernia prunastri*) (all at 1% in petrolatum). This mixture, which also includes sorbitan sesquioleate (5%) as emulsifier, is called FM I, and is included in the baseline patch test series containing the most common allergens in Europe (Table 1).

However, additional fragrance ingredients were found to be contact allergens. Thus, FM I was deemed to be not sufficient for the diagnosis of fragrance allergy. Subsequently, Fragrance Mix II (FM II) was devised to supplement FM I in a European multicentre study (15, 16). Since then, FM II has been included in the European baseline series, containing citronellol (0.5%), citral (1%), coumarin (2.5%), hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC) (2.5%), farnesol (2.5%), and α -hexylcinnamal (5% in pet.) (Table 2). In addition to being tested in FM II, HICC is also tested separately at a 5% test concentration in the baseline series (17).

For a number of reasons, the bulk of evidence regarding the frequency of contact allergy to these and other fragrance substances and mixes relies on clinical data, that is, the history, clinical presentation and test results of patients patch tested for suspected allergic contact dermatitis – in general, and not specifically caused by fragrance ingredients. The frequency of contact allergy to fragrance ingredients (or other contact allergies, for that matter) cannot be related to the population directly, as it is derived from a subgroup selected for specific morbidity. Nevertheless, these data can be examined epidemiologically, with the use, if necessary, of suitable adjustment for potentially confounding factors such as age or sex (18).

A distinction must be made between patch testing 'consecutive' patients, that is, all patients who are patch tested for suspected contact sensitization, and 'aimed'

Table 1. European results with Fragrance Mix I published since 1999

Country (reference)	Population	Years	No. tested	Crude % positive (95% CI)
Sweden (19)	Consecutive patients	1999–2001	3790	6.9 (6.1–7.8)
Hungary (20)	Consecutive patients	1998–1999	3604	8.2 (7.3–9.1)*
Czech Republic (21)	Consecutive patients	1997–2001	12 058	5.8 (5.4–6.2)*
Ljubljana, Slovenia (22)	Consecutive patients	1989–1998	6129	5.9 (5.3–6.5)*
Germany (23)	Consecutive IVDK patients	1996–2002	59 298	11.3 (11.0–11.5)*
Germany (24)	Consecutive IVDK patients	2005–2008	36 961	7.3 (7.0–7.6)*
Vienna, Austria (9)	Consecutive patients of one clinic	1997–2000	2660	9.1 (8.1–10.3)*
Groningen, The Netherlands (25)	Patients (fragrance allergy suspected)	April 2005 to June 2007	295	5.8 (3.4–9.1)*
The Netherlands (26)	Consecutive patients	September 1998 to April 1999	1825	10.6 (9.2–12.1)
The Netherlands (27)	Patients (cosmetic allergy suspected)	1994–1998	757	14.8 (12.3–17.5)*
Leuven, Belgium (28)	Consecutive patients	1990–2005	10 128	9.1 (8.6–9.7)*
Coimbra, Portugal (29)	Consecutive patients	July 1989 to June 1999	2600	10.9 (9.7–12.2)*
Spain (30)	Consecutive patients	October 2005 to June 2008	1253	4.5 (3.4–5.8)*
Sheffield, United Kingdom (31)	Consecutive patients	1994–1995	744	11.4 (9.2–13.9)*
St John's, London, United Kingdom (32)	Consecutive patients	1980–2004	34 072	(7.4–8.0)*
Copenhagen, Denmark (33)	Consecutive patients	1985–2007	16 173	7.2 (6.8–7.6)*

CI, confidence interval; IVDK, Information Network of Departments of Dermatology.

*If not given in the publication, the CI was calculated from the absolute numbers where possible.

Table 2. European results with Fragrance Mix II, conceived by a study published in 2005 (15)

Country (reference)	Population	Years	No. tested	Crude % positive (95% CI)
EU (15)	Six clinical departments	October 2002 to June 2003	1701	2.9 (2.2–3.9)*
IVDK, Germany (39)	Consecutive patients	January 2005 to December 2008	35 633	4.9 (4.7–5.1)*
Groningen, The Netherlands (25)	Patients (fragrance allergy suspected)	April 2005 to June 2007	227	9.3 (5.8–13.8)*
Leuven, Belgium (28)	Consecutive patients	2005 only	335	2.1 (0.8–4.3)*
Spain (30)	Consecutive patients	October 2005 to June 2008	1253	0.6 (0.2–1.1)*
Denmark (40) on behalf of the DCDG, 2010	Consecutive patients	2005–2008	12 302	4.5 (4.1–4.9)*

CI, confidence interval; DCDG, Danish Contact Dermatitis Group; IVDK, Information Network of Departments of Dermatology.

*If not given in the publication, the confidence interval (CI) was calculated from the absolute numbers.

patch testing, that is, application of allergens only in the subset of patients in whom exposure to the particular allergens of the applied 'special series' is suspected. For any given allergen, the latter 'aimed' approach will usually yield higher sensitization prevalences than the testing of not-further-selected 'consecutive' patients. Thus, information on the inclusion of an allergen either in a baseline series (tested in almost all patients) or in a special series (applied in an aimed fashion) must be considered, and is given in the following tables, where available in the cited references.

Notwithstanding the potential pitfalls of clinical data in terms of selection bias, they have proven useful in identifying emerging trends or persisting problems, and also in evaluating the effect of preventive action – regarding either the entire population or subgroups thereof, such as certain occupations.

FM I ('Larsen mix'). Regarding a time trend of sensitization to FM I, a significant increase in positive reactions to FM I until 1998 and a significant drop thereafter was noted in the Information Network of Departments of Dermatology (IVDK) study covering 1996–2002 (23). A similar drop from 1999 to 2007 has been observed in female, but not male, patients from Copenhagen (33). In accordance with these findings, the prevalence of positive reactions to FM I approximately doubled from 1989–1993 to 1994–1998 in Ljubljana, Slovenia (22).

Within Europe, a comparison between different countries and clinical departments is possible. A European Environmental and Contact Dermatitis Research Group study covering 1996–2000 found 9.7% positive reactions to FM I (range: 5.0–12.6%) in 10 departments from seven European countries (34). A different European study, covering October 1997 to October 1998, found 11.3% [95% confidence interval (CI) 9.9–12.9%] positive reactions to FM I in 1855 patients; the variation between centres was marked (35). In the first study of the European Surveillance System on Contact Allergies (ESSCA),

covering 2002 and 2003, 9663 patients were patch tested with FM I, overall yielding 7.1% positive reactions, with marked variation between participating departments. In Dortmund, Germany, the minimum frequency, namely 3.7% was found, whereas in Lahti, Finland, the highest prevalence, namely 10.4%, was found (36). Subsequently, in the year 2004, the overall prevalence was 7.6%; that is, it was largely unchanged (37). In a more recent study by the ESSCA, based on 2005–2006 patch test data across Europe, significant differences were again noted, this time on the aggregated level of European regions, with FM I sensitization being least frequent in the southern countries (4.8%, 95% CI 3.9–5.5%) (age-standardized and sex-standardized prevalence) versus 7.7% (95% CI 7.0–8.4%) in the central European departments, with the Finnish, Polish and Lithuanian departments (5.7%, 95% CI: 4.6–6.8%) and the UK network (6.8%, 95% CI 6.3–7.3%) being in an intermediate position (38).

Fragrance Mix II. Results obtained with this recent addition to the baseline series are shown in Table 2.

Hydroxyisohexyl 3-cyclohexene carboxaldehyde. HICC (known, for example, as Lyrall[®]) was the most frequently reported chemical causing fragrance allergy in the last decade. In total, reports of ~1500 cases have been published in the scientific literature (see below). HICC was recognized as an allergen in 1994 in a case report on dermatitis caused by a deodorant (41), and its significance was confirmed by a subsequent multicentre study (42); it was later included in the new perfume mixture, FM II (43), which is routinely used for the diagnosis of perfume allergy (see above). Furthermore, separate testing with HICC is recommended, because it is a very frequent allergen (17), and detects relevant fragrance sensitization that would otherwise have been missed (30). In the studies performed in European dermatology clinics, 0.5–2.7% of

eczema patients have been found to be allergic to HICC, with the highest frequency in central Europe (38). For further details, see Table 3.

M. pereirae (balsam of Peru). *M. pereirae* is a balm obtained from a Central American tree. It is used as a screening substance for fragrance allergy in Europe and other geographical areas. Although the crude balm is not used in Europe in cosmetics, extracts and distillates thereof are used (47). This natural mixture has been employed as a screening agent in the baseline series for many decades. Hence, a wealth of data is available; Table 4 summarizes results from the past 10 years.

Oil of turpentine. This natural extract, which is a high-volume fragrance raw material [International Fragrance Association (IFRA), pers. comm. 2010], is not tested in all baseline series. It is considered to be a minor screening material for fragrance contact allergy. Table 5 summarizes results from the past 10 years for patch testing of consecutive patients.

An 'overall burden' of fragrance contact allergy, in terms of the prevalence of contact allergy to at least one of the up to five screening allergens present in the baseline series (FM I, FM II, HICC, *M. pereirae*, and oil of turpentine), has not been given in the published studies. A re-analysis

of data from the two published studies of the IVDK (24, 39), covering central Europe from 2005 to 2008 (Germany, Austria, and Switzerland), yielded an estimate of such an overall prevalence of 16.2% (95% CI 15.8–16.6%) (IVDK technical report, 18 November 2011).

Population-based epidemiology

In principle, the examination of a representative sample of the population is the most valid approach for estimating disease frequency, as there is no systematic selection process. However, in practice, participation of much less than 70% of those approached introduces the possibility of self-selection and thus of biased morbidity (or risk) estimates. Moreover, the resources needed prohibit regular, for example yearly, patch test studies in a sample of several thousand persons. For these reasons, few studies exist (Tables 6 and 7).

In 1990, 1998, and 2006, samples of the Danish adult population living in the Copenhagen area were patch tested with the European baseline series. In total, 4299 individuals aged 18–69 years (18–41 years only in 1998) completed a pre-mailed questionnaire, and were patch tested with FM I and *M. pereirae* (56, 58, 59) (Table 6). When the age group of 18–41 years was analysed, the prevalence of FM I sensitization followed

Table 3. European results with hydroxyisohexyl 3-cyclohexene carboxaldehyde (5% pet. if not stated otherwise) in consecutive patients

Country (reference)	Years	No. tested	Crude % positive (95% CI)
Lithuania (44)	April 2006 to October 2008	816	0.9 (0.3–1.8)*
Spain (30)	October 2005 to June 2008	852	0.8 (0.3–1.7)*
Germany (CH, AT) (45)	March 2000 to February 2001	3245	1.9 (1.5–2.4)*
Germany (CH, AT) (46)	January 2003 to December 2004	21 325	2.4 (2.2–2.6)*
Germany (CH, AT) (39)	January 2005 to December 2008	35 582	2.3 (2.2–2.5)*
Belgium (28)	2002–2005	2901	2.1 (1.6–2.7)*
Denmark (40)	2005–2008	12 302	2.4 (2.1–2.7)*

*If not given in the publication, the CI was calculated from the absolute numbers.

CI, confidence interval; AT, Austria; CH, Switzerland.

Table 4. European results with *Myroxylon pereirae* resin (balsam of Peru) (25% pet.) in consecutive patients

Country (reference)	Years	No. tested	Crude % positive (95% CI)*
Seville, Spain (48)	2002–2004	863	5.8 (4.3–7.6)
Ankara, Turkey (49)	1992–2004	1038	2.1 (1.3–3.2)*
Vienna, Austria (9)	1997–2000	2660	5.4 (4.6–6.3)*
Czech Republic (21)	1997–2001	12 058	7.3 (6.8–7.8)*
Spain (30)	October 2005 to June 2008	1253	6.4 (5.1–7.9)*
Copenhagen, Denmark (33)	1985–2007	16 173	3.9 (3.6–4.2)*
Sweden (19)	2000	3790	6.5
Nine European countries (36)	2002–2003	9672	6.1
Germany, three Swiss departments and one Austrian department (24)	2005–2008	36 919	8.0 (7.7–8.3)
Ten departments in seven EU countries (34)	1996–2000	26 210	6.0

CI, confidence interval.

*If not given in the publication, the CI was calculated from the absolute numbers where possible.

Table 5. European results with oil of turpentine (10% pet.)

Country (reference)	Population	Years	No. tested	Crude % positive (95% CI)*
Lisbon, Portugal (50); almost no δ^3 -carene	Consecutive patients	1979–1983	4316	2.3 (1.9–2.8)*
Birmingham, United Kingdom (51)	Potters with occupational hand dermatitis	6 months; prior to 1996	24	14/24 positive to 'Indonesian turpentine'
Austria/Germany (IVDK) (52)	Consecutive patients	1992–1995	27 658	0.47 (0.39–0.55)*
Austria/Germany (IVDK) (23)	Consecutive patients	1996–2002	59 478	Annual prevalence 1.6–4.4%
Augsburg, Germany (53)	Population sample	1998	1141	1.2 (at the population level)
Europe (ESSCA) (36)	Consecutive patients	2002/2003	3767	1.6
Austria/Germany/Switzerland (IVDK) (24)	Consecutive patients	2005–2008	37 163	1.8

CI, confidence interval; ESSCA, European Surveillance System on Contact Allergies; IVDK, Information Network of Departments of Dermatology.

*If not given in the publication, the CI was calculated from the absolute numbers where possible.

Table 6. European results from patch testing with Fragrance Mix I in different population-based groups

Country (reference)	Population	Years	No. tested	% positive (95% CI)
Italy (54)	Females without eczema	Not given	619	1.3 (0.6–2.5)*
Italy (55)	Male recruits	Not given	593	0.5 (0.1–1.5)*
Denmark (56)	Population sample adults, aged 15–69 years	1990–1991	567	1.1 (0.3–2.3)
Denmark (57)	Schoolchildren aged 12–16 years	1995–1996	1146	1.8 (1.1–2.8)*
Denmark (56, 58)	Population sample adults, aged 15–41 years	January to November 1998	469	2.3 (1.2–4.2)
Denmark (59)	Population sample adults, aged 18–69 years	June 2006 to May 2008	3460	1.6 (1.2–2.1)*
Norway (60)	Population sample adults, aged 18–69 years (results reported in 2007)	1994 (61)	1236	1.8 (1.1–2.7)*
Germany (53)	Subgroup of MONICA sample, aged 25–74 years	1994–1995	1141	11.4
Sweden (62)	Population sample adults, aged 20–65 years, reporting hand eczema	1983–1984	1087	5.8 [†] (4.6–7.3)*

CI, confidence interval.

*If not given in the publication, the CI was calculated from the absolute numbers where possible.

[†]Testing performed with Fragrance Mix I, containing 16% allergens; the currently used Fragrance Mix I contains 8% allergens (see above).

Table 7. Results from patch testing with *Myroxylon pereirae* in different population-based groups

Country (reference)	Population	Years	No. tested	% positive (95% CI)*
Germany (53)	Subgroup of MONICA sample, aged 25–74 years	1994–1995	1141	2.4
Denmark (56, 59)	Population sample, aged 18–69 years	1990	567	1.1 (0.3–2.3)
		2006	3460	0.1 (0–0.3)*

CI, confidence interval.

*If not given in the publication, the CI was calculated from the absolute numbers.

M. pereirae is a balm obtained from a Central American tree. It is used as a screening material for fragrance allergy in Europe and other geographical areas. Although the crude balm is not used in Europe in cosmetics, extracts and distillates are used (47).

an inverted V-pattern among women, that is, an increase from 0.7% in 1990 to 3.9% in 1998, followed by a decrease to 2.3% in 2006. The participation rate varied in the three samples from 71.5% in 1990, to 52.4% in 1998, and to 43.7% in 2006 (56, 58, 59).

Contact sensitization to FM I is strongly age-related, with the relative risk more than doubling in the older age groups, as compared with younger patch tested patients. This has been found in both bivariate (63) and

adjusted multifactorial analyses (64). Hence, in older samples of the population, the prevalence of contact allergy to fragrance ingredients in general, and to FM I in particular, can be expected to be higher than in younger samples. The strikingly high prevalence observed in the MONICA/KORA allergy study in Augsburg, Germany may be explained by this (Table 6) (53), together with some residual confounding from the rather complex sampling process.

Available epidemiological studies have hitherto not addressed the important aspect of the risk associated with certain mutations relevant for the integrity of the skin barrier or metabolic activation of allergens. For instance, up to 10% of the European population carry mutations that impair the skin barrier and that possibly increase the risk of fragrance allergy.

Clinical relevance, socioeconomic impact, and prevention

The previous sections have addressed clinical aspects and the distribution of contact allergy to fragrances in different settings. However, contact allergy, as diagnosed by patch testing, is a latent stage, and additional information is needed to describe the significance of this condition for a patient. Clinical relevance is such a concept: a reaction is deemed to be relevant if contact allergy to the substance is associated with previous or current episodes of allergic contact dermatitis. Thereby, the evaluation of clinical relevance links past exposure to morbidity. For the evaluation of relevance, past or recent exposure(s) to the allergen need to be identified in the patient's history. The success of this process generally depends on:

- the patient's understanding and awareness;
- the dermatologist's knowledge concerning exposures;
- ingredient labelling; and
- information about the actual chemical composition of the implicated product.

As these requirements may be met to varying extents, the validity of relevance information as reported in clinical studies may also be variable. However, information on clinical relevance is important, in principle, because the proportion of currently relevant sensitizations reflects the amount of current exposure and the resulting disease state, which may increase or decrease with time. In this way, current relevance also reflects the direct burden of a fragrance contact allergy to the individual and indirectly to society. Further important aspects of the evaluation of clinical relevance as a final step of patch testing have been discussed (65–68).

It should be noted that statements on clinical relevance refer to the past history of a patient. This implies that a lack of, or unknown, clinical relevance does not make future allergen avoidance unnecessary.

In the context of contact allergy to fragrance ingredients, several concepts of relevance have been used, for example:

- a history of intolerance to perfume or to perfumed products;

- a history of intolerance to perfume actually containing the allergen diagnosed;
- detection of the culprit allergen in a perfume previously used.

In case reports or small series, the clinical relevance of positive patch test reactions is usually well established and presented in detail. Moreover, a few large-scale clinical studies on contact allergy to fragrance ingredients have reported results on clinical relevance, which will be presented and discussed in this section. The studies can be subdivided into those that focus on medical history, patch testing with consumer products, or detection of specific allergens in consumer products used by patients.

Clinical relevance according to medical history

A series of studies conducted in the 1990s showed that most individuals with contact allergy to fragrance ingredients were aware that they could not tolerate fragranced products on their skin, and were able to specifically name product categories that initiated their disease (8). In this context, colognes, deodorants and lotions were named significantly more often by fragrance-allergic dermatitis patients than by patients without fragrance contact allergy (1, 2). Important current studies are outlined below.

The definition of 'present' clinical relevance in a North American network study from 2009 (69) required:

- a positive use or patch test result with the suspected item(s) for 'definite' relevance; and
- verification of the presence of the allergen in known skin contactants, and consistent clinical presentation for 'probable' relevance.

If these conditions were not met, but skin contact with items generally containing the item was likely, 'possible' was used. Regarding fragrance allergens, the proportions were as described in Table 8.

In a multicentre study from 2002, 1855 consecutive patients were patch tested with FM I and a series of a further 14 fragrance chemicals (35). Prior to the test, the history of adverse reactions to fragrances was classified as 'certain' (6.6%), 'probable' (8.0%), 'questionable' (9.2%), or 'none' (76.1%) (43).

A series of 18 essential oils or components thereof, together with FM I, was assessed in 1606 consecutive patients (70). As in the above study, the proportions of patients with a 'certain' or 'probable' history (or otherwise) and positive reactions to either FM I or the special series, or both, were cross-tabulated. It is of note that 53.7% of patients with positive reactions to FM I only had no history. Similarly, 54.2% of patients with

Table 8. Extract from [(69) Table 3] regarding the proportion of patients with 'present clinical relevance' (see text) and 'past clinical relevance' (criteria not given)

Fragrance allergen	n tested	% positive	Current relevance (%)			Past relevance (%)
			Definite	Probable	Possible	
<i>Myroxylon pereirae</i>	4449	11.9	1.3	33	53	2.7
Fragrance Mix I	4439	11.5	2.0	29.4	54.3	4.3
Cinnamal	4435	3.1	1.5	33.8	50	2.9
Ylang-Ylang oil	4434	1.5	4.6	10.8	73.8	1.5
Jasmine absolute	4447	1.1	0	24.5	67.3	6.1

positive reactions to only one of the essential oils had no history. However, in cases of reactivity to both FM I and one of the essential oils, the proportion of patients with no history was only 36.5%.

In a multicentre study from 2005, the diagnostic properties of FM I and the new FM II were evaluated in 1701 consecutive patients patch tested in six European centres (15). Contrasting a 'certain' history (found in 8.7% of patients) with 'no history' (75.3% of patients), the sensitivity of FM I was 25.2%, and the positive predictive value was 45.1%. In comparison, the sensitivity of FM II at 14% was 13.5% and the positive predictive value was 55.6%. The combination of the two mixes was important, as more patients with a 'certain' history, but also independently of history, reacted to just one of the mixes rather than to both.

Among 12 302 consecutive patients patch tested in seven Danish dermatology clinics and three university hospitals, 10.6% were positive to one or more of the fragrance allergy markers (FM I, FM II, *M. pereirae*, or HICC) (40). Clinical relevance covered current and/or past relevance based on: (i) medical history; (ii) results of patch and/or use tests; (iii) ingredient labelling; or (iv) chemical analysis. Clinical relevance was found in 71.0% of those positive to FM I, 72.2% of those positive to FM II, and 76.7% of those positive to HICC. These proportions were higher than the average for other cosmetic allergens, such as preservatives and hair dyes, which gave relevant reactions in ~50% of those positive, as did *M. pereirae*. *M. pereirae* itself is not used in cosmetics, as it is banned, but sensitization may be caused by exposures to related substances, and relevance may therefore be difficult to determine.

Epidemiological relevance in patients allergic to their own cosmetic products

Popular fine fragrances (71), as well as toilet soaps, shampoos, lotions, deodorants, and aftershaves, have been shown to provoke allergic contact dermatitis in

patients when used for patch testing (71–74). Moreover, commercially available fragrance formulae and dilutions of individual fragrance allergens have been shown to be strong elicitors of allergic contact dermatitis under simulated use conditions (75–77).

More recently, deodorants spiked with the fragrance allergens cinnamal, hydroxycitronellal and HICC in realistic in-use concentrations were shown to elicit allergic contact dermatitis in 89–100% of the fragrance-allergic individuals tested (78–80). In 87.5% of HICC-sensitized individuals, the use of a cream (and, in 82.8%, the use of an ethanol solution) spiked with HICC provoked dermatitis (81).

A different perspective on clinical relevance is provided by assessing the proportion of positive reactions to FM I or single fragrance allergens in patients who had not tolerated certain perfumed products, such as deodorants and aftershaves, and who were patch test-positive to these cosmetics (82). Tables 9 and 10 are taken from this publication.

Of the 66 patients with a positive patch test reaction to their own deodorant, most had positive reactions to one or more fragrance allergens. This prevalence was much higher than in those patients in whom no positive reaction to their deodorant was observed. This observation supports the notion that the respective fragrance allergens are important in contact allergy to fragrance ingredients caused by deodorants.

Similar results were obtained from the subgroup of patients with a positive reaction to their eau de toilette, aftershave (hydroalcohol solutions), or perfumes (Table 10). However, notable differences were: (i) the greater relative importance of *E. prunastri* (oak moss absolute); and (ii) generally an extremely high proportion of positive reactions to various other fragrance ingredients.

Socioeconomic impact of contact allergy to fragrances

Skin diseases in general are known to affect quality of life significantly (83); this also applies to eczema, for which

Table 9. Extract from [(82) Table 2] regarding the frequency of positive reactions to fragrance allergens in patients with and without positive patch test reactions to their own deodorants

Fragrance allergen	Concentration (%)	Deodorant-positive (n = 66)		Deodorant-negative (n = 855)	
		n tested	% positive (95% CI)	n tested	% positive (95% CI)
Fragrance Mix I	8	61	38.0 (24.1–51.9)	805	15.0 (12.5–17.5)
<i>Myroxylon pereirae</i>	25	60	22.9 (12.7–33.1)	806	9.1 (7.2–11.0)
Hydroxycitronellal	1	33	6.5 (0.7–12.3)	204	4.3 (1.5–7.1)
Isoeugenol	1	33	6.5 (0.7–12.3)	204	7.2 (3.6–10.8)
Cinnamal	1	29	11.3 (0–24.1)	133	1.1 (0–2.7)
Geraniol	1	29	8.3 (0–20.4)	141	0 (0–2.1)

CI, confidence interval.

Table 10. Extract from [(82) Table 2] regarding the frequency of positive reactions to fragrance allergens in patients with and without positive patch test reaction to their own aftershave, eau de toilette or perfume

Fragrance allergen	Concentration (%)	Product-positive (n = 63)		Product negative (n = 819)	
		n tested	% positive (95% CI)	n tested	% positive (95% CI)
Fragrance Mix I	8	56	57.1 (46.2–68.1)	764	13.9 (11.4–16.4)
<i>Myroxylon pereirae</i>	25	56	13.9 (7.3–20.4)	766	8.8 (6.8–10.7)
HICC	5	20	58.3 (37.5–79.0)	310	1.3 (0–2.7)
<i>Evernia prunastri</i>	1	28	22.1 (7.0–37.2)	153	8.8 (4.2–13.4)
Hydroxycitronellal	1	33	6.5 (0.7–12.3)	204	4.3 (1.5–7.1)
<i>Cananga odorata</i> (ylang-ylang oil)	10	7	16.3 (2.0–30.5)	43	5.0 (0–11.3)

CI, confidence interval; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde.

most studies concern atopic dermatitis and hand eczema patients (84, 85). Hand eczema has a poor prognosis, and may affect self-image, limit social activities, and lead to occupational restrictions (85, 86). The quality of life in hand eczema patients with fragrance contact allergy is affected to a similar degree as that of patients with other contact allergies (87).

In a questionnaire study of 117 patients recently diagnosed with contact allergy to fragrance ingredients, most presented with hand or facial eczema. In response to the question of whether and how fragrance allergy had affected their life situation, 67.5% replied that they often had to take special precautions, 47.0% replied that they were often bothered by eczema and itch, 17.1% said that they had had to take sick leave because of their fragrance contact allergy, and 45.3% felt that fragrance contact allergy had significantly influenced their daily living (88).

Contact allergy is known to influence the severity and prognosis of hand eczema (89, 90), including the risk of sick leave (87). Fragrance contact allergy is mostly of a non-occupational origin (64), being related to the personal use of scented cosmetics, but may have secondary occupational consequences. This may be because exposure to fragrance ingredients also occurs in the workplace, or because hand eczema has developed. Hand eczema itself may make it impossible to remain in the trade, even if protective equipment is used. In

young people, fragrance allergy may limit the choice of occupations, as it will be difficult to work as a hairdresser or as a cosmeticist, or in other occupations with significant skin exposure to fragranced products.

In a population-based study of 3460 individuals, contact allergy to FM I was found in 1.6%; logistic regression analyses showed that medical consultation because of cosmetic dermatitis [odds ratio (OR) 3.37, 95% CI 1.83–6.20] and cosmetic dermatitis (OR 3.53, 95% CI 2.02–6.17) within the past 12 months was significantly associated with sensitization to FM I (59). Furthermore, as mentioned above, fragrance allergy may lead to sick leave (88). No specific cost estimates for fragrance allergy exist, but the yearly total costs of contact dermatitis in western Europe was estimated to be €5.2 billion in 1997. Prices were based on the Allergy White Paper (1997) and on the results of investigations and extrapolations of known data for western Europe (91). Fragrance allergy is the second most frequent cause of contact allergy after nickel allergy, and is seen in approximately every tenth patient investigated for contact allergy. Even a modest reduction in nickel allergy has been estimated to have a value of €12 million/year/million people in Denmark (Environmental Project No. 929, 2004; <http://www2.mst.dk/Udgiv/publications/2004/87-7614-295-7/pdf/87-7614-296-5.pdf>, last accessed 13 November 2011). The costs are likely to differ in other countries, being higher in some and lower in others.

These estimates show that the cost of contact allergy in the population may be considerable.

Prevention (exposure control)

Generally, 'allergen avoidance' can be regarded as having two aspects: (i) primary prevention of the acquisition of contact allergy, achieved by avoiding or limiting exposure of the general population, or certain parts of it, to allergens; and (ii) secondary prevention, in terms of avoiding (re-) elicitation of allergic contact dermatitis in sensitized individuals.

The main aim of public health is the primary prevention of disease in populations. Allergic contact dermatitis (caused by fragrances) has the potential to have a significant impact on quality of life, including effects on fitness for work, as outlined above. Moreover, it is a common phenomenon, and a reduction in exposure to (fragrance) allergens must therefore be an objective of effective public health measures.

Means of limiting or eliminating exposure to fragrance allergens include the following:

- *Prohibition* by regulatory measures or other means.
- *Restriction* by regulatory measures or other means of the maximum permissible concentration of a substance, or a critical component of natural mixtures, possibly according to different uses and product types.
- *Substitution* with suitable, but less allergenic or non-allergenic, compounds. Substitution with a component that is chemically different, but effectively not different in terms of allergenicity or cross-reactivity, is not adequate.
- *Formulating the fragrance* with the aim of limiting or eliminating those substances for which a sensitizing potential has been shown. One difficulty with this approach is that, sometimes, no sensitization data exist for those components of a fragrance formula that are used to replace a 'known sensitizer'.
- *Deliberate avoidance* of the use of fragrances when they are not essential to the function of a finished product, but are used merely to add to its appeal. Examples could include most cosmetics, topical medicaments, detergents, etc., but obviously not perfumes, eau de toilette, and other products used for their actual scent.
- *Information, for example labelling*, so that the consumer, or particularly the diagnosed and informed patient, may make an informed choice to avoid exposure to a particular ingredient.

In clinical dermatology, avoidance of re-exposure to an allergen is central to the care of sensitized patients.

Contact sensitization, as a latent condition, persists life-long, and allergen avoidance is therefore the only means of avoiding potentially severe and/or handicapping disease, which affects quality of life and may affect fitness for work, that is, allergic contact dermatitis.

Contact allergy to a particular chemical is established by means of diagnostic patch testing; further discussion of this topic may be found in (68, 92). In this context, the valid diagnosis of sensitization is a prerequisite for successful allergen avoidance.

In the case of fragrances, a history clearly indicative of 'fragrance dermatitis', but in which patch testing with commercially available test preparations has given negative results, most probably reflects a shortcoming of the patch test procedure, namely, a false-negative investigation. An important cause is inadequate information on the presence of fragrance substances present in cosmetic products and products in general. This means that patients cannot be tested for relevant substances.

A false-negative investigation can also be attributable to a number of other factors: (i) non-adherence to scientific recommendations (68) or guidelines [e.g. (93)]; (ii) a suboptimal patch test concentration; or (iii) the use of non-oxidized material if oxidized material is the true allergen.

In an 'ideal' case, from the point of view of successful patient management, the test procedure identifies all of the allergen(s) to which the patient has developed contact allergy, according to the information on the culprit product(s) brought in by the patient. Such contact sensitization is termed 'clinically relevant' (69), and the need for allergen avoidance in the future is unequivocally evident in these cases. However, not infrequently, the clinical relevance of an allergic patch test reaction cannot be ascertained for various reasons, which may be beyond control by the clinician (see above). Nevertheless, future elicitation of allergic contact dermatitis by sufficient contact with the identified 'non-relevant' allergen may be expected. Hence, the patient will need to avoid the respective substance(s).

In a less 'ideal' case, only some of the fragrance allergens that have caused allergic contact dermatitis are identified (and can subsequently be avoided), whereas others remain unidentified, for instance because they are: (i) not labelled on the product; and/or (ii) not available for routine diagnostic patch testing (special investigations, such as chemical analysis of the culprit product, and breakdown patch testing of its individual components, are performed rarely). Such 'residual' undetermined sensitization will hamper the success of secondary prevention of allergic contact dermatitis caused by fragrances.

The above consideration raises the question for the patient of how to identify fragrance chemicals in cosmetics and other products coming into contact with the skin, such as detergents and household products, topical medicaments, products used professionally (e.g. by hairdressers, beauticians, masseurs, aromatherapists), and in other industrially used categories of product (94). In this regard, labelling as 'perfume' or 'contains fragrances' does not provide sufficient information. Moreover, such general labelling has two main disadvantages:

- It does not aid in the identification of past exposure to specific agents when planning a patch test and, later, when interpreting possible positive patch test results regarding clinical relevance.
- The diagnosis of allergic contact sensitization to unidentified fragrance allergens will lead to unnecessary avoidance of other fragrance substances to which the patient is not sensitized, but that are included under the label 'perfume'.

Furthermore, the attribute 'fragrance-free' may be misleading, as it merely states that no substance was added to the product to give it a scent. Nevertheless, fragrance substances used for other purposes, for example as preservatives, may expose the 'fragrance-allergic' patient to the allergen even in a 'fragrance-free' product (95). However, in terms of European cosmetic ingredient labelling, such other uses are less problematic, as each ingredient not used as a fragrance component must be labelled. Similarly, natural products (essential oils), when used as preservatives, must be labelled.

Ingredient labelling of 26 individual fragrance ingredients, identified as allergens in humans, was introduced for cosmetics in 2005. The intention was to provide a tool for clinicians for optimizing the investigation of patients with suspected fragrance allergy, as well as for fragrance-allergic patients for avoiding products containing substances to which they have been shown to be allergic. Both of these aims are objectives of secondary prevention, and seem to have been well accepted. In a study of fragrance-allergic patients and their utilization of ingredient labelling (88), most responded that they used the ingredient labelling (86.3%), and, of those who used it, the majority (65.3%) found it helpful (88). Most allergic patients used the ingredient labelling (83.2%) to determine whether the product was scented, and 35.6% also looked for specific ingredients. Many (84.9%) found that clearer labelling, for example easier names and a larger font size, would increase the benefit of the labelling.

Methods: Retrieval of Evidence and Classification of Fragrance Substances

For a systematic review, a structured approach for identifying, grading and aggregating available information should be used. Regarding the classification of substances as allergens, a number of approaches have been suggested (96–98). The categorization of skin sensitizers according to sensitizing potency has also been proposed (99, 100). For the SCCS opinion (101) (see http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_102.pdf, last accessed 6 March 2013), these discussions were extended to reconcile different perspectives and to arrive at a strategy that is both consistent and applicable in practice.

By default, positive human evidence (clinical data) overrides negative results obtained in animals. This implies that the observation of a sufficient number of positive clinical cases is more important than potency information derived from animal experiments [local lymph node assay (LLNA)].

Retrieval of evidence

A systematic search strategy was employed for the retrieval of clinical data, as outlined below. Experimental data are often not published, so an exact definition of the scope considered for the review is necessary, and is given below. Additional LLNA data were reviewed, if identified by the search strategy as 'additional information'. This supplemental evidence was, however, not considered for the final categorization in Table 23.

The literature search was conducted as follows:

- (1) Manual search of the issues of the journal *Contact Dermatitis* up to October 2010, identifying all studies with fragrance substances. Regarding the 26 'annex substances', which had been extensively reviewed (1), inclusion started in 1999.
- (2) PubMed search of CAS numbers identified in the previous opinion (1), reviews, and already identified clinical studies, and manual screening of identified publications (narrowed for the last 10 years for the 26 'annex substances'), if necessary narrowing the search results by adding 'dermatitis' or 'allergy'. For example, for citral: 5392-40-5 AND (dermatitis or allergy), translated into '5392-40-5'[EC/RN Number] AND ('dermatitis'[MeSH Terms] OR 'dermatitis'[All Fields])
OR

('hypersensitivity'[MeSH Terms] OR 'hypersensitivity'[AllFields] OR 'allergy'[AllFields] OR 'allergy and immunology'[MeSH Terms] OR ('allergy'[AllFields] AND 'immunology'[AllFields]) OR 'allergy and immunology'[AllFields])

- (3) Manual search of all RIFM reviews published in supplement issues of *Food and Chemical Toxicology* (Elsevier B.V, Amsterdam) in the past 20 years. In cases of the least evidence on human sensitization, the substances were preliminarily selected and further research was initiated.
- (4) Consideration of the most important ('top 100') fragrance compounds in terms of volumes used (disregarding functional additives such as solvents) as supplied by the IFRA (pers. comm. 2010).
- (5) Consideration of fragrance compounds ranking 101–200 on the list of use volumes, if they were self-classified by manufacturers as skin sensitizers (R 43) (IFRA, pers. comm. 2010).

For the present systematic overview of available clinical data, only original studies were considered, as only these provide direct evidence; other reviews, being partly based on the same original reports, served only to identify additional literature. In contrast, selected reviews, guidelines and similar publications were used as the basis for methodological approaches.

A critical point in understanding this scheme is that there is publication bias in reporting allergens. This is because, once a substance has been reported and accepted as a contact allergen in humans, further reports are less likely to be published unless they are part of an epidemiological survey or when there is a novel source of exposure. Moreover, the number of patients showing positive test reactions obviously depends not only on the underlying prevalence of sensitization, but also on how often a substance is patch tested. This implies that inclusion of an allergen or allergen mixture in the baseline patch test series (as for FM I, FM II, *M. pereirae*, and HICC, and partly also other substances/mixtures) will yield the maximum possible number of cases. In contrast, patch testing in 'special' series, for example as a breakdown of single constituents of the respective mix in the case of a positive reaction to the latter, or with application only in the case of strongly suspected fragrance intolerance, will mostly result in higher relative numbers than testing the same compound consecutively, but also in lower absolute numbers.

The IFRA was requested to submit data on animal tests performed with fragrance substances in a structured format. In response, a report consisting of LLNA protocol summaries on 59 fragrance substances in (102), which

had also been presented as a poster (103), was submitted. EC3 values for some additional fragrance substances in two published reviews (104, 105) have also been considered. Additional EC3 values may be available in the scientific literature and there may also be other unpublished data.

Grading of evidence

Assembled evidence has to be graded in two steps: (i) the quality of each single study, and (ii) the strength of evidence underlying the eventual classification as an allergen. Generally, studies (published or not) that are eligible for consideration will contribute to the final overall judgement to different degrees. In this context, small study groups will contribute less precise information than larger studies of otherwise similar quality. As a minimum requirement, the sizes of the study groups and the numbers of events must be stated in the reports.

Two major types of clinical study must be distinguished, because they provide a different scope of information:

- (1) Case reports or small case series, focusing on patients with positive (test) reactions to the target substance, sometimes including a set of non-exposed, possibly non-diseased 'control patients'; these should present a concise summary of all relevant aspects of the patient's history, diagnostic procedures, and, possibly, further outcomes.
- (2) Clinical series in which results of a group of patients patch tested with the target substance, often combined with other substances, are presented. In this type of report, usually only a minority of patients tested show a positive reaction to the test substance. This implies that the majority of patients can be used to illustrate the proportion of irritant, doubtful and negative reactions. The degree of detail on the patients' histories is usually limited in such studies, as compared with case reports.

Some of the basic quality criteria in clinical patch testing that should be considered are as follows:

- International patch test guidelines (67, 68) must be adhered to.
- Material(s) tested should be characterized.
- Total number of patients tested must be given.
- Patient selection should be described.
- Relevance may be shown either on a case-by-case basis, following pertinent guidelines, or in terms of a significant epidemiological association between sensitization and exposure or valid markers of exposure.

Concerning relevance, it must be noted that, although clinical relevance can provide important information, it is ideally based on comprehensive knowledge of prior exposures. Since the implementation of the labelling of 26 fragrances on cosmetics and household detergents, previous exposure to these can often be ascertained in the assessment of relevance of a positive patch test reaction (25). However, exposure to substances not listed on a product ingredient label is obscure, except in very rare cases where elaborate diagnostics and chemical analyses are feasible [e.g. (106)]. Thus, a lack of information on relevance (reported in studies) does not invalidate the impact of diagnosed contact sensitization.

Regarding experimental studies, international guidelines such as the pertinent Organization for Economic Co-operation and Development (OECD) guidelines for testing sensitization have been developed and adopted. Experimental studies following these guidelines are considered to be valid. However, a vast number of non-guideline studies are available, and should be assessed on a case-by-case basis.

Supporting evidence besides human and animal (experimental) data comprises *in vitro* test systems, *in chemico* experiments, and structure–activity relationships (SARs). At present, SAR analysis has no formal regulatory validation for skin sensitization; nevertheless, it may provide useful indicative information on sensitizing potential when no or limited clinical or animal data are available. SAR studies must consider the possible formation of haptens (allergens) from compounds that are able to act as prehapten by, for example, autoxidation outside the body, as well as metabolic activation in the skin of compounds that are able to act as prohaptens (107, 108).

Aggregating evidence for a final conclusion

The criteria listed below are followed as a flow chart to arrive at a conclusion. This implies that, if classification into one category is achieved, subsequent categories need not be considered. On the basis of the above criteria, fragrance substances were selected for inclusion in the present opinion (101) if they were classified in one of the categories defined below.

For a substance to qualify as an established contact allergen in humans, at least one of the following criteria in terms of ‘sufficient human evidence’ must be met:

- At least two clinical series fulfilling the quality criteria from two different centres with cases of sensitization, or at least three separate clinical series from different centres if a study, or studies, do not meet all quality criteria
- or

- Case reports from at least two independent centres describing more than 2 patients altogether in whom clinically relevant contact sensitization had unequivocally been proven
- or
- At least one clinical series fulfilling the quality criteria, together with at least one case report of clinically relevant contact sensitization
- or
- Experimentally induced sensitization (e.g. unequivocally positive human maximization tests/repeated insult patch test)¹

For a substance to qualify as an established contact allergen in animals, the following criterion must be met:

- At least one positive animal study carried out according to accepted guidelines, providing evidence of a sensitization potential (sufficient animal evidence present).

For a substance to qualify as a likely contact allergen, if classification as ‘established . . .’ is not applicable, at least two of the following criteria must be met, whereas for a substance to qualify as a possible contact allergen, at least one of the three above criteria must be met:

- Individual cases of allergic patch test reactions not fulfilling the requirements for sufficient evidence (limited human evidence present)
- or
- At least one positive non-guideline animal study, which should be evaluated on a case-by-case basis (limited animal evidence present)
- or
- Other evidence, for example results from *in chemico* experiments or *in vitro* tests or from structure–activity considerations based on sufficiently valid results for closely related compounds (other evidence present).

Reported Fragrance Allergens from the Clinical Perspective: Individual Fragrance Chemicals

In this section, clinical evidence regarding sensitization to individual fragrance chemicals is given, and in the following section, clinical evidence regarding sensitization to natural extracts (essential oils) is given. ‘Single chemicals’ refers to chemicals of natural or synthetic origin whose chemical identity is fully known. The term

¹ It should be noted that such tests are considered to be unethical (109).

'natural extracts' refers to plant-derived or animal-derived mixtures of chemicals whose composition may be variable and may or may not have been fully or partly established. Full information, including possible synonyms, structural formulae (in the case of single chemicals only), a short summary of available evidence, and further information, for example on regulatory status, is presented in File S1 to this review, which is available online.

Regarding nomenclature, INCI names are used wherever possible. If an INCI name is not available, the perfuming name as listed by CosIng (<http://ec.europa.eu/consumers/cosmetics/cosing/>, last accessed 1 March 2013) is used. Several substances are currently banned from use in cosmetic products by Annex II of the Cosmetics Directive, based on concerns regarding one or more toxicological endpoints. These substances have not been further evaluated and are thus not included here.

Substances that have been established to be contact allergens in humans (Table 11), according to the criteria outlined above, were categorized according to the number of patients reacting positively and to the number of patients tested, based on the publications considered. The following categories were used: +, up to 10 positive test reactions reported; ++, 11–100; +++, 101–1000; and +++, > 1000.

If an allergen has been tested in < 1000 patients, this is indicated by 'r.t.' (rarely tested) in the tables. For this categorization, absolute numbers of cases of sensitization, and not the relative frequency of positive patch tests, were used, because relative frequencies depend heavily on the selection of patients for patch testing. Thereby, an important allergen tested routinely, in the baseline series, may yield 1–2% positive reactions (usually in several thousand patients), whereas an allergen tested in a selective fashion (in many fewer patients) may yield an even higher relative frequency. Moreover, case reports/series cannot be interpreted in terms of relative frequencies, and the use of absolute numbers allows the pooling of studies with different selection criteria. The calculation of absolute numbers was based on all available literature. Therefore, regarding the 26 substances already listed in Annex III to the Cosmetics Directive, data already evaluated in the first opinion (1) are included.

Those substances that were categorized as +++ or more, that is, those with the most reported cases, were also the top-ranking substances in large series of patients tested with the 26 labelled fragrance ingredients [(25, 46) and additionally (110)]. Geraniol is an exception, as it was completely negative in the Danish study (110), but was still among the top 10 in the Dutch and German studies (25, 46), with 0.5–0.6% positive reactions. Geraniol has,

in addition, caused many cases of contact allergy in other areas of Europe (30).

Limonene and linalool were not tested in their oxidized forms in the three studies (25, 46, 110), and would not have been identified if only these publications had been the basis of assessment. It should be noted that oxidized fragrance terpenes with defined content of the major haptens formed after autooxidation have not been commercially available for testing in dermatology clinics. In the published clinical studies that tested oxidized fragrance terpenes, the patch test preparations were obtained specifically for the performed multicentre studies (more details will be presented in a subsequent review on oxidized fragrance substances).

Table 12 lists those substances that gave rise to a few reported cases of contact sensitization only, or where results were reported from just one clinical department. Thus, the level of evidence concerning human data must be regarded as limited, according to the definitions given above.

For a number of substances, negative patch tests results were obtained, usually in rather small patient samples (maximum of 313 patients) (Table 13). For some of these substances, exposure is substantial, according to data from the IFRA. It should be noted that a negative result does not rule out a notable sensitization prevalence, as the study size has to be larger than, for example, $n = 299$ to yield an upper 95% CI that excludes a prevalence of 1%, and larger than $n = 598$ to exclude a prevalence of 0.5%.

For yet another subset of substances, no human data were publicly available. However, exposure to these substances is important, as they are used in high volumes (this being the sole criterion for inclusion in this list), and their hazard with regard to contact sensitization therefore has been examined by applying SAR considerations (see below).

Clearly, clinical data on even more fragrance substances are needed, especially those that (i) are used extensively and (ii) show alerts regarding sensitization potential, to assess more fully the epidemiology of fragrance contact allergy and pinpoint the culprit substances for induction and elicitation of contact allergy in humans.

Reported Fragrance Allergens from the Clinical Perspective: Natural Extracts/Essential Oils

Natural raw materials in the form of extracts are used in the fragrance and flavour industry for various reasons. Most importantly, several naturally occurring mixtures have a very complex composition. Perfumes based on natural materials are popular (131).

Table 11. Established contact allergens in humans: individual chemicals

INCI name (or, if none exists, perfuming name according to CosIng)	CAS no.	Human evidence: see text
ACETYLCEBRENE	32388-55-9	+
AMYL CINNAMAL*	122-40-7	++
AMYL CINNAMYL ALCOHOL*	101-85-9	++
AMYL SALICYLATE	2050-08-0	+
<i>trans</i> -ANETHOLE	4180-23-8	+ (r.t.)
ANISE ALCOHOL*	105-13-5	+
BENZALDEHYDE	100-52-7	+
BENZYL ALCOHOL*	100-51-6	++
BENZYL BENZOATE*	120-51-4	++
BENZYL CINNAMATE*	103-41-3	++
BENZYL SALICYLATE*	118-58-1	++
BUTYLPHENYL METHYLPROPIONAL*	80-54-6	++
CAMPHOR	76-22-2/464-49-3	+ (r.t.)
β -CARYOPHYLLENE (ox.)	87-44-5	+ (non-ox.) + (ox.)
CARVONE	99-49-0/6485-40-1/2244-16-8	+ (r.t.)
CINNAMAL*	104-55-2	+++
CINNAMYL ALCOHOL*	104-54-1	+++
CITRAL*	5392-40-5	+++
CITRONELLOL*	106-22-9/1117-61-9/7540-51-4	++
COUMARIN*	91-64-5	+++
(DAMASCENONE) ROSE KETONE-4	23696-85-7	+ (r.t.)
α -DAMASCONE (TMCHB)	43052-87-5/23726-94-5	++
<i>cis</i> - β -DAMASCONE	23726-92-3	+
δ -DAMASCONE	57378-68-4	+
DIMETHYLBENZYL CARBINYL ACETATE (DMBCA)	151-05-3	+
EUGENOL*	97-53-0	+++
FARNESOL*	4602-84-0	+++
GERANIOL*	106-24-1	+++
HEXADECANOLACTONE	109-29-5	+ (r.t.)
HEXAMETHYLINDANOPYRAN	1222-05-5	++
HEXYL CINNAMAL*	101-86-0	++
HYDROXYISOHEXYL 3-CYCLOHEXENE CARBOXALDEHYDE (HICC)*	31906-04-4/51414-25-6	++++
HYDROXYCITRONELLAL*	107-75-5	+++
ISOEUGENOL*	97-54-1	+++
α -ISOMETHYL IONONE*	127-51-5	++
(DL)-LIMONENE*	138-86-3	++ (non-ox.) +++ (ox.)
LINALOOL*	78-70-6	++ (non-ox.) +++ (ox.)
LINALYL ACETATE	115-95-7	+ (non-ox.) ++ (ox.)
MENTHOL	1490-04-6/89-78-1/2216-51-5	++
6-METHYL COUMARIN	92-48-8	++
METHYL 2-OCTYNOATE*	111-12-6	++
METHYL SALICYLATE	119-36-8	+
3-METHYL-5-(2,2,3-TRIMETHYL-3-CYCLOPENTENYL)PENT-4-EN-2-OL	67801-20-1	++ (r.t.)
α -PINENE and β -PINENE	80-56-8 and 127-91-3, respectively	++
PROPYLIDENE PHTHALIDE	17369-59-4	+ (r.t.)
SALICYLALDEHYDE	90-02-8	++
α -SANTALOL and β -SANTALOL	115-71-9 and 77-42-9, respectively	++
SCLAREOL	515-03-7	+
TERPINEOL (mixture of isomers)	8000-41-7	+
α -TERPINEOL	10482-56-1/98-55-5	
Terpinolene	586-62-9	+
TETRAMETHYL ACETYLOCTAHYDRONAPHTHALENES	54464-57-2/54464-59-4/68155-66-8/68155-67-9	+
TRIMETHYL-BENZENEPROPANOL (Majantol)	103694-68-4	++
VANILLIN	121-33-5	++

'ox.', oxidized; 'non-ox.', non-oxidized; 'r.t.', rarely tested.

For categorization of importance (+ to ++++), see text. Allergens of special concern are substances for which between 100 and 1000 cases (+++) and > 1000 cases (+++++) have been published. These are set in bold. Fragrance substances identified as allergens in the 1999 opinion of the Scientific Committee on Non-Food Products intended for Consumers (1) are marked with an asterisk.

Table 12. Fragrance substances with positive human data, which are, however, not sufficient for categorization as 'established contact allergen in humans'

INCI name (or, if none exists, perfuming name according to CosIng)	CAS no.	Comment	References
AMBRETTOLIDE	7779-50-2	3.4% positive reactions in 178 patients	(111)
CARVACROL	499-75-2	2/28 patients positive	[Meynadier, after (112)]
CUMINALDEHYDE	122-03-2	3/179 patients positive	(113)
CYCLOHEXYL ACETATE	622-45-7	0.5% of 218 selected patients positive	(114)
CYCLOPENTADECANONE	502-72-7	3/178 patients positive	(111)
<i>trans-trans</i> -8-DAMASCONE	71048-82-3	One positive HRIPT (2/15 with 1%)	(115)
2,3-DIHYDRO-2,2,6-TRIMETHYLBENZALDEHYDE	116-26-7	One positive HRIPT (5/53)	(116).
DIMETHYLTETRAHYDRO BENZALDEHYDE	68737-61-1	2.3% positive reactions to isomer mixture in 178 patients	(111)
ETHYLENE DODECANEDIOATE	54982-83-1	2/218 positive PT reactions	(114)
ETHYL VANILLIN	121-32-4	1 occupational case	(117)
HELIOTROPINE	120-57-0	6/1606 consecutive patients positive	(70)
HYDROXYCITRONELLOL	107-74-4	6.0% positive PT reactions in 218 patients	(114)
ISOAMYL SALICYLATE	87-20-7	1 positive in 179 patients, possibly 'excited back syndrome' 0/95 in another study using one tenth of above test concentration	(113, 42)
ISOLONGIFOLENEKETONE	33407-62-4	1/178 patients positive	(111)
METHOXYCITRONELLAL	3613-30-7	Positive PT data of unknown validity from Nakayama et al. in 22/137 patients	(118)
METHOXYTRIMETHYLHEPTANOL	41890-92-0	0.9% positive PT reactions	(114)
METHYL <i>p</i> -ANISATE	121-98-2	1/182 patients positive	(119)
METHYL CINNAMATE	103-26-4	6/142 patients positive	(120)
METHYL DIHYDROJASMONATE	24851-98-7	3/1606 patients positive 0/100	(70, 42)
METHYLIONANTHEME	55599-63-8	1 case	(121)
5-METHYL- α -IONONE	79-69-6	5/1606 patients positive	(70)
METHYL OCTINE CARBONATE	111-80-8	1 case	(122)
MYRCENE	123-35-3	1/1511 patients positive to oxidized myrcene	(123)
MYRTENOL	515-00-4	Two HRIPTs with one positive each	(124)
NEROL	106-25-2	6.0% positive	(114)
Nerolidol (isomer not specified)	7212-44-4	Few, unconfirmed positive cases according to RIFM review	(125)
NOPYL ACETATE	128-51-8	2/179 patients positive, possibly 'excited back syndrome'	(113)
PHENETHYL ALCOHOL	60-12-8	1/179; 0/100	(113, 42)
PHENYLACETALDEHYDE	122-78-1	1.1% of 182 patients positive 1 case	(119, 126)
PHENYLPROPANOL	122-97-4	2/218 patients positive	(114)
PHYTOL	150-86-7	1 case in human maximization test	(127)
RHODINOL	6812-78-8	Several positive HRIPTs, clinical data of uncertain validity	(128)
<i>trans</i> -ROSE KETONE-5	39872-57-6	2/22 positive HRIPTs	(129)

HRIPT, Human repeated insult patch test; PT, Patch test; RIFM, Research Institute for Fragrance Materials.

More detailed information forming the basis of this evaluation can be found in Annex I of the Scientific Committee on Consumer Safety of the European Commission opinion (101).

The three main methods used to concentrate plant fragrance substances (132) – distillation, mechanical separation ('pressing'), and solvent extraction – yield very different extracts:

- Essential oils are obtained by water steam, water, ethanol or water/ethanol distillation. Essence oils are

essential oils that separate from the aqueous phase in the distillation receiver during the distillative concentration of fruit, usually citrus, juices.

- Citrus peel oils, apart from distilled lime oil, are prepared in a special way by pressing the peel to release mostly volatile substances from the pericarp

Table 13. Fragrance substances with negative human data, that is, patch tests of patients with suspected contact allergy to fragrance ingredients who gave negative results

INCI name (or, if none exists, perfuming name according to CosIng)	CAS number	Results/comment	References
6-ACETYL-1,1,2,4,4,7-HEXAMETHYLTETRALINE	21145-77-7	0/313 consecutive patients in two centres	(42)
AMYL CYCLOPENTANONE	4819-67-4	0/178	(111)
BENZYL ACETATE	140-11-4	0/100 consecutive patients in one centre	(42)
2-TERT-BUTYL CYCLOHEXYL ACETATE	88-41-5	0/313 consecutive patients in two centres	(42)
4-tert-Butylcyclohexyl acetate	32210-23-4	0/107 consecutive patients in one centre	(42)
6-ETHYLIDENEOCTAHYDRO-5,8-METHANO-2H-BENZO-1-PYRAN	93939-86-7	0/178	(111)
3 α ,4,5,6,7,7 α -HEXAHYDRO-4,7-METHANO-1H-INDEN-5(OR 6)-YL ACETATE	54830-99-8	0/313 consecutive patients in two centres	(42)
HEXYL SALICYLATE	6259-76-3	0/218 'Top 100' substance and classified as R43	(114)
HIBISCOLIDE	6707-60-4	0/178	(111)
α -IONONE	127-41-3	0/205	(42)
β -IONONE	79-77-6	0/205 'Top 100' substance	(42)
ISOBORNYL ACETATE	125-12-2	0/107 'Top 100' substance	(42)
METHYL ANTHRANILATE	134-20-3	0/91 'Top 100' substance	(130)
METHYL IONONE (mixture of isomers)	1335-46-2	0/100 'Top 100' substance	(42)
OXALIDE	1725-01-5	0/178	(111)
TERPINEOL ACETATE (isomer mixture)	8007-35-0	0/106 'Top 100' substance	(42)
α -TERPINYL ACETATE	80-26-2	0/179	(113)
TRIMETHYL-PROPYL CYCLOHEXANEPROPANOL	70788-30-6	0/178	(111)

in small oil glands, mostly highly volatile terpene hydrocarbons. However, they also contain small amounts of non-volatile compounds such as dyes, waxes, and furocoumarins.

- The method of solvent extraction is generally applied in the separation of heat-labile materials or if an essential oil can only be obtained in very low yield, for example from blossoms. It is also used if the non-volatile components are desired for their fixative properties, for example in the preparation of resinoids from exudates. The most important extracts are termed: (i) concretes, an extract of fresh plant material with non-polar solvents, containing not only volatile substances, but also a large proportion of non-volatile substances, such as waxes; and (ii) absolutes, which are prepared by taking up concretes in ethanol – compounds that precipitate on cooling are removed by filtration, yielding a wax-free residue called absolute. Resinoids, used for their fixative properties, are prepared by extracting plant exudates with alcohols or non-polar solvents. The products are usually highly viscous, and are therefore sometimes diluted, for example with phthalates or benzyl benzoate. Oleoresins are concentrates prepared from spices by solvent extraction (131).

An International Standardization Organization (ISO) norm exists regarding the nomenclature of aromatic natural raw materials (ISO/DIS 9235 Aromatic raw materials – vocabulary).

Regarding clinical data in terms of contact allergy to essential oils and natural extracts, the main focus is on general dermatological patients with complaints related to the use of cosmetics and other consumer products. However, series of cases with occupational exposure to essential oils with occupational allergic contact dermatitis have also been reported [e.g. masseurs, physiotherapists (133, 134), aromatherapists (135–139), and beauticians performing massages (140)].

In Table 14, essential oils with sufficient human evidence for them to be categorized as established contact allergens in humans are listed.

Table 15 lists a number of essential oils, mostly tested in just one clinical department, and thus, or for other reasons, not satisfying the criteria for being categorized as established contact allergen in humans (i.e. limited human evidence present).

Table 16 gives an indicative list of natural extracts for which published human data are lacking, but which are of interest: (i) as high-volume exposure; (ii) because of published positive animal experiments; or (iii) because they contain well-known (established) contact allergens.

Table 14. Established contact allergens in humans: natural extracts

INCI name (or, if none exists, perfuming name according to CosIng)	CAS no.	Human evidence: see text
CANANGA ODORATA and ylang-ylang oil	83863-30-3; 8006-81-3	+++
CEDRUS ATLANTICA BARK OIL	92201-55-3; 8000-27-9	++
CINNAMOMUM CASSIA LEAF OIL/CINNAMOMUM ZEYLANICUM BARK OIL	8007-80-584649-98-9	++ (r.t.)
CITRUS AURANTIUM AMARA FLOWER/PEEL OIL	8016-38-4; 72968-50-4	++
CITRUS BERGAMIA PEEL OIL EXPRESSED	89957-91-5	+ (r.t.)
CITRUS LIMONUM PEEL OIL EXPRESSED	84929-31-7	++
CITRUS SINENSIS (syn.: AURANTIUM DULCIS) PEEL OIL EXPRESSED	97766-30-8; 8028-48-6	++
CYMOPOGON CITRATUS/SCHOENANTHUS OILS	89998-14-1; 8007-02-1; 89998-16-3	++
EUCALYPTUS spp. LEAF OIL	92502-70-0; 8000-48-4	++
EUGENIA CARYOPHYLLUS LEAF/FLOWER OIL	8000-34-8	+++
EVERNIA FURFURACEA EXTRACT*	90028-67-4	+++
EVERNIA PRUNASTRI EXTRACT*	90028-68-5	+++
JASMINUM GRANDIFLORUM/OFFICINALE	84776-64-7; 90045-94-6; 8022-96-6	+++
JUNIPERUS VIRGINIANA	8000-27-9; 85085-41-2	++
LAURUS NOBILIS	8002-41-3; 8007-48-5; 84603-73-6	++
LAVANDULA HYBRIDA	91722-69-9	+ (r.t.)
LAVANDULA OFFICINALIS	84776-65-8	++
MENTHA PIPERITA	8006-90-4; 84082-70-2	++
MENTHA SPICATA	84696-51-5	++
MYROXYLON PEREIRAE	8007-00-9;	++++
NARCISSUS spp.	Diverse	++
PELARGONIUM GRAVEOLENS	90082-51-2; 8000-46-2	++
PINUS MUGO/PINUS PUMILA	90082-72-7/97676-05-6	++
POGOSTEMON CABLIN	8014-09-3; 84238-39-1	++
ROSE FLOWER OIL (ROSA spp.)	Diverse	++
SANTALUM ALBUM	84787-70-2; 8006-87-9	+++
TURPENTINE (oil)	8006-64-2; 9005-90-7; 8052-14-0	++++
VERBENA ABSOLUTE	8024-12-2	++

r.t., rarely tested.

For categorization of importance (+ to ++++), see text. Allergens of special concern are substances for which between 100 and 1000 cases (+++) and > 1000 (+++++) have been published. These are set in bold. Fragrance substances identified as allergens in the 1999 opinion of the Scientific Committee on Non-Food Products intended for Consumers (1) are marked with an asterisk.

Animal data

The animal test methods used in harmonized classification of substances, according to their potential to cause skin sensitization, are the guinea-pig maximization test (GPMT) and the Buehler test in guinea-pigs (147) and the LLNA (148) in mice. These methods are used in hazard identification and risk assessment for regulatory purposes under REACH (149). For registration in REACH, the LLNA is the preferred method for measuring skin sensitization potential in animals, and justification for the use of other methods needs to be provided. According to the directives on classification and labelling (Directives 67/548/EEC and 1999/45/EC), substances and preparations meeting positive criteria in these tests shall be classified as sensitizing and assigned the symbol 'Xi' and the risk phrase 'R43: May cause sensitization by skin contact'; or, according to the recent regulation on classification, labelling and packaging [CLP (Regulation No. 1272/2008)] 'H317: May cause an allergic skin reaction'.

As yet, there is no officially validated *in vitro* test method for skin sensitization. Therefore, for cosmetic ingredients, the LLNA, the GPMT and the Buehler test have also been used in risk assessment for regulatory purposes. Positive results from the OECD guideline animal tests mentioned above that are sufficient to classify a substance as a skin sensitizer (R43) are:

- GPMT; at least 30% of the animals have a positive response.
- Buehler test; at least 15% of the animals have a positive response.
- LLNA; at least a three-fold increase in lymph node cell proliferative activity is induced, as compared with vehicle-treated controls (stimulation index ≥ 3). For positive LLNAs, an EC3 value is calculated, which gives the estimated concentration of a chemical necessary to give a three-fold increase in proliferative activity as compared with vehicle-treated controls.

Table 15. Natural extracts with positive human data, which are, however, not sufficient for categorization as an 'established contact allergen in humans'

INCI name (or, if none exists, perfuming name according to CosIng) in bold; plant part/type of extract (partly indicative) in plain font	CAS no.	Comment	References
ACORUS CALAMUS ROOT OIL	84775-39-3	7 positive reactions to 'calamus'	(141)
CEDRUS DEODARA WOOD OIL	91771-47-0	Rudzki (1976/1986) found 3/3 positive reactions	(141, 142).
CITRUS AURANTIUM AMARA LEAF OIL	72968-50-4	Several cases in two series from one centre	(141, 142)
CITRUS TANGERINA	223748-44-5	1 case	(143)
CYBOPOGON NARDUS/WINTERIANUS HERB OIL	89998-15-2; 91771-61-8	Several cases in two series from one centre	(141, 142)
ILICIIUM VERUM FRUIT OIL	84650-59-9	Cases of active sensitization; 34% consecutive patients positive to 1%	(144)
LAVANDULA SPICA	97722-12-8	Several cases in two series from one centre	(141, 142)
LITSEA CUBEBA	90063-59-5	Several cases in two series from one centre	(141, 142)
PELARGONIUM ROSEUM	90082-55-6	2.1% of 1483 patients positive	(145)
ROSMARINUS OFFICINALIS	84604-14-8	3 cases in two series from one centre	(141, 142)
SALVIA spp.	Diverse	Several cases in two series from one centre	(141, 142)
TAGETES PATULA	91722-29-1	1 case (aromatherapist)	(135)
THYMUS spp.	84929-51-1	4/84 positive	(141)
VETIVERIA ZIZANOIDES	8016-96-4; 84238-29-9	1/200 and 9/86 positive	(141, 142)

More detailed information forming the basis of this evaluation can be found in Annex I of the Scientific Committee on Consumer Safety of the European Commission opinion (101).

Table 16. Indicative list illustrating natural extracts containing established human allergens or being labelled with R43 or yielding positive local lymph node assay (LLNA) results, but lacking published human data

INCI name (or, if none exists, perfuming name according to CosIng) in bold; plant part/type of extract (partly indicative) in plain font	CAS no.	Comment
CITRUS PARADISI PEEL OIL	8016-20-4	High volume, classified as R43
CYBOPOGON MARTINI HERB EXTRACT	84649-81-0	Positive LLNA study by RIFM: EC3 value 9.6% (146)
MENTHA ARVENSIS	68917-18-0	High volume, classified as R43
OCIMUM BASILICUM	84775-71-3	Positive LLNA study by RIFM: EC3 value of < 2.5% (146)
PIMENTA RACEMOSA	85085-61-6	Contains, among other substances, the established contact allergen eugenol (42–56%)
SANTALUM SPICATA	8024-35-9	Contains, among other substances, the established contact allergens santalol (75%) and farnesol (10%)

RIFM, Research Institute for Fragrance Materials.

Further categorization of substances classified with R43 into three groups according to allergen potency (extreme, strong, and moderate) has been proposed by a European Commission expert group on skin sensitization (99, 150), and has also been proposed in the European Chemicals Agency guidance document on application of the CLP criteria (100). Such categorization is based on EC3 values in the LLNA, on the intradermal induction concentration in the GPMT, and on the topical induction concentration in the Buehler test. The potency categories and their default concentration values based

on EC3 values in the LLNA as defined in (99) are as follows: extreme sensitizer ($EC3 \leq 0.2$); strong sensitizer ($EC3 > 0.2$ and ≤ 2); and moderate sensitizer ($EC3 > 2$). When LLNA EC3 values are available from more than one study, the lowest value should normally be used. Where multiple animal datasets lead to different categorization of the same substance, the higher potency category should apply (99, 150). The potency categorization of substances based on the LLNA is applied by the Scientific Committee on Consumer Products in the risk assessment of cosmetic ingredients, particularly hair dye substances (151).

Table 17. Summary of local lymph node assay (LLNA) data on 66 fragrance substances, based on a report submitted by the Research Institute for Fragrance Materials [RIFM, 2009 (102)] and published reviews by Gerberick et al. (104) and Kern et al. (105)

Substance	CAS no.	EC3 value		References
		%	M	
Hexyl salicylate	6259-76-3	0.18	0.008	(102, 105)
Cinnamal	104-55-2	0.2	0.015	(102)
Methyl 2-octynoate	111-12-6	< 0.5	< 0.032	(102, 105)
Isoeugenol	97-54-1	0.54	0.033	(102)
Citral	5392-40-5	1.2	0.079	(102)
2-Hexylidene cyclopentanone	17373-89-6	2.4	0.14	(102)
Methyl octine carbonate	111-80-8	2.5	0.15	(102)
Balsam of Peru absolute	8007-00-9	2.5	n.a.	(102)
<i>trans</i> -2-Hexenal	6728-26-3	2.6	0.26	(102)
Benzyl salicylate	118-58-1	2.9	0.23	(102, 105)
Butylphenyl methylpropional	80-54-6	2.9	0.14	(102)
Phenylacetaldehyde	122-78-1	3	0.25	(102, 104)
Allyl phenoxycetate	7493-74-5	3.1	0.16	(102)
Benzylideneacetone	122-57-6	3.7	0.25	(104)
3-Propylidenephthalide	17369-59-4	3.7	0.21	(102, 104)
<i>Evernia prunastri</i> extract oak moss	90028-68-5	3.9	n.a.	(102)
Balsam of Peru oil (<i>Myroxylon pereirae</i> Klotzsch)	8007-00-9	4	n.a.	(102)
Farnesol	4602-84-0	4.1	0.18	(102)
<i>p</i> -tert-Butyl-dihydrocinnamaldehyde	18127-01-0	4.3	0.23	(102)
α -Methyl cinnamic aldehyde	101-39-3	4.5	0.31	(102, 104)
Eugenol	97-53-0	5.3	0.32	(102)
Hexyl cinnamal	101-86-0	5.3	0.25	(102)
Dihydrocoumarin	119-84-6	5.6	0.38	(104)
Geraniol	106-24-1	5.6	0.36	(102)
Carvone	6485-40-1	5.7	0.38	(102)
Diethyl maleate	141-05-9	5.8	0.34	(104)
2-Methoxy-4-methylphenol	93-51-6	5.8	0.42	(102, 104)
Anise alcohol	105-13-5	5.9	0.43	(102, 105)
Jasmine absolute (<i>J. grandiflorum</i>)	8022-96-6	5.9	n.a.	(102)
Dibenzyl ether	103-50-4	6.3	0.32	(102)
<i>Cananga odorata</i> leaf/flower oil ylang ylang 'extra'	8006-81-3	6.8	n.a.	(102)
Isocyclocitral	1335-66-6	7.3	0.48	(102)
2,3-Dihydro-2,2,6-trimethylbenzaldehyde	116-26-7	7.5	0.50	(104)
Amyl cinnamal	122-40-7	7.6	0.38	(102)
Perillaldehyde <i>p</i> -mentha-1,8-dien-7-al	2111-75-3	8.1	0.54	(102, 104)
<i>p</i> -Isobutyl- α -methyl hydrocinnamaldehyde	6658-48-6	9.5	0.46	(102)
D-Limonene*	5989-27-5	< 10	< 0.73	(102)
Methylundecanal	110-41-8	10	0.54	(104)
Acetylcedrene	32388-55-9	13.9	0.57	(105)
Methylenedioxyphenyl methylpropanal	1205-17-0	16.4	0.85	(102, 105)
Benzyl benzoate	120-51-4	17	0.80	(104)
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	31906-04-4	17.1	0.81	(102, 104)
Benzyl cinnamate	103-41-3	18.4	0.77	(102, 105)
Hydroxycitronellal	107-75-5	19.3	1.12	(102)
Cinnamyl alcohol	104-54-1	21	1.57	(104)
α -iso-Methyllionone	127-51-5	21.8	1.06	(102, 105)
Cyklamen aldehyde	103-95-7	22	1.64	(104)
4-Methoxy- α -methyl benzenpropanal	5462-06-6	23.6	1.32	(102)
Amyl cinnamyl alcohol	101-85-9	~ 25	~ 1.22	(102, 105)
Tetramethyl acetyloctahydronaphthalene	54464-57-2	25.1	1.07	(102)
Ethyl acrylate	140-88-5	28	2.8	(104)
Linalool*	78-70-6	30	1.94	(104)
Trimethylbenzenepropanol (majantol)	103694-68-4	30	~ 1.68	(102)
Jasminum Sambac flower CERA/extract/water	91770-14-8	35.4	n.a.	(102)
Citronellol	106-22-9	43.5	2.78	(102, 105)

Table 17. Continued

Substance	CAS no.	EC3 value		References
		%	M	
No EC3 value was established; higher concentrations should also have been tested				
6-Methyl-3,5-heptadien-2-one	1604-28-0	> 5	> 0.40	(102)
<i>Camellia sinensis</i> leaf tea leaf absolute	84650-60-2	> 5	n.a.	(102)
Cinnamyl nitrile	1885-38-7	> 10	> 0.77	(102)
Menthadiene-7-methyl formate	68683-20-5	> 10	> 0.51	(102)
<i>Evernia furfuracea</i> extract (tree moss absolute)	90028-67-4	> 20	n.a.	(102)
Isocyclogeraniol	68527-77-5	> 25	> 1.62	(102)
1-Octen-3-yl acetate	2442-10-6	> 30	> 1.76	(102)
Benzyl alcohol	100-51-6	> 50	> 4.62	(102)
Coumarin	91-64-5	> 50	> 3.42	(102)
Vanillin	121-33-5	> 50	> 3.3	(102)
No EC3 value calculated				
Benzaldehyde	100-52-7	–	–	(104)

n.a., not applicable (mixture of compounds).

M: EC3 based on molar concentration. EC3 values (% and M) are given. The substances are ordered by decreasing sensitization potency as assessed by LLNA EC3 values (lowest EC3 value indicating highest potency).

*Material with low levels of oxidation according to (102).

Results with the LLNA

Table 17 shows the EC3 values for fragrance substances in the report submitted by industry (102). EC3 values for some additional fragrance substances in two published reviews (104, 105) are also included in Table 17. Table 18 shows LLNA results for oxidized substances. Table 19 summarizes the distribution of fragrance substances, by potency category, according to the EC3 values in Table 17. Additional EC3 values may be available in the scientific literature. Many more animal experiments may have been performed, but not been published.

For fragrance substances that can autoxidize upon air exposure, it is also important to investigate the sensitization potency after air exposure. Oxidized compounds represent what consumers could come in contact with in perfumes and fragranced products. Table 18 shows the LLNA data for some of the most commonly used fragrance substances, pure and after autoxidation. The EC3 values obtained for the pure substances are 5–10 times higher than those obtained for the same substances after air exposure (a lower EC3 value indicating higher potency).

For 10 substances, no EC3 value could be established. These substances should have been tested at higher concentrations – some of these would most probably have generated an EC3 value indicating sensitization potential. However, here we report 'No EC3 value established'. Five substances should have been tested also at lower concentrations, and in these cases the EC3 value could have been lowered, meaning that a more severe potency category could have been achieved.

In all, ~150 experiments were reported in (102), and are listed in Annex II to the SCCS opinion (101). Substances with an EC3 value of ≤ 2 may be categorized as strong or extreme sensitizers. Such potent sensitizers are comparatively rare among fragrance substances assessed in the LLNA. Nevertheless, fragrances are important allergens in humans, which points to repeated skin exposure to less potent sensitizers as a factor that strongly determines sensitization risk.

Methodological considerations

In the report submitted by industry (102), the LLNA weighted mean EC3 values ($\mu\text{g}/\text{cm}^2$) are presented. It is considered misleading to present EC3 values as mean values from tests performed with different vehicles. It is generally agreed that the lowest EC3 value should be used if there is more than one study fulfilling the OECD guideline requirements (99, 150), and these have been introduced into Table 17. The EC3 values in the reviews by Gerberick et al. and Kern et al. (104, 105) were based on single representative experiments with a vehicle described in OECD guideline 429 (see above), and preferably with acetone/olive oil.

The most frequently used vehicle in the submission by industry (102) was ethanol/diethyl phthalate (1:3), followed by acetone/olive oil (4:1). In some experiments, antioxidants were mixed with ethanol/diethyl phthalate. The vehicle was not reported in some of the references, and no rationale for using vehicles other than those recommended was given in the report (102). According to

Table 18. Local lymph node assay data on four fragrance substances and one essential oil before and after air exposure, comparing the sensitization potency of the pure (non-oxidized) substance with the potency of the oxidized substance

Substance	CAS no.	Dose % (wt/vol) Vehicle: A/OO 4:1*	EC3 value (% wt/vol)	References
D-Limonene (ox. 10 weeks)	5989-27-5	1, 5, 25	3.0	(152)
D-Limonene (pure)	5989-27-5	25, 50, 100	30	(152)
Linalool (ox. 10 weeks)	78-70-6	5, 10, 25	9.4	(153)
Linalool (ox. 45 weeks)	78-70-6	2.5, 10, 25	4.8	(153)
Linalool (pure)	78-70-6	25, 50, 100	46.2	(153)
Linalyl acetate (ox. 10 weeks)	115-95-7	0.5, 10, 40	3.6	(154)
Linalyl acetate (pure)	115-95-7	10, 30, 100	25	(154)
Geraniol (ox. 10 weeks)	106-24-1	1, 3, 6, 10, 20	4.4	(155)
Geraniol (ox. 45 weeks)	106-24-1	0.5, 1, 3, 6, 10	5.8	(155)
Geraniol (pure)	106-24-1	5, 10, 15, 20, 30	22.4	(155)
Lavender oil (ox. 10 weeks)		1, 5, 10, 20, 50	11	(156)
Lavender oil (ox. 45 weeks)		1, 5, 10, 20, 50	4.4	(156)
Lavender oil (not ox.)		5, 25, 100	36	(156)

Pure: purified before testing, as most commercially available fragrance substances are not pure. Not ox.: not purified, but used as delivered, as this is a complex mixture and not a specific substance. Ox.: oxidized by air exposure for the specified number of weeks.

*Acetone/olive oil.

Table 19. Summary of EC3 values for fragrance substances in Table 17, taken from (102, 104, 105)

EC3 value interval	Fragrance substances	
	n	%
≤ 0.2	2	3
> 0.2 to ≤ 2	3	4
> 2	50	71
No EC3 value established*	10	14
No EC3 value calculated	5	7
All substances	70	–

The EC3 value intervals for potency categorization (99, 150) were used for comparison of fragrance substances.

*Substances should also have been tested at higher concentrations.

OECD guideline 429 (see above), the recommended vehicles are acetone/olive oil (4:1), *N,N*-dimethylformamide, methyl ethyl ketone, propylene glycol, and dimethyl sulfoxide, but others may be used if a sufficient scientific rationale is provided. It is well known that a difference in the EC3 value can be obtained for the same substance, depending on which vehicle is used in the LLNA. Thus, as an additional control, supplementary to the guideline-based LLNA control, a clinically relevant solvent or the commercial formulation in which the test substance is marketed may be used.

According to OECD guideline 429 (see above), a minimum of three concentrations should be tested. The number of consecutive doses used in the reported data was generally five, sometimes three, and, in a few experiments, two. The SCCS considered that too few concentrations were tested in four studies, in which only two concentrations were used. Lower concentrations

than those tested should have been used in experiments with five fragrance substances, in which the EC3 value could not be determined. Higher concentrations than those tested should also have been used in experiments with 12 substances, in which the EC3 value could not be determined. The number of animals per dose group was generally four plus a non-exposed control group, sometimes five, and, in a few experiments, six; the minimum according to the OECD guideline is four.

In the submission by industry (102), the EC3 values are given as weight per unit area ($\mu\text{g}/\text{cm}^2$). The SCCS considered that the EC3 values (%) are the values of primary interest in communicating risk assessment, as EU legislation, OECD guideline 429 and the scientific literature refer to EC3 values (%). However, the SCCS recommended that molar (M) EC3 values should be considered, as they give the concentration based on the molecular weight of substances. They have thus been calculated and included in Table 17. EC3 values (%) overestimate the intrinsic molecular sensitization potency for low molecular weight compounds, whereas compounds with a high molecular weight are underestimated. Regarding the differences in molecular weight between the studied fragrance substances, a variation is seen if the ranking list of the sensitization potency is based on EC3 (%) or EC3 (M), as some substances have a molecular weight twice as high as others.

Considerations about the animal data

- Several studies in the industry submission (102) were of insufficient quality, not following the OECD guidelines. In some cases, either too few

concentrations had been used in LLNAs, or concentrations were insufficient to achieve a three-fold increase of the SI, because either too low or too high concentrations were used. It is important to remember that the production of unreliable data is a waste of animals.

- OECD guideline 429 recommends several vehicles. It is well known that a difference in the EC3 value can be obtained for the same substance, depending on which vehicle is used in the LLNA. Thus, as an additional control, supplementary to the guideline-based LLNA control, a clinically relevant solvent or the commercial formulation in which the test substance is marketed may be used.
- Experimental results are often not published by the companies that have performed the tests. Access to such results would be important for the scientific community, for example in the context of REACH, or independently, either for the public domain, or for a Public Trustee.
- Most experimental studies are performed on individual fragrance ingredients, whereas exposure to allergens in cosmetic products is usually to mixtures of allergens. The risk of sensitization and elicitation may depend on the mixture of substances, but very few studies on this exist. It is necessary to improve the knowledge base on 'cocktail effects' on sensitization/elicitation to improve the basis of risk assessment and management.

SARs: Grouping of Substances Based on Expert Judgement

Whether or not a particular chemical will be a sensitizer, and how potent it will be if it is a sensitizer, depends on its ability, either directly or after activation, to react with appropriate proteins in the skin. This fundamental concept was initially demonstrated by Landsteiner and Jacobs in 1936 (157), and subsequently validated by numerous studies with various types of chemicals [some key references: (158–162)]. The ability to predict sensitization potency, or the lack of it, depends on being able to predict reactivity to skin proteins. This is the basis of SAR analysis for skin sensitization. The prediction can often be made on the basis of the chemical structure, recognizing structural features (referred to as structural alerts) that are associated with reactivity.

The relationships between molecular structure and reactivity that form the basis of structural alerts are based on well-established principles of mechanistic organic chemistry (163). Examples of structural alerts

are aliphatic aldehydes (alerting to the possibility of sensitization via a Schiff base reaction with protein amino groups), and α,β -unsaturated carbonyl groups, $C=C-CO-$ (alerting to the possibility of sensitization via Michael addition of protein thiol groups). Major mechanistic reactivity domains have been discussed in detail by Aptula and Roberts (164). Prediction of the sensitization potential of compounds that can act via abiotic or metabolic activation (prehaptens or prohaptens) is more complex than that for compounds that act as direct haptens without any activation. The autoxidation patterns can differ because of differences in the stability of the intermediates formed; for example, it has been shown that autoxidation of the structural isomers linalool and geraniol results in different major haptens/allergens. Moreover, the complexity of the prediction increases further for those compounds that can act both as prehaptens and as prohaptens. In such cases, the impact on the sensitization potency depends on the degree of abiotic activation (e.g. autoxidation) in relation to the metabolic activation.

These structural alerts can be applied by computerized expert systems, that is, *in silico*, or by estimations made by organic chemists (*in cerebro*) using their experience. When organic chemists look at a chemical structure, they recognize parts of the structure that they can associate with reactivity, the type of reactivity (i.e. assign the reaction mechanistic domain), and other features of the molecular structure that will affect the reactivity positively or negatively. Human experts should be aware of the complexities, and how structural modification can alter the reactivity associated with structural alerts, etc. Importantly, they can also recognize unfamiliar structural features whose effects they cannot confidently predict. In such cases, they can call for experimental chemistry work (*in chemico*) to be performed to ascertain the presence, nature and degree of reactivity. *In chemico* methods include organic chemistry experimentation to identify chemical reaction products resulting from oxidation and/or reaction with model nucleophiles, and to identify reaction mechanisms. In so-called *in chemico* reactivity methods, the ability of a specific chemical to react with selected peptides is determined, for prediction of the sensitization potential of the chemical under investigation (165, 166). To enable *in chemico* reactivity methods to predict the activity of prohaptens, the addition of horseradish peroxidase and hydrogen peroxide oxidation systems has been tested to model enzymatic oxidation in the skin (167, 168).

Although computerized expert systems are derived from input by human experts, they are less well able to capture the subtleties of structure–reactivity

relationships, and they sometimes fail to detect aspects of chemistry that are obvious to organic chemists. Human experts should be aware of the complexities, as well as how structural modification can alter the reactivity associated with structural alerts, etc.

Depending on the type of reactivity (the reaction mechanistic domain), it is sometimes possible to make a quantitative prediction of potency in the LLNA, which can be used to predict potency in humans relative to related known human sensitizers. These predictions use quantitative mechanistic models (QMMs) based on reactivity expressed quantitatively by model parameters, and sometimes in combination with hydrophobicity. For example, the potency of aliphatic aldehydes and ketones (the Schiff base domain) in the LLNA is modelled by a combination of reactivity and hydrophobicity (169), whereas the LLNA potency of dinitrochlorobenzene analogues (the S_NAr domain) is well modelled by reactivity alone (170).

QMMs aimed at not only predicting the potential of a substance to be a sensitizer, but also predicting the potency, promise to be useful in non-animal-based risk assessment for skin sensitization. However, in the field of fragrance substances, there are major gaps in our present ability to apply quantitative SARs (QSARs)/QMMs. This is largely because many of the fragrance substances of interest have the potential to act via abiotic or metabolic activation (prehaptens and/or prohaptens); that is, they are only weak sensitizers or non-sensitizers, but have the potential to be activated to form more potent sensitizers. The resulting sensitization potency will depend on the extent of activation and the nature of the resulting products. It is possible to apply SAR analysis to identify these possibilities, but QSAR modelling for these cases is not yet developed. However, much progress has been made in identifying structural alerts for the various activation mechanisms that have been recognized. This is reviewed by Karlberg et al. (107).

Chemicals with no structural alerts for direct reactivity, or for known activation mechanisms, and no unfamiliar structural features that might be associated with as yet unidentified activation mechanisms, can be predicted to be non-sensitizing. Chemicals that do have alerts for reactivity (direct or via activation) are not necessarily sensitizers – they may be insufficiently reactive and/or insufficiently hydrophobic.

Substances meeting the inclusion criteria, but for which no categorization as an established contact allergen in humans or an established contact allergen in animals was possible, have been assessed for structural alerts. The results are presented in four tables based on the

prediction made for the actual substance. The following SAR assessments have been used:

- Predicted sensitizer, structural alerts – compounds with structural alerts, comprising directly reactive compounds and compounds that, after specific abiotic or metabolic activation (prehaptens and prohaptens), can be predicted to be sensitizers by structural comparison with known allergens (Table 20).
- Possible sensitizer, structural alerts – compounds with structural alerts that, in comparison with known allergens with similar structures, were expected to be less reactive and hence less likely to be sensitizing. Also, compounds with structural alerts indicating possible abiotic or metabolic activation (possible prehaptens or prohaptens) but with no structural data available for comparison, were included in this group. Consequently, a possible sensitizer may turn out to be a non-sensitizer when tested *in vivo* (Table 21).
- Predicted non-sensitizer, no obvious structural alerts (Table 22).
- Not predictable, owing to insufficient/conflicting data (Table 23).

These predictions are based on chemical reactivity and the recognition of structural features in a substance

Table 20. Predicted sensitizers

Substance (INCI) name	CAS no.	Structural alerts
<i>p</i> -tert-Butyldihydrocinnamaldehyde*	18127-01-0	Schiff base
Citronellal	106-23-0	Schiff base and possible prehapten
Citronellyl nitrile	51566-62-2	Possible prehapten
Decanal	112-31-2	Schiff base
3,7-Dimethyl-1,6-nonadien-3-ol	10339-55-6	Prehaptens
Geranyl acetate	105-87-3	Prehaptens and prohaptens
Isoamyl salicylate	87-20-7	Acyl transfer agent
Methyl cinnamate	103-26-4	Michael acceptor
Methylundecanal	110-41-8	Schiff base
Myrcene	123-35-3	Prehaptens
Nerol	106-25-2	Prehaptens and prohaptens
Nerolidol (isomer not specified)	7212-44-4	Possible prehaptens
Oxacyclohexadecanone	34902-57-3	Michael acceptor
Phenethyl salicylate	87-22-9	Acyl transfer agent
<i>trans</i> -Rose ketone-5	39872-57-6	Michael acceptor and possible prehaptens

*Classified as R43.

Table 21. Possible sensitizers

Substance (INCI) name	CAS no.	Structural alerts
Ambrettolide	7779-50-2	Possible prehaptens
Amylcyclopentanone	4819-67-4	Schiff base; the combination of reactivity and hydrophobicity may be enough to confer sensitization
Benzyl acetate	140-11-4	Prohaptens via hydrolysis leading to benzyl alcohol
Carvacrol	499-75-2	Possible prehaptens
Cuminaldehyde	122-03-2	Schiff base and possible prehaptens
α -Cyclohexylidene benzeneacetonitrile	10461-98-0	Possible Michael acceptor
Cyclopentadecanone	502-72-7	Schiff base; the combination of reactivity and hydrophobicity may be enough to confer sensitization
<i>trans</i> - β -Damascone	23726-91-2	Possible Michael acceptor
<i>trans-trans</i> - δ -Damascone	71048-82-3	Possible Michael acceptor and possible prehaptens
γ -Damascone	35087-49-1	Possible Michael acceptor and possible prehaptens
Dihydromyrcenol	18479-58-8	Possible prehaptens
2,3-Dihydro-2,2,6-trimethylbenzaldehyde	116-26-7	Possible Michael acceptor and possible prehaptens and possible prohaptens
2,4-Dimethyl-3-cyclohexen-1-carboxaldehyde*	68039-49-6	Schiff base and possible prehaptens
Dimethyltetrahydrobenzaldehyde	68737-61-1	Schiff base and possible prehaptens
6-Ethylideneoctahydro-5,8-methano-2 <i>H</i> -benzo-1-pyran	93939-86-7	Possible prehaptens
2-Ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol	19-61-6	Possible prehaptens
Ethyl vanillin	121-32-4	Complex
Heliotropine	120-57-0	Possible prohaptens
3 α ,4,5,6,7,7 α -Hexahydro-4,7-methano-1 <i>H</i> -inden-5(or 6)-yl acetate	54830-99-8	Possible prehaptens
Hexahydro-methanoindenyl propionate	68912-13-0	Possible prehaptens
Ionone isomeric mixture	8013-90-9	Possible Michael acceptor and possible prehaptens
α -Ionone	127-41-3	Possible Michael acceptor and possible prehaptens
β -Ionone	79-77-6	Possible Michael acceptor
Isobergamate	68683-20-5	Possible prehaptens
Isolongifoleneketone	33407-62-4	Schiff base; the combination of reactivity and hydrophobicity may be enough to confer sensitization
Longifolene*	475-20-7	Possible prehaptens
Methoxycitronellal	3613-30-7	Schiff base
Methyl decenol	81782-77-6	Possible prehaptens
Methyl ionone (mixture of isomers)	1335-46-2	Possible Michael acceptor and possible prehaptens
Methylionanthrene	55599-63-8	Possible Michael acceptor and possible prehaptens
5-Methyl- α -ionone	79-69-6	Possible Michael acceptor and possible prehaptens
Myrtenol	515-00-4	Possible prehaptens
Nopyl acetate	128-51-8	Possible prehaptens
Phytol	150-86-7	Possible prehaptens and/or prohaptens
Rhodinol	6812-78-8	Possible prehaptens
Terpineol acetate (isomer mixture)	8007-35-0	Possible prehaptens
α -Terpinyl acetate	80-26-2	Possible prehaptens
Tricyclodecenyl propionate	17511-60-3	Possible prehaptens
Verdyl acetate	2500-83-6/5413-60-5	Possible prehaptens

*Classified as R43.

that are the same as the structural features that have been shown to cause sensitization by other substances. In cases where the SAR analysis indicates a sensitization potential, the substance should be investigated further to confirm or reject the conclusion drawn from the SAR analysis. Prediction of the sensitization potential of compounds that can act via abiotic or metabolic

activation (prehaptens or prohaptens) becomes more complex than for compounds that act as direct haptens without any activation. The complexity of the prediction increases further for those compounds that can act both as prehaptens and as prohaptens. Prediction of the sensitization potential of compounds that can act as prehaptens is further complicated by the fact that the

Table 22. Predicted non-sensitizers with no obvious structural alerts

Substance (INCI) name	CAS no.	Structural alerts
6-Acetyl-1,1,2,4,4,7-hexamethyltetraline	21145-77-7	–
Benzyl acetone	2550-26-7	Schiff base; the combination of reactivity and hydrophobicity may not be enough to confer sensitization
2-tert-Butylcyclohexyl acetate	88-41-5	–
4-tert-Butylcyclohexyl acetate	32210-23-4	–
Cyclohexyl acetate	622-45-7	–
Diphenyl ether	101-84-8	–
Ethyl 2-methylbutyrate	7452-79-1	–
Ethylene dodecanoate	54982-83-1	–
Ethylene brassylate	105-95-3	–
Eucalyptol	470-82-6	–
Hexyl acetate	142-92-7	–
Hibiscolide	6707-60-4	–
Hydroxycitronellol	107-74-4	Dehydration followed by autoxidation could give sensitizing impurities
Isoamyl acetate	123-92-2	–
Isobornyl acetate	125-12-2	–
Methoxytrimethylheptanol	41890-92-0	–
Methyl <i>p</i> -anisate	121-98-2	–
Methyl anthranilate	134-20-3	–
Methylbenzyl acetate	93-92-5	–
Methyl dihydrojasmonate	24851-98-7	Schiff base; the combination of reactivity and hydrophobicity may not be enough to confer sensitization
Oxalide	1725-01-5	–
Pentadecalactone	106-02-5	–
Phenethyl acetate	103-45-7	–
Phenethyl alcohol	60-12-8	–
Phenoxyethyl isobutyrate	103-60-6	–
Phenylisohexanol	55066-48-3	–
Phenylpropanol	122-97-4	–
Tetrahydrolinalool	78-69-3	–
Tetrahydro-methyl-methylpropyl-pyran-4-ol	63500-71-0	–
Trimethylhexyl acetate	58430-94-7	–
Trimethyl-propylcyclohexanepropanol	70788-30-6	–
γ -Undecalactone	104-67-6	–

Table 23. Not predictable

Substance (INCI) name	CAS no.	Structural alerts
Anisaldehyde	123-11-5	Owing to insufficient/conflicting data; structural similarities to benzaldehyde suggest certain activity in humans
Trichloromethyl phenyl carbonyl acetate	90-17-5	Owing to insufficient/conflicting data
Methyl β -naphthyl ether	93-04-9	Owing to insufficient/conflicting data

autoxidation patterns can differ because of differences in the stability of the intermediates formed; for example, it has been shown that autoxidation of the structural

isomers of linalool and geraniol results in different major haptens/allergens.

Categorization of fragrances as contact allergens

For the present review, clinical, epidemiological and experimental studies were evaluated, as well as modelling studies, to establish lists of: (i) established fragrance allergens (in humans and animals); (ii) likely fragrance allergens; and (iii) possible fragrance allergens. Further reviews will: (i) address fragrances that, on modification by oxidation or by enzyme-mediated processes, can produce allergens; and (ii) examine available dose–response data to determine whether safe thresholds can be established for the most common fragrance allergens.

Table 24. Fragrance substances categorized as established contact allergens in animals

INCI name (or, if none exists, perfuming name according to CosIng)	CAS no.	Human evidence: see text	EC3 value (%)
Individual chemicals			
Allyl phenoxyacetate	7493-74-5	NA	3.1
<i>p</i> -tert-Butyldihydrocinnamaldehyde	18127-01-0	NA	4.3
CYCLAMEN ALDEHYDE	103-95-7	NA	22
Dibenzyl ether	103-50-4	NA	6.3
2,3-DIHYDRO-2,2,6-TRIMETHYLBENZALDEHYDE	116-26-7	Limited	7.5
<i>trans</i> -2-Hexenal	6728-26-3	NA	2.6
2-Hexylidene cyclopentanone	17373-89-6	NA	2.4
HEXYL SALICYLATE	6259-76-3	Negative	0.18
<i>p</i> -Isobutyl- α -methyl hydrocinnamaldehyde	6658-48-6	NA	9.5
Isocyclocitral	1335-66-6	NA	7.3
α -Methyl cinnamic aldehyde	101-39-3	NA	4.5
METHYLENEDIOXYPHENYL METHYLPROPANAL	1205-17-0	NA	16.4
METHYLUNDECANAL	110-41-8	NA	10
2-Methoxy-4-methylphenol	93-51-6	NA	5.8
4-Methoxy- α -methyl benzenpropanal	5462-06-6	NA	23.6
METHYL OCTINE CARBONATE	111-80-8	Limited	2.5
Perillaldehyde <i>p</i> -mentha-1,8-dien-7-al	2111-75-3	NA	8.1
PHENYLACETALDEHYDE	122-78-1	Limited	3
Natural extracts			
Jasminum Sambac flower CERA/extract/water	91770-14-8	NA	35.4

NA, none available.

Table 25. Fragrance substances categorized as likely contact allergens by a combination of evidence

INCI name (or, if none exists, perfuming name according to CosIng)	CAS no.	Human evidence: see text	EC3 value (%)	SAR
AMBRETTOLIDE	7779-50-2	Limited	NA	+
CARVACROL	499-75-2	Limited	NA	+
CUMINALDEHYDE	122-03-2	Limited	NA	+
CYCLOPENTADECANONE	502-72-7	Limited	NA	+
<i>trans-trans</i> - δ -DAMASCONONE	71048-82-3	Limited	NA	+
DIMETHYLTETRAHYDROBENZALDEHYDE	68737-61-1	Limited	NA	+
ETHYL VANILLIN	121-32-4	Limited	NA	+
HELIOTROPINE	120-57-0	Limited	NA	+
ISOAMYL SALICYLATE	87-20-7	Limited	NA	++
ISOLONGIFOLENEKETONE	33407-62-4	Limited	NA	+
METHOXYCITRONELLAL	3613-30-7	Limited	NA	+
METHYL CINNAMATE	103-26-4	Limited	NA	++
METHYLIONANTHEME	55599-63-8	Limited	NA	+
5-METHYL- α -IONONE	79-69-6	Limited	NA	+
MYRCENE	123-35-3	Limited	NA	++
MYRTENOL	515-00-4	Limited	NA	+
NEROL	106-25-2	Limited	NA	++
Nerolidol (isomer not specified)	7212-44-4	Limited	NA	++
NOPYL ACETATE	128-51-8	Limited	NA	+
PHYTOL	150-86-7	Limited	NA	+
RHODINOL	6812-78-8	Limited	NA	++
<i>trans</i> -ROSE KETONE-5	39872-57-6	Limited	NA	++

NA, none available; SAR, structure–activity relationship.

Known fragrance allergens were categorized as established contact allergens in humans, as listed in Table 11 (n = 54) and Table 14 (n = 28). Further substances, for which sufficient animal evidence was present, were categorized as established contact allergens

in animals, as listed in Table 24 (n = 19). For a number of other fragrance substances, combinations of limited clinical data together with SAR considerations have been applied to indicate likely fragrance allergens in humans (Table 25, n = 22). Moreover, two single substances

Table 26. Fragrance substances categorized as possible contact allergens

INCI name (or, if none exists, perfuming name according to CosIng)	CAS no.	Human evidence: see text	EC3 value (%)	SAR
Individual chemicals				
CYCLOHEXYL ACETATE	622-45-7	Limited	NA	0
ETHYLENE DODECANEDIOATE	54982-83-1	Limited	NA	0
HYDROXYCITRONELLOL	107-74-4	Limited	NA	0
METHOXYTRIMETHYLHEPTANOL	41890-92-0	Limited	NA	0
METHYL <i>p</i> -ANISATE	121-98-2	Limited	NA	0
METHYL DIHYDROJASMONATE	24851-98-7	Limited	NA	0
PHENETHYL ALCOHOL	60-12-8	Limited	NA	0
PHENYLPROPANOL	122-97-4	Limited	NA	0
AMYL CYCLOPENTANONE	4819-67-4	Negative	NA	+
BENZYL ACETATE	140-11-4	Negative	NA	+
6-ETHYLIDENEOCTAHYDRO-5,8-METHANO-2 <i>H</i> - BENZO-1-PYRAN	93939-86-7	Negative	NA	+
3 α ,4,5,6,7,7 α -HEXAHYDRO-4,7-METHANO-1 <i>H</i> - INDEN-5(OR 6)-YL ACETATE	54830-99-8	Negative	NA	+
α -IONONE	127-41-3	Negative	NA	+
β -IONONE	79-77-6	Negative	NA	+
METHYL IONONE (mixture of isomers)	1335-46-2	Negative	NA	+
TERPINEOL ACETATE (mixture of isomers)	8007-35-0	Negative	NA	+
α -TERPINYL ACETATE	80-26-2	Negative	NA	+
CITRONELLYL NITRILE	51566-62-2	NA	NA	++
α -CYCLOHEXYLIDENE BENZENEACETONITRILE	10461-98-0	NA	NA	+
DECANAL	112-31-2	NA	NA	++
DIHYDROMYRCENOL	18479-58-8	NA	NA	+
3,7-DIMETHYL-1,6-NONADIEN-3-OL	10339-55-6	NA	NA	++
2-ETHYL-4-(2,2,3-TRIMETHYL-3-CYCLOPENTEN-1- YL)-2-BUTEN-1-OL	28219-61-6	NA	NA	+
GERANYL ACETATE	105-87-3	NA	NA	++
HEXAHYDRO-METHANOINDENYL PROPIONATE	68912-13-0	NA	NA	+
IONONE (mixture of isomers)	8013-90-9	NA	NA	+
ISOBERGAMATE	68683-20-5	NA	NA	+
METHYL DECENOL	81782-77-6	NA	NA	+
TRICYCLODECENYL PROPIONATE	17511-60-3	NA	NA	+
OXACYCLOHEXADecenONE	34902-57-3	NA	NA	++
VERDYL ACETATE	2500-83-6/ 5413-60-5	NA	NA	+
<i>trans</i> - β -Damascone	23726-91-2	NA	NA	+
γ -Damascone	35087-49-1	NA	NA	+
Citronellal	106-23-0	NA	NA	++
Phenethyl salicylate	87-22-9	NA	NA	++
Natural extracts				
<i>ACORUS CALAMUS</i> ROOT OIL	84775-39-3	Limited	NA	-
<i>CEDRUS DEODARA</i> WOOD OIL	91771-47-0	Limited	NA	-
<i>CITRUS AURANTIUM AMARA</i> LEAF OIL	72968-50-4	Limited	NA	-
<i>CITRUS TANGERINA</i>	223748-44-5	Limited	NA	-
<i>CYMOPOGON NARDUS/WINTERIANUS</i> HERB OIL	89998-15-2; 91771-61-8	Limited	NA	-
<i>ILLICIAM VERUM</i> FRUIT OIL	84650-59-9	Limited	NA	-
<i>LAVANDULA SPICA</i>	97722-12-8	Limited	NA	-
<i>LITSEA CUBEBA</i>	90063-59-5	Limited	NA	-
<i>PELARGONIUM ROSEUM</i>	90082-55-6	Limited	NA	-
<i>SALVIA</i> spp.	Diverse	Limited	NA	-
<i>TARGETES PATULA</i>	91722-29-1	Limited	NA	-
<i>THYMUS</i> spp.	84929-51-1	Limited	NA	-
<i>VETIVERIA ZIZANOIDES</i>	8016-96-4; 84238-29-9	Limited	NA	-

NA, none available.

Table 27. Established fragrance contact allergens of special concern (single chemicals only)

Cinnamal
Cinnamyl alcohol*
Citral
Coumarin
Eugenol*
Farnesol*
Geraniol*
Hydroxycitronellal
Hydroxyisohexyl 3-cyclohexene carboxaldehyde
Isoeugenol*
Limonene (oxidized)
Linalool* (oxidized)

*Including their respective esters.

[2,4-dimethyl-3-cyclohexen-1-carboxaldehyde (CAS no. 68039-49-6) and longifolene (CAS no. 475-20-7)] and two natural extracts [*Citrus paradisi* (CAS no. 8016-20-4) and *Mentha arvensis* (CAS no. 68917-18-0)] were classified as R43, according to the submission by the IFRA. The evidence on which this classification was based was not available, so the validity of classification cannot be assessed. Nevertheless, the four substances/substance mixtures should additionally be treated as likely contact allergens. Finally, SAR has also been applied to substances for which human data are lacking, to identify fragrance chemicals that have the structural potential to be contact allergens. Substances with insufficient human data were also considered as possible fragrance allergens. For these, further tests (experimental/clinical data) are required (Table 26).

Regarding the above categorization of fragrance substances, the following aspects need to be considered when interpreting an outcome other than established contact allergen in humans:

- If human evidence is negative, there is still a potential risk, as, in this set of substances, the number of (consecutive) patients tested was low, that is, up to a few hundred.
- If EC3 values were given as higher than a certain value, an exact EC3 could not be established, as the substance had been tested in too low concentration(s). In these cases, it was not possible to categorize the substances as an established contact allergen in animals.
- For SAR, the categories of prediction are: non-sensitizer (0); possible sensitizer (+); predicted sensitizer (++); and not predictable (for details, see Tables 20–23). SAR predictions are only considered when human and animal data are limited or missing.

- Several substances are currently banned from use in cosmetic products by Annex II of the Cosmetics Directive, because of concerns regarding one or more toxicological endpoints. Although available clinical evidence regarding this set of substances is listed in Annex I to the SCCS opinion (101), these substances have not been further evaluated.

The fragrance ingredients listed in Tables 11 and 14 have clearly caused disease in humans, and, based on the clinical experience alone, these 82 substances were classified as established contact allergens in humans – 54 individual chemicals and 28 natural extracts (mixtures of chemicals) – including all 26 fragrance allergens previously identified by the SCCNFP (1). For a number of other substances, no patch test data were available, but positive animal data, obtained by a validated guideline method (LLNA) addressing hazard, indicate that a risk for humans is very likely to exist, given sufficient exposure (Table 24). In other cases, only a relatively small number of patients tested positive (limited human evidence). Here, combination with SAR analyses corroborates the conclusion that these substances, too, are sufficiently qualified to be regarded as likely fragrance allergens (Table 25).

Of those 82 substances identified as established contact allergens in humans, 12 chemicals (listed in Table 27) and eight natural extracts are considered to be of special concern, as they have given rise to at least 100 reported cases. These substances pose a particularly high risk of sensitization to the consumer. One substance, HICC, has been shown to be the cause of allergic contact dermatitis in > 1500 reported cases since 1999. The cases are only those reported in scientific publications, and therefore the actual number of cases is severely underestimated.

Information on the presence of all of the substances shown in Tables 11, 14, 24 and 25, and the four additional likely allergens, in cosmetic products is important in order to enable aimed testing of patients with contact dermatitis and to diagnose fragrance allergy without delay. Furthermore, this information is important to sensitized consumers, as it will enable them to avoid cosmetic products that they may not tolerate. Additionally, these 127 substances also have to be listed on detergent products [Detergents Regulations: Regulation (EC) 648/2004, March 2004]. Restrictions and labelling of allergenic fragrances in toys (Directive 2009/48/EC of the European Parliament and of the Council of 18 June 2009 on the Safety of Toys) are now linked to the Cosmetics Directive, requirements that will enter into force on 20 July 2013.

The substances shown in Table 26 are possible contact allergens, and further data are required to judge whether these are contact allergens in humans and give rise to contact allergy in consumers.

The presence of the chemicals in Table 27 should be limited to a level that will be safe for most consumers. On the basis of the available evidence, this level is a maximum of 100 ppm in the finished cosmetic product [see link to opinion (101) for further information on how this has been derived]. Three substances have either caused an exceptionally high number of cases (HICC) or have been shown to have high allergenic potential as constituents of the natural extracts *E. prunastri* and *Evernia furfuracea* (chloroatranol and atranol). These three substances should not be present in cosmetic products.

Conclusions

The present review of clinical and experimental data shows that many fragrance substances have been shown to be sensitizers in humans. Moreover, animal experiments indicate that additional fragrance substances can be expected to be contact allergens in humans, although human evidence is currently lacking. Additionally, limited human and/or animal evidence together with SAR

analysis suggests that other fragrance ingredients may be a cause of concern with regard to their potential to cause contact allergy in humans.

Ingredient listing is important in clinical practice for the management of patients who are allergic to one or more of the listed fragrance chemicals. It is also important for the diagnosed patients, in order to avoid future exposure to fragrance contact allergens that they may not tolerate. The substances falling in the above three categories represent those fragrance ingredients that the consumer should be made aware of when present in cosmetic products.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

File S1. Catalogue of fragrance chemicals and natural mixtures

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Annex I to “Fragrance Allergens in Cosmetic Products”

Contents

Single chemicals.....	2
Catalogue of single chemicals evaluated.....	5
Natural extracts / essential oils.....	74
Catalogue of natural extracts / essential oils evaluated.....	75
References	110

Single chemicals

Often, results with the single constituents of the FM I or, yet more rarely, FM II, are presented in one paper. As the main ordering of this annex is by allergen, core information on these studies is presented in a tabular format and referenced by a unique acronym in the single sections, to avoid redundancy. Regarding nomenclature, terms which are often not officially an INCI Name but Perfuming Name as listed by CosIng are used. “Current Regulation” refers to the EU Cosmetics Directive only.

Table 1: Background information on studies reporting results with (all) single constituents of the FM I (**amyl cinnamal, cinnamyl alcohol, cinnamal, eugenol, geraniol, hydroxycitronellal, isoeugenol, EVERNIA PRUNASTRI**)

Reference	Country	Study period, Patients	Comments by reviewers
Larsen 2002 c (1)	7 industrial countries worldwide	Prior to 2002 n=218 patients with known contact allergy to fragrance ingredients	Test concentrations identified as non-irritating in serial dilution testing in 20 healthy volunteers
Utrecht 1999 (2)	Utrecht, The Netherlands	1994-1998 n=757 patients with suspected ACD to cosmetics	All patients tested with FM I and single constituents
Sheffield 1999 (3)	UK	1994-1995 n=744, 40 of these positive to FM I and tested with single constituents	
IVDK 2007 (4)	Germany + one centre in Austria and Switzerland each	01/2003 – 12/2004, n=1658 to 21325, see text, consecutive patients	
Hungary 2002 (5)	Hungary, multicentre study,	1998-1999, n=3604 patients	recruitment not clear, presumably consecutive patients
Groningen 2009 (6)	Groningen, The Netherlands	04/2005-06/2007 n=320	patients selected according to history or site suspicious of contact allergy to fragrance ingredients
IVDK 2010 (7)	Germany, Switzerland and one centre in Austria	2005-2008 n=36961 tested with FM I, n=4167 with FM II and all SC	

Table 2: Results of PTing with single constituents of the FM I in patients positive to the FM I (as percent)

N(pos) to FM I, ref.	<i>Evernia prun.</i>	Isoeug.	Hydroxy-citron.	Cinnamal	Cinnamyl alcohol	Eugenol	Geralniol	Alphamyl cinnamal
N=160 (5)	13.1%	14.8%	2.5%	8.1%	20.6%	8.8%	7.5%	5.0%
N= 991 (8)	18.4%	11.2%	10.1%	6.1%	6.1%	6.6%	4.6%	2.4%
N=50 (2)	19.6%	14.3%	8.9%	8.9%	7.1%	5.4%	2.7%	0%
n=40 Sheffield 1999 (3)	30%	20%	2.5%	12.5%	10%	5%	0%	0%
N=226 Coimbra 2000 (9)	22.1%	19.9%	6.6%	13.3%	7.9%	14.6%	8.4%	4.4%
N=655 IVDK 2010 (7)	29.8%	18.0%	12.8%	11.6%	9.6%	6.7%	4.7%	2.8%

Table 3: Background information on studies reporting results with (all) single constituents of the FM II (**citronellol, citral, coumarin, hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC), Farnesol, alpha-Hexyl-cinnamic aldehyde**)

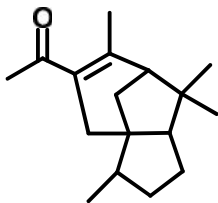
Reference	Country	Study period, Patients	Comments by reviewers
IVDK 2007 (4)	Germany + one centre in Austria and Switzerland each	01/2003 – 12/2004, n=1658 to 21325, see text, consecutive patients	
EU 2005 (10)	6 European centres	10/2002 – 06/2003, n=1701	Applied in consecutive patients
Groningen 2009 (6)	Groningen, The Netherlands	04/2005-06/2007 n=320	patients selected according to history or site suspicious of contact allergy to fragrance ingredients
IVDK 2010b (11)	Germany, Switzerland and one centre in Austria	2005-2008 n=35633 tested with FM II, n=2217 with all SC	

Table 4: Background information on studies reporting results with several fragrance compounds not, or only partly, corresponding to mixes (later created) or with essential oils

Reference	Country	Study period, Patients
deGroot 2000 (12)	The Netherlands (multicentre)	09/1998-04/1999 n=1825 consecutive patients
An 2005 (13)	South Korea (multicentre)	04/2002 – 06/2003 n=422 consecutive patients
Sugiura 2000 (14)	Nagoya, Japan	1990-1998 n=1483 patients with suspected cosmetic dermatitis
Frosch 1995 (15)	11 European depts.	Prior to 1995

Reference	Country	Study period, Patients
		n=1069 consecutive patients
Frosch 2002 a (16)	6 European depts.	10/1997-10/1998 n=1855 consecutive patients
Frosch 2002 b (17)	6 European depts.	Prior to 2002 n=1606 consecutive patients
Coimbra 2000 (9)	Portugal	07/1989-06/1999 n=226 with FM I SC n=67 also with other fragrances
Larsen 1977 (18)	US	1977 n=20 “perfume-sensitive patients”
Larsen 2001 (19)	worldwide multicentre	? (prior to 2001) n=178 patients with known contact allergy to fragrance ingredients
Belsito 2006 (20)	North American (5 US, 1 Canadian) depts.	2003 n=1603 patients
NACDG 2009 (21)	US and Canada	2005-2006 n= 4454 patients
Wöhrl 2001 (22)	“FAZ” clinic Vienna	1997-2000 n=747 of 2660 consecutive patients tested with special series
EECDRG 1995 (15)	European, multicentre	Different fragrances, tested in 2 concentrations, in sets of about 100 patients each in different centres
Goossens 1997 (23)	Leuven, Belgium	1978-1987 n=111 “Japanese perfume series” (highly selected patients)
Malten 1984 (24)	Dutch multicentre	N=182 patients with suspected cosmetic dermatitis tested with 22 fragrance compounds
DeGroot 1985 (25)	Dutch	N=179 patients with suspected cosmetic dermatitis tested with 16 fragrance compounds
Rudzki 1976 (26)	Warsaw, Poland	N=200 consecutive patients
Rudzki 1986 (27)	Warsaw, Poland	N=86 patients of 299 (of 5315) patients with positive reaction to FM I tested with essential oils series
Santucci 1987 (28)	Rome, Italy	N=1500 consecutive patients; n=63 reacting positively to FM I re-tested with extended fragrance series
Nakayama 1974 (after (29))	Japan	N=183 patients with cosmetic dermatitis
IVDK 2010c (30)	Germany, Switzerland and one centre in Austria	15682 patients tested with at least one essential oil in different test series
Trattner/David (31)	Tel Aviv, Israel	N=641 consecutive patients

Catalogue of single chemicals evaluated

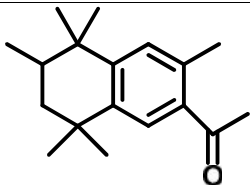
ACETYLCEDRENE	
CAS # 32388-55-9	
EC # 251-020-3	
1-[(3R,3aR,7R,8aS)-2,3,4,7,8,8a-hexahydro-3,6,8,8-tetramethyl-1H-3a,7-methanoazulen-5-yl]-ethanone	
Other names 1-(2,3,4,7,8,8a-hexahydro-3,6,8,8-tetramethyl-1H-3a,7-methanoazulen-5-yl)-, [3R-(3 α ,3a β ,7 β ,8a α)]-ethanone; 1H-3a,7-Methanoazulene, ethanone deriv.; Acetyl- α -cedrene; Lixetone; Vertofix	
Current regulation: /	

Clinical data:

In the Frosch 2002 a study, a total of 0.2% had positive PT reactions (16). In the Frosch 1995 dose-finding pilot study, 1 positive reaction to 1% and none to 5% “Vertofix ®” in pet., tested in 100 consecutive patients in Stockholm, were observed (15). In a case report, a 28-year-old patient with axillary dermatitis after using 2 different deodorants tested positive not only to HICC, but also to acetyl cedrene (tested 10.8% in diisopropylene glycol (20 healthy controls negative) (32). In this case report it is stated that “Acetyl cedrene (Vertofix Coeur) is a complex reaction mixture of which a principal constituent is methyl cedryl ketone”.

Additional information:

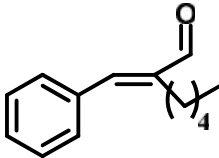
Acetyl cedrene (Vertofix®, IFF) is a complex mixture obtained from cedar wood oil by the acetylation of terpenes. The principal component of acetyl cedrene is methyl cedryl ketone (CAS 32388-55-9). It is a “top 100” substance (IFRA, pers. comm.2010)

6-ACETYL-1,1,2,4,4,7-HEXAMETHYLTETRALINE	
CAS # 21145-77-7	
EC # 216-133-4 / 244-240-6	
1-(5,6,7,8-Tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthalenyl)-ethanone	
AHMT (perfume), AHTN, Extralide, Fixolide, Musk tonalid, NSC 19550, Tentarome, Tetralide, Tonalid, Tonalide.	
Current regulation: Annex III, part 1, entry 182	

Clinical data:

In the Frosch 1995 dose-finding pilot study, no positive reaction to 1% and 5% “Tonalide ®” in pet., tested in 313 consecutive patients in Bordeaux and London, were observed (15).

Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).

AMYL CINNAMAL	
CAS # 122-40-7	
EC # 204-541-5	
2-(Phenylmethylene)-heptanal	
Cinnamaldehyde, α -amyl- (4CI); Cinnamaldehyde, α -pentyl- (6CI,7CI,8CI); 2-(Phenylmethylene)heptanal; 2-Benzylideneheptanal; Amylcinnamaldehyde; Amylcinnamic acid aldehyde; Amylcinnamic aldehyde; Flomine; Jasminal; Jasminaldehyde; Jasmine aldehyde; NSC 6649; Pentylcinnamaldehyde; α -Amyl- β -phenylacrolein; α -Amylcinnamal; α -Amylcinnamaldehyde; α -Pentylcinnamaldehyde	
Current regulation: Annex III, part 1, entry 67	

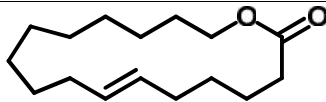
Clinical data:

In the “background information” section of the 1999 opinion (33), amyl cinnamal (synonymous: alpha amyl cinnamaldehyde) has been classified as frequently reported contact allergen because it has been identified as a cause of allergic reactions in persons with eczema from cosmetic products.

Since the last SCCNFP-opinion of 1999, the IVDK 2007 study yielded n=4, i.e., 0.2% (95% CI: 0.1 – 0.5%) positive reactions to this compound (1% pet.) in 2062 consecutively PTed patients (4). In the Groningen 2009 study, no positive reactions to this allergen, tested at 2% pet., were observed (6). The Larsen 2001 study yielded 2.3% positive reactions in 178 patients with known contact allergy to fragrance ingredients (test concentration: 5% pet.) (19). In the Wöhrl 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded n=2 (0.3%) positive reactions to amyl cinnamal (22). The IVDK 2010 study, 0.26% (95% CI: 0 – 0.60%) of 1214 consecutively tested patients reacted to the compound, while 0.61% (95% CI: 0.36 – 0.86%) of 4375 of patients tested in a more aimed manner, partly as break-down testing to the FM I, had a positive PT reaction (7).

Additional information:

It is a “top 100” substance and classified as R43 (IFRA, pers. comm. 2010).

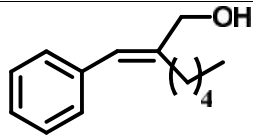
AMBRETTOLIDE	
CAS # 7779-50-2	
EC # 231-929-1	
Oxacycloheptadec-7-en-2-one	
1-Oxa-7-cycloheptadecen-2-one; 16-Hydroxy-6-hexadecenoic acid lactone; 16-Hydroxy-6-hexadecenoic acid ω -lactone	
Current regulation: /	

Clinical data:

The Larsen 2001 study, using omega-6-hexadecenlactone (HDL, 5% pet.) as test concentration, diagnosed 3.4% positive reactions in 178 patients with known contact allergy to fragrance ingredients (19).

Additional information:

Ambrettolide is 1 of 2 components of Ambrette seed oil (obtained from *Hibiscus abelmoschus* L., *Malvaceae*) responsible for the musk odour. In Surburg/Panten, the compound has the chemical name (Z)-7-hexadecen-16-olide (or Hexadec-7-en-16-olide according to CosIng), CAS 123-69-3 (34).

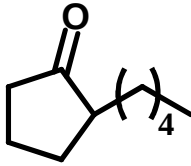
AMYL CINNAMYL ALCOHOL	
CAS # 101-85-9	
EC # 202-982-8	
2-(Phenylmethylene)-heptan-1-ol,	
2-Benzylidene- (6CI,8CI)1-heptanol; 2-Amyl-3-phenyl-2-propen-1-ol; 2-Benzylidene-1-heptanol; 2-Pentyl-3-phenyl-2-propen-1-ol; Buxinol; α -Amylcinnamic alcohol; α -Amylcinnamyl alcohol	
Current regulation: Annex II, Part 1, entry 74	

Clinical data:

In the “background information” section of the 1999 opinion, amyl cinnamyl alcohol is mentioned to cross-react with amyl cinnamal. Moreover, this compound has been identified as a cause of allergic reactions in a notable number of persons with eczema from the use of cosmetic products (33).

Since the last SCCNFP-opinion of 1999, the IVDK 2007 study yielded 0.4% (95% CI: 0.1 – 0.7%) positive reactions in 1977 consecutively PTed patients (4). The IVDK 2010 study, 0.79% (95% CI: 0.54 – 1.04%; percentages standardised for age and sex) of 5650 patients PTed reacted to the compound (7). In the Groningen 2009 study, 0.6% (95% CI: 0.1 – 2.2%) had positive reactions to this allergen (6).

Additional information: A RIFM review is available (35) where selected clinical studies published until 1994 were considered.

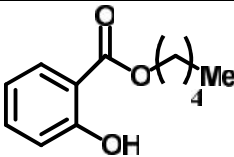
AMYLCYCLOPENTANONE	
CAS # 4819-67-4	
EC # 225-392-2	
2-Pentylcyclopentanone	
2-Pentyl-1-cyclopentanone; 2-Pentylcyclopentanone; 2-Pentylcyclopenten-1-one; 2-n-Amylcyclopentanone; 2-n-Pentylcyclopentanone; Delphone	

Current regulation: /

Clinical data:

In the Larsen 2001 study, none of 178 patients with contact allergy to fragrance ingredients reacted positively to this ingredient, PTed at 5% pet. (19).

Additional information: /

AMYL SALICYLATE	
CAS # 2050-08-0	
EC # 218-080-2	
Pentyl-2-hydroxybenzoate	
Amyl ester salicylic acid, (4CI); Pentyl ester salicylic acid, (6CI,8CI); 2-Hydroxybenzoic acid pentyl ester; Amyl salicylate; NSC 403668; NSC 44877; NSC 46125; Pentyl salicylate	

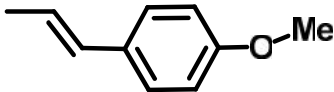
Current regulation: /

Clinical data:

In the Frosch 2002 a study, a total of n=3 (0.2%) had positive PT reactions (16). In the Frosch 1995 dose-finding pilot study, no positive reaction to 1% amyl salicylate and 1 positive reaction to 5% amyl salicylate were observed in 100 consecutive patients patch tested in Stockholm (15).

Additional information:

A RIFM review is available (36). It is a “top 100” substance (IFRA, pers. comm.2010)

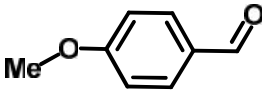
<i>trans</i>-ANETHOLE	
CAS # 4180-23-8	
EC # 224-052-0 / 203-205-5	
1-Methoxy-4-(1E)-1-propen-1-yl-benzene	
(E)-p-Propenyl-anisole (8CI); (E)-1-Methoxy-4-(1-propenyl)-benzene; 1-methoxy-4-(1E)-1-propenyl-benzene (9CI); (E)-1-(4-Methoxyphenyl)propene; (E)-1-p-Methoxyphenylpropene; (E)-Anethol; (E)-Anethole (REACH, EINECS); <i>E</i> -Anethole (INCI); 1-Methoxy-4-[(1E)-1-propenyl]benzene; (E)-1-Methoxy-4-(1-propenyl)-benzene (CosIng); NSC 209529; trans-1-(4-Methoxyphenyl)-1-propene; trans-1-(p-Methoxyphenyl)-1-propene; trans-1-(p-Methoxyphenyl)propene; trans-1-p-Anisylpropene; trans-4-(1-Propenyl)anisole; trans-Anethol; trans-Anethole; trans-p-Anethole; trans-p-Methoxy-β-methylstyrene	
Current regulation: /	

Clinical data:

A case of a 64 year old patient, who developed severe cheilitis and a loss of taste has been described (37). Both were reversible after the cessation of use of previous toothpastes. The patch test was strongly positive to anethole (isoform not given) 5% pet.; this was found an ingredient of the causative toothpaste. Two cases of occupational allergic contact dermatitis occurring in a traditional cake factory due to anise oil have been described, both testing (strongly) positive to anise oil (5% o.o.) and anethole (5% pet.) (38).

Additional information:

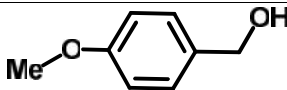
It is a “top 100” substance (IFRA, pers. comm.2010). trans-Anethole can be purified from star anise oil (34, 39), see 3.2., and is the main component of anise, star anise and fennel oils (38)

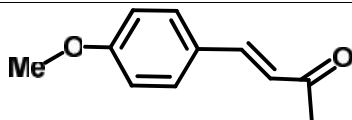
ANISALDEHYDE	
CAS # 123-11-5	
EC # 204-602-6	
4-Methoxy-benzaldehyde	
p-Methoxybenzaldehyde; p-Anisaldehyde; 4-Anisaldehyde; Aubepine; Crategine; NSC 5590; Obepin; p-Anisic aldehyde; Anisic aldehyde; p-Formylanisole.	

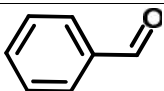
Current regulation: /

Clinical data: /

Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).

ANISYL ALCOHOL	
CAS # 105-13-5	
EC # 203-273-6	
4-Methoxy-benzenemethanol	
p-Methoxy-benzyl alcohol (8CI); (4-Methoxyphenyl)methyl alcohol; 4-(Hydroxymethyl)anisole; 4-(Methoxyphenyl)methanol; 4-Methoxy- α -hydroxytoluene; 4-Methoxybenzenemethanol; 4-Methoxybenzyl alcohol; Anise alcohol; Anisic alcohol; NSC 2151; [4-(Methoxy)phenyl]methanol; p-(Methoxyphenyl)methanol; p-Anisalcohol; p-Anisyl alcohol; p-Methoxybenzyl alcohol	
Current regulation: Annex III, part 1, n° 80	
Clinical data:	
In the “background information” section of the 1999 opinion, anisyl alcohol is classified as “less frequently reported allergen”; 2 studies were identified where 3 and 4 cases, respectively, with cosmetic dermatitis due to contact allergy to anisyl alcohol had been reported (33). Since the last SCCNFP-opinion of 1999, the IVDK 2007 study yielded n=1, i.e., 0.1% (95% CI: 0.00 – 0.3%) positive reactions in 2004 consecutively PTed patients, patch test concentration: 1% pet. (4). Similar results were obtained in the following period, with n=1 (and n=3 irritant and n=6 doubtful) reactions in 986 patients tested with 1% in pet. (30). In the Groningen 2009 study, no positive reactions to this allergen, tested at 5% pet., were observed in 320 patients (6). This test concentration has been regarded as relatively high by Hostynek and Maibach (40). Additional information: /	

ANISYLIDENE ACETONE	
CAS # 943-88-4	
EC # 213-404-9	
4-(4-Methoxyphenyl)-3-Buten-2-one	
1-(p-Methoxyphenyl)-1-buten-3-one; 4-(4-Methoxyphenyl)-3-buten-2-one; 4-(p-Methoxyphenyl)-3-buten-2-one; 4-Methoxybenzalacetone; 4-Methoxybenzylideneacetone; 4-Methoxystyryl methyl ketone; 4'-Methoxybenzylideneacetone; Anisalacetone; Methyl p-methoxystyryl ketone; NSC 31752; NSC 7946; p-Anisalacetone; p-Methoxybenzalacetone; p-Methoxybenzylideneacetone; p-Methoxystyryl methyl ketone	
Current regulation: Annex III, part 1, n° 443	
Clinical data:	
In the Malten 1984 study, 1.1% of 182 patients displayed a positive PT reaction to anisylidene acetone 2% pet. (24)	
Additional information: /	

BENZALDEHYDE	
CAS # 100-52-7	
EC # 202-860-4	
Benzaldehyde	

Artificial Almond Oil; Benzaldehyde FFC; Benzenecarbonal;
Benzenecarboxaldehyde; Benzoic acid aldehyde; Benzoic
aldehyde; NSC 7917; Phenylformaldehyde; Phenylmethanal

Current regulation: /

Clinical data:

In the Wöhrle 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded n=3 (0.4%) positive reactions to benzaldehyde 5% pet. (22). The IVDK 2010 study, 6 weak positive reactions were observed, i.e., 0.16% (95% CI: 0.03 – 0.29%; percentages standardised for age and sex) of 2820 patients PTed reacted to the compound (7). A review is available in the Int. J. Toxicol. (41). In the case of a 19 year old pastry maker, Seite-Bellezza et al. report on immediate reactions to MP, cinnamal and benzaldehyde (tested at 5% pet.) subsiding after a few hours, in line with the patient's history (42).

Additional information: /

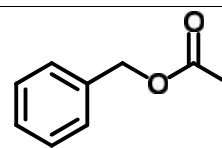
BENZYL ACETATE

CAS #140-11-4

EC # 205-399-7 / 202-940-9

Benzyl acetate

Benzyl ester acetic acid; Benzyl alcohol, acetate (6CI);
(Acetoxymethyl)benzene; Benzyl ethanoate; NSC 4550;
Phenylmethyl acetate; Methyl Phenylacetate; α -Acetoxytoluene
; Methyl α -Toluate



Current regulation: /

Clinical data:

In the Frosch 1995 dose-finding pilot study, no positive reaction to 1% and 5% benzyl acetate in pet., tested in 100 consecutive patients in Odense, DK, were observed (15). Benzyl acetate is a component of several natural mixtures, for example a major constituent of Narcissus abs., and a minor constituent of Jasmine abs. (17).

Additional information: It is a "top 100" substance (IFRA, pers. comm.2010).

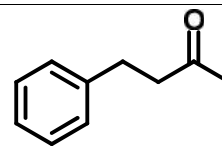
BENZYL ACETONE

CAS # 2550-26-7

EC # 219-847-4

4-Phenyl-2-butanone

4-Phenylbutan-2-one (REACH, EINECS); Benzylacetone;
Methyl 2-phenylethyl ketone; Methyl phenethyl ketone; NSC
44829; NSC 813M; Phenethyl methyl ketone; 1-Phenyl-3-
butanone; 2-Phenylethyl methyl ketone



Current regulation: /

Clinical data: /

Additional information:

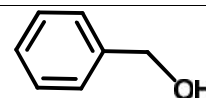
It is a "top 100" substance (IFRA, pers. comm.2010). A RIFM review is available (43).

BENZYL ALCOHOL

CAS # 100-51-6

EC # 202-859-9

Phenylmethanol



Benzyl alcohol; (Hydroxymethyl)benzene; Benzenecarbinol; Benzylic alcohol; NSC 8044; Phenylcarbinol; Benzenemethanol; Phenylmethyl alcohol; Sunmorl BK 20; TB 13G; α -Hydroxytoluene; α -Toluenol	
Current regulation: Annex III, part 1, n° 45; Annex VI, part1, n ° 34	

Clinical data:

In the “background information” section of the 1999 opinion, benzyl alcohol is classified as allergen frequently causing allergic reactions. It has been found to cause allergic reactions in 1.2 to 15% of patients with eczema from cosmetic products (33). A CIR expert panel review is available in the Int. J. Toxicol. (44).

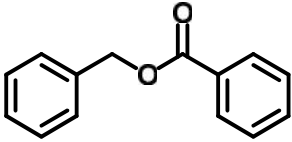
Since the last SCCNFP-opinion of 1999, the IVDK 2007 study yielded 0.3% (95% CI: 0.1 – 0.7%) positive reactions in 2166 consecutively PTed patients (4). In the Groningen 2009 study, n=1, i.e. 0.3% (95% CI: 0.01 – 1.7%) had positive reactions to this allergen (6). Both in terms of case reports (45-47) and clinical epidemiology data (0.22 % [95% CI: 0.16 – 0.28%] positive tested with benzyl alcohol in the context of a “topical drugs” series, n=26448 (7)) the relevance of this alternative exposure is highlighted. In a study from Alicante, Spain, 86 selected patients were tested with benzyl alcohol, yielding 2 positive reactions (48).

After application of saline soaks preserved with benzyl alcohol onto his stasis dermatitis, a 53 year old patient developed a rash, which was, according to test results obtained by J. D. Guin and J. Goodman, at least partly due to an immediate hypersensitivity to benzyl alcohol, as verified by an intense urticarial reaction at the test site lasting several days (49).

According to 2 cases reported by A. A. Fisher, PT-proven, relevant delayed type hypersensitivity is not associated with immediate reactions in scratch or intradermal tests (50). D. W. Shaw describes a patient with allergic contact dermatitis caused by benzyl alcohol in a hearing aid impression material and in topical medications (51). Another contribution points to covert exposures to benzyl alcohol even in products labelled “fragrance free” (52) probably because benzyl alcohol is used as preservative, or an essential oil containing benzyl alcohol is used as cosmetic ingredient.

Additional information:

Benzyl alcohol is a component of several natural mixtures, including Myroxylon pereirae resin, which have been used for extraction, but is nowadays synthesised (53). It is permitted in certain foodstuffs (liquors: < 100 mg/l, sweets and cakes: < 250 mg/kg) under the coding “E 1519” (http://www.zusatzstoffe-online.de/zusatzstoffe/317.e1519_benzylalkohol.html, last accessed 2009-11-27). In addition to being a fragrance compound (which may be used, even in relatively high concentration, to scent topical medications (54)), benzyl alcohol is used as antioxidant in topical therapeutics or cosmetics. The German “Rote Liste” (<http://www.rote-liste.de>, last accessed 2009-11-11), for instance, lists 205 specialties containing benzyl alcohol. Benzyl alcohol may be used up to 1.0% as a preservative in cosmetic products according to the Cosmetic Directive 76/768/EEC

BENZYL BENZOATE	
CAS # 120-51-4	
EC # 204-402-9	
Benzyl benzoate	
Benzyl ester benzoic acid; Ascabin; Ascabiol; Benylate; Benzyl benzenecarboxylate; Benzyl benzoate; Benzyl phenylformate; Benzylets; Colebenz; NSC 8081; Nicca Sunsolt LM 7EX; Novoscabin; Pelemol B66; Peruscabin; Phenylmethyl benzoate; Scabagen; Scabanca; Scabcare BB; Scabide; Scabiozon; Scobenol; Vanzoate; Venzonate	

Current regulation: Annex III, part 1, n° 85

Clinical data:

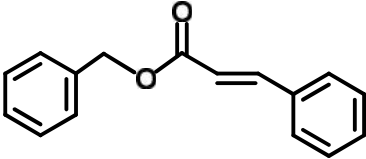
In the “background information” section of the 1999 opinion, benzyl benzoate is classified as “less frequently reported allergen”; in several studies, only single cases had been reported in each, except for patients sensitive to MP (33).

Since the last SCCNFP-opinion of 1999, the IVDK 2007 study yielded n=1, i.e., 0.1% (95% CI: 0.00 – 0.3%) positive reactions in 2003 consecutively PTed patients, test concentration 1% pet. (4). In the subsequent period (2005-2008), n=1062 patients were tested in the IVDK 2010 study, with no positive reactions (7). In the Groningen 2009 study, no positive reactions to this allergen, tested at 5% pet., were observed in 320 patients (6). Thus, the pooled proportion of positive patch test reactions is 1 / 3385 (0.03%, exact upper 1-sided 95% CI: 0.14%)

Additional information:

Benzyl benzoate naturally occurs in MP resin and ylang-ylang oil. Nowadays it is synthesised and used for a variety of purposes (53). These include use as a scabicide (one brand specialty on the German market, using a concentration of 10% for children and 25% for adults), possibly with some differences among European countries. In France, a combination of benzyl benzoate 10% and sulfiram 2% is reported to be used most often (55). Hausen et al. review the older literature and mention a study identifying 1 sensitised patient in 73 patients treated for scabies (details not given) (53). According to the mandatory factsheet (see PDF “benzylbenzoate_infosheet_DE.pdf”) dermatitis after anti-scabies treatment is “rare”, in a range between 1:1000 and 1:10000.

It is a “top 100” substance (IFRA, pers. comm.2010).

BENZYL CINNAMATE	
CAS # 103-41-3	
EC # 203-109-3	
Benzyl 3-phenylprop-2-enoate	
Benzyl ester cinnamic acid; 3-phenyl-phenylmethyl ester 2-propenoic acid; 3-Phenyl-2-propenoic acid benzyl ester; Benzyl 3-phenylpropenoate; Benzyl γ-phenylacrylate; Cinnamein; NSC 11780; NSC 44403	

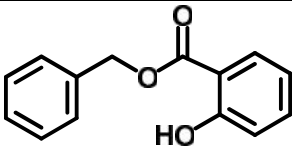
Current regulation: Annex III, part 1, n° 81

Clinical data:

In the “background information” section of the 1999 opinion, benzyl cinnamate (synonymous: benzyl 3-phenyl-2-propenoate, cinnamein) is classified as “less frequently reported allergen”; one study of patients with contact allergy to cosmetic products was identified and further a study where benzyl cinnamate associated with contact sensitisation to MP (33).

Since the last SCCNFP-opinion of 1999, the IVDK 2007 study yielded 0.3% (95% CI: 0.1 – 0.6%) positive reactions in 2042 consecutively PTed patients, test concentration 5% pet. (4). The IVDK 2010 study, n=4 weak positive were observed, amounting to 0.12% (95% CI: 0 – 0.25%; percentages standardised for age and sex) of 2872 patients PTed reacted to the compound (7). In the Groningen 2009 study, no positive reactions to this allergen, using the same test concentration, were observed in 320 patients (6). In the Wöhr 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded n=3 (0.4%) positive reactions (22).

Additional information: A RIFM review is available (56).

BENZYL SALICYLATE	
CAS # 118-58-1	
EC # 204-262-9	
Benzyl 2-hydroxybenzoate	
Salicylic acid, benzyl ester; Benzoic acid, 2-hydroxy-, phenylmethyl ester; Benzyl o-hydroxybenzoate; NSC 6647	

Current regulation: Annex III, part 1, n° 75

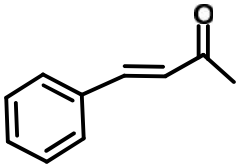
Clinical data:

In the “background information” section of the 1999 opinion (33), benzyl salicylate is classified among the frequent allergens, with 0.2 to 10% of patients with eczema from cosmetic products testing positively. In one study, benzyl salicylate accounted for 75% of reactions to commercial products (33).

Since the last SCCNFP-opinion of 1999, the IVDK 2007 study yielded n=2, i.e. 0.1% (95% CI: 0.01 – 0.4%) positive reactions in 2041 consecutively PTed patients (test concentration 1% pet.) (4). The IVDK 2010 study, 2 of 3775 patients PTed reacted weakly positive to the compound (7). In the Groningen 2009 study, n=1, i.e. 0.3% (95% CI: 0.01 – 1.7%) had positive reactions to this allergen, tested at 2% pet. (6). In the deGroot 2000 study, 10 of 1825 consecutive patients tested positive to benzyl salicylate (2% pet.), of these, 3 were not detected by the FM I (12). In the Wöhrle 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded n=3 (0.4%) positive reactions (22). Trattner/David found 2 positive cases in 641 consecutive eczema patients (31). In a study from Alicante, Spain, 86 selected patients were tested with benzyl salicylate, yielding 2 positive reactions (48).

Additional information:

It is a “top 100” substance and classified as R43 (IFRA, pers. comm.2010). A RIFM review is available, including internal results on, e.g. HRIPT, and a review of LLNA results, where benzyl salicylate is classified as “weak” allergen (57).

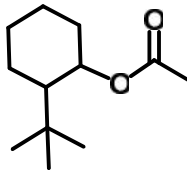
BENZYLIDENEACETONE	
CAS # 122-57-6	
EC # 204-555-1	
4-Phenyl-3-buten-2-one	
4-Phenylbut-3-en-2-one; 2-Butenone, 4-phenyl- (2CI); Ketone, methyl styryl (7CI); 1-Phenyl-1-buten-3-one; 2-Phenylethenyl methyl ketone; 2-Phenylvinyl methyl ketone; 4-Phenyl-3-buten-2-one; 4-Phenyl-3-buten-2-one; 4-Phenylbutenone; Acetocinnamone; Benzalacetone; Benzylideneacetone; Methyl 2-phenylvinyl ketone; Methyl phenylvinyl ketone; Methyl styryl ketone; Methyl β-styryl ketone; NSC 5605; Styryl methyl ketone	

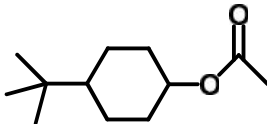
Current regulation: Annex II, n° 356

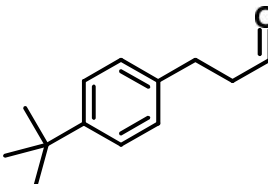
Clinical data:

In the Malten 1984 study, none of 182 patients displayed a positive PT reaction to benzylidene acetone 0.5% pet. (24).

Additional information: /

2-TERT-BUTYLCYCLOHEXYL ACETATE	
CAS # 88-41-5	
EC # 201-828-7	
2--(1,1-dimethylethyl)cyclohexyl acetate	
Cyclohexanol, 2-(1,1-dimethylethyl)-, acetate ; Cyclohexanol, 2-tert-butyl-, acetate; 2-tert-Butylcyclohexanol acetate; Verdox; o-tert-Butylcyclohexyl acetate	
Current regulation: /	
Clinical data:	
In the Frosch 1995 dose-finding pilot study, no positive reaction to 1% and 5% “Verdox ®” in pet., tested in 313 consecutive patients in Bordeaux and London, were observed (15)	
Additional information:	
It is a “top 100” substance (IFRA, pers. comm.2010). A RIFM review is available (58).	

4-TERT-BUTYLCYCLOHEXYL ACETATE	
CAS # 32210-23-4	
EC # 250-954-9	
4-(1,1-Dimethylethyl)cyclohexyl acetate	
Boisinol A 464D; Cyclohexanol, 4-tert-butyl-, acetate; Cyclohexanol, 4-(1,1-dimethylethyl)-, acetate; 4-(1,1-Dimethylethyl)cyclohexyl acetate; 4-tert-Butylcyclohexanol acetate; Dorisyl; Madeflor; NSC 163103; Oryclone, Oryclone special, Oryclon extra; p-t-BCHA; p-tert-Butylcyclohexyl acetate; para-tert-Butylcyclohexyl acetate; PTBCHA; Velvetone; Verbeniax; Vertenex; Vertinate; Vertopol; Ylanate	
Current regulation: /	
Clinical data:	
In the Frosch 1995 dose-finding pilot study, no positive reaction to 1% and 5% “Vertenex ®” in pet., tested in 107 consecutive patients in High Wycombe, were observed (15).	
Additional information:	
It is a “top 100” substance (IFRA, pers. comm.2010). A RIFM review is available (59).	

<i>p</i>-tert. -Butyldihydrocinnamaldehyde	
CAS # 18127-01-0	
EC # 242-016-2	
4-(1,1-Dimethylethyl)-benzenepropanal	
p-tert-Butyl-hydrocinnamaldehyde; 3-(4-tert-Butylphenyl)propanal; Bourgeonal; p-tert-Butyldihydrocinnamaldehyde	

Current regulation: III/155

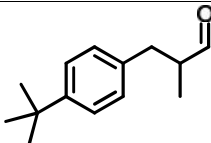
Clinical data: /

Additional information:

It is a “top 200” substance and classified as R43 (IFRA, pers. comm.2010)

http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details_v2&id=

[39132](#)

BUTYLPHENYL METHYLPROPIONAL (Lilial®)	
CAS # 80-54-6	
EC # 201-289-8	
3-(4-tert-Butylphenyl)-2-methylpropanal	
p-t-Butyl-alpha-methylhydrocinnamic aldehyde; 2-(4-tert-Butylbenzyl)propionaldehyde (REACH, EINECS); 4-(1,1-dimethylethyl)-α-methyl-benzenepropanal; Hydrocinnamaldehyde, p-tert-butyl-α-methyl-; (±)-2-Methyl-3-(4-tert-butylphenyl)propanal; 2-Methyl-3-(4-tert-butylphenyl)propanal; 2-[(4-tert-Butylphenyl)methyl]propanal; 3-(4-tert-Butylphenyl)-2-methylpropanal; 3-(p-tert-Butylphenyl)-2-methylpropionaldehyde; 3-(p-tert-Butylphenyl)isobutylaldehyde; 4-(1,1-Dimethylethyl)-α-methylbenzenepropanal; 4-tert-Butyl-α-methylhydrocinnamic aldehyde; Lilestralis; Lilial; Lysmeral; NSC 22275; lilestral; p-tert-Butyl-α-methylhydrocinnamaldehyde; p-tert-Butyl-α-methylhydrocinnamic aldehyde; pt-bucinal; α-Methyl-p-tert-butylhydrocinnamaldehyde; β-Lilial	

Current regulation: Annex III, part 1, n° 83

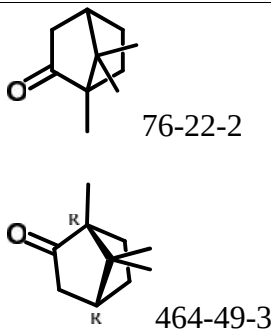
Clinical data:

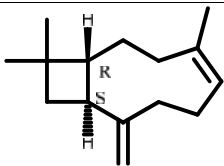
In the “background information” section of the 1999 opinion, lilial is classified as “less frequently reported allergen”; with 2 cases of contact allergy reported in 1 study of 176 eczema patients and 1 case with contact allergy to Lilial from a deodorant; a number of other reported positive cases were considered to possibly have been false positive (33).

Since the last SCCNFP-opinion of 1999, the Frosch 2002a study yielded 0.2% positive reactions to Lilial® (10% pet.) among the 1855 consecutive patients tested (16). The IVDK 2007 study yielded 0.4% (95% CI: 0.2 – 0.8%) positive reactions in 2004 patients consecutively tested (4). The IVDK 2010 study, 0.62% (95% CI: 0.04 – 1.21%; percentages standardised for age and sex) of 1947 patients PTed reacted to the compound (7). In the Groningen 2009 study, n=2, i.e. 0.6% (95% CI: 0.1 – 2.2%) had positive reactions to this allergen, tested at only 1% pet. (6). In the deGroot 2000 study, 9 of 1825 consecutively tested patients had a positive reaction to lilial® (5% pet.) (12). Lilial® has been identified as constituent of perfumes used by a patient, causing ACD (60).

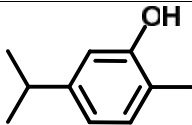
Additional information:

It is a “top 100” substance and classified as R43 (IFRA, pers. comm.2010).

CAMPHOR	
CAS # 76-22-2 / 464-49-3	
EC # 207-355-2 / 200-945-0	
1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-one (76-22-2) (1R,4R)-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-one (464-49-3)	
76-22-2: DL-Bornan-2-one (REACH, EINECS); 2-Bornanone; Bornan-2-one, INCI name according to CAS; CAMPHOR/DL-bornan-2-one; Camphor; (±)-Camphor; DL-Camphor; 1,7,7-Trimethylnorcamphor; 2-Camphanone; Alphanon; Borneo camphor; Root bark oil; Spirit of camphor 464-49-3: (1R)-1,7,7-trimethyl-bicyclo[2.2.1]heptan-2-one; (1R,4R)-(+)- amphor; (+)-2-Bornanone; (+)-Camphor; (1R)-(+)-Camphor; (1R)-Camphor; (1R,4R)-(+)-Camphor; (R)-(+)-Camphor; (R)-Camphor; Camphor; D-Camphor; D-(+)-Camphor; Alcanfor; Japanese camphor.	
Current regulation: /	
Clinical data:	
From the UK, a case of allergic contact dermatitis after application of Earex ® ear drops due to rectified camphor oil (tested 10% pet.) was reported (61). Application of a liquid rubefacient of Asian origin caused allergic contact dermatitis in a 58-year-old patient, according to the positive PT result with 10% camphor (“alcaonfor”) in pet. due to this ingredient (62). In the US, a case of contact dermatitis due to “Vics VapoRub” has been reported (63).	
Additional information: It is a “top 100” substance (IFRA, pers. comm. 2010).	

<i>beta</i>-CARYOPHYLLENE	
CAS # 87-44-5	
EC # 201-746-1	
(1R,4E,9S)-4,11,11-Trimethyl-8-methylene-bicyclo[7.2.0]undec-4-ene	
(E)-(1R,9S)-(-)-4,11,11-trimethyl-8-methylene-bicyclo[7.2.0]undec-4-ene; [1R-(1R*,4E,9S*)]-4,11,11-trimethyl-8-methylene-bicyclo[7.2.0]undec-4-ene; (-)-(E)-Caryophyllene; (-)-Caryophyllene; (-)-E-Caryophyllene; (-)-trans-Caryophyllene; (-)-β-Caryophyllene; (E)-Caryophyllene; Caryophyllene; Caryophyllene B; NSC 11906; l-Caryophyllene; trans-Caryophyllene; β-Caryophyllen; β-Caryophyllene; (-)-β-Caryophyllene	
Current regulation: /	
Clinical data:	
In the Frosch 2002 b study, 0.6% positive reactions to caryophyllene (5% pet.) in 1606 consecutive were observed (17).	
Additional information:	
<i>beta</i> -Caryophyllene autoxidizes at air exposure. As the primary oxidation products, the hydroperoxides, are very unstable and immediately form epoxides with low sensitizing capacity, the increase in allergenic activity caused by autoxidation is comparably low (64). A multicenter study identified 0.5% positive reactions to oxidized <i>beta</i> -caryophyllene (3.0% pet.) in 1511 consecutive patients (65). Of these, 2 patients (0.1%) reacted to the major	

oxidation product (caryophyllene oxide) (3.9% pet.).

CARVACROL	
CAS # 499-75-2	
EC # 207-889-6	
2-Methyl-5-(1-methylethyl)-phenol	
2-Hydroxy-1-methyl-4-(1-methylethyl)benzene; 2-Hydroxy-p-cymene; 2-Methyl-5-(1-methylethyl)phenol; 2-Methyl-5-isopropylphenol; 3-Isopropyl-6-methylphenol; 5-Isopropyl-2-methylphenol; 5-Isopropyl-o-cresol; 6-Methyl-3-isopropylphenol; Antioxine; Dentol; Isopropyl o-cresol; Isothymol; NSC 6188; p-Cymen-2-ol	
Current regulation: /	

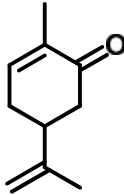
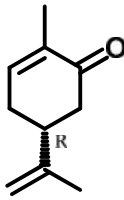
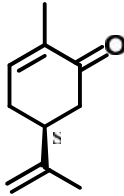
Current regulation: /

Clinical data:

The DeGroot 1985 study identified 2 (1.1%) positive reactions among 179 patients using a 5% PT preparation of this compound – these reactions may have been at least partly due to an “excited back syndrome” and are thus of limited evidence (25). Meynadier et al.¹ patch tested 28 patients with contact allergy to fragrance ingredients using 2% carvacrol in pet. Positive reactions were observed in 3 of 28 patients (after (66)).

Additional information:

Carvacrol is derived from p-cymene by sulfonation followed by alkali fusion. Carvacrol can also be derived from savory, thyme, marjoram, oregano, lovage root, and Spanish origanum oil (66). Carvacrol is a flavor ingredient that can be found in alcoholic beverages, baked goods, chewing gum, condiment relish, frozen dairy, gelatin pudding, non-alcoholic beverages, and soft candy at concentrations from 0.1 to 28.54 ppm (RIFM 2001, according to (66)).

CARVONE		
CAS # 99-49-0 / 6485-40-1 / 2244-16-8		
EC # 202-759-5 / 229-352-5 / 218-827-2		
2-Methyl-5-(1-methylethenyl)-2-cyclohexen-1-one (99-49-0) (5R)-2-Methyl-5-(1-methylethenyl)-2-cyclohexen-1-one (6485-40-1) (5S)-2-Methyl-5-(1-methylethenyl)-2-cyclohexen-1-one (2244-16-8)		99-49-0 6485-40-1
99-49-0: p-Mentha-6,8-dien-2-one; (±)-Carvone; 2-Methyl-5-isopropenyl-2-cyclohexenone; 5-Isopropyl-2-methyl-2-cyclohexen-1-one; Carvone; DL-Carvone; Karvon; Limonen-6-one; NSC 6275; p-Mentha-1(6),8-dien-2-one 6485-40-1: R)-(-)-p-Mentha-6,8-dien-2-on); (-)-(5R)-Carvone; (-)-(R)-Carvone; (-)-Carvone; (-)-p-Mentha-6,8-dien-2-one; (4R)-(-)-Carvone; (R)-(-)-Carvone; (R)-Carvone; L-(-)-Carvone; L-Carvone; l-1-Methyl-4-isopropenyl-6-cyclohexen-2-one; l-Carvone		2244-16-8

¹ Meynadier, J. M., J. Meynadier, J. L. Peyron, and L. Peyron. 1986. Clinical forms of skin manifestations in allergy to perfume. *Ann. Dermatol. Venerol.* 113:31–39.

2244-16-8: (S)-(+)-p-Mentha-6,8-dien-2-one; (+)-Carvone; (S)-(+)-Carvone; (S)-(+)-p-Mentha-6,8-dien-2-one; (S)-Carvone; (+)-Carvone; D-(+)-Carvone; D-Carvone; Talent; d-1-Methyl-4-isopropenyl-6-cyclohexen-2-one; (S)-2-Methyl-5-(1-methylvinyl)cyclohex-2-en-1-one; d-Carvone

Current regulation: /

Clinical data:

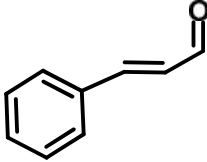
Cases of allergic contact cheilitis due to L-carvone in toothpastes have been reported (67-69). In an earlier study, 15 of 541 (2.8%) of consecutive PT patients tested also with L-Carvone (5% pet.) exhibited positive reactions, which were (i) associated with positive PT results to *Compositae* mix and (ii) mostly were not considered clinically relevant. Upon re-testing with lower concentrations (2% and 1% pet.) only 2 of 8 patients thus tested were positive (70). “Carvone has occasionally been reported as an allergen, usually in flavourings. Isomers of carvone have been either a mint or a rye flavour and aroma. We report a woman with positive patch-test reactions to carvone (newly added to the North American Contact Dermatitis Group standard series) and dermatitis on the head. She had used a hair conditioner with a “mint” scent, and the dermatitis resolved when she discontinued using this product. While the manufacturer would not confirm carvone as an ingredient, the clinical course, patch-test results, and ingredient list strongly suggest that this was a relevant allergen in this case of allergic contact dermatitis”²

Additional information:

D-Carvone occurs in caraway seed oil and dill oil in a concentration of up to 60%. L-Carvone is a component of the oil from *Mentha spicata* (spearmint).

R-Carvone is identified as a secondary oxidation product in autoxidized limonene (71).

However, it is not a major allergen in this oxidation mixture and only one of 30 patients with known contact allergy to oxidized R- limonene reacted when tested with carvone (3% pet.) (72). Experimental findings in guinea pigs show no cross reactivity between R- and S carvone, but both enantiomers were found to be equally strong sensitizers (73).

CINNAMAL	
CAS # 104-55-2	
EC # 203-213-9	
3-Phenyl-2-propenal	
Cinnamaldehyde; 3-Phenyl-2-propen-1-al; 3-Phenyl-2-propenaldehyde; 3-Phenylacrolein; 3-Phenylacrylaldehyde; 3-Phenylpropenal; Abion CA; Benzylideneacetaldehyde; Cassia aldehyde; Cinnacure; Cinnamal; Cinnamic aldehyde; Cinnamite; Cinnamyl aldehyde; NSC 16935; NSC 40346; Phenylacrolein; Zimtaldehyde; β-Phenylacrolein	

Current regulation: Annex III, part 1, n° 76

Clinical data:

In the “background information” section of the previous opinion (33), cinnamal, one of the 8 constituents of the FM I, is classified as frequent allergen, causing allergic reactions in a notable persons with eczema from cosmetic products in several studies (33).

Since the last SCCNFP-opinion of 1999, the IVDK 2007 study yielded 1.0% (95% CI: 0.6 – 1.6%) positive reactions in 2063 consecutively PTed patients (4). In the Groningen 2009 study, 1.6% (95% CI: 0.5 – 3.6%) had positive reactions to cinnamal (6). In a study by the North American Contact Dermatitis Group, no significant trend of cinnamal contact

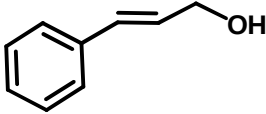
² <http://www.ncbi.nlm.nih.gov/pubmed/20233552>

sensitisation in the consecutive patients analysed was observed between 1984 (5.9% pos.) and 2000 (3.6% pos.); tested at 1% pet. (74). In the An 2005 study, 7 of 422 consecutive patients, i.e., 1.7%, had positive reaction (13). The Belsito 2006 study (20) yielded 1.7% positive reactions. In the Wöhrl 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded 1.9% positive reactions (22). The NACDG study found 3.1% positive reactions in 4435 patients tested (21). The IVDK 2010 study, 1.43% (95% CI: 0.67 – 2.18%) of 1214 consecutively tested patients reacted to the compound, while 2.64% (95% CI: 2.16 – 3.13%) of 4527 of patients tested in a more aimed manner, partly as break-down testing to the FM I, had a positive PT reaction (7). In a study from Alicante, Spain, 86 selected patients were patch tested with an extended fragrance series; n=7 reacted positively to cinnamal (48).

While, in addition to typical ACD due to contact sensitisation, immediate reactions to some fragrance compounds (and MPR, see below) are observed not infrequently, such immediate type reactions may rarely be very severe (anaphylaxis) and possibly immunologically mediated, as illustrated by the case of a 42 year old nurse with anaphylaxis (maximum grade of contact urticaria syndrome) 20 min after application of cinnamal (75). Following industrial use as “odour masking” agent, cinnamal caused occupational ACD in an exposed worker (76).

Additional information:

A specific RIFM review is available (77); another RIFM review addresses several cinnamic compounds (78).

CINNAMYL ALCOHOL	
CAS # 104-54-1	
EC # 203-212-3	
3-Phenyl-2-propen-1-ol	
Cinnamyl alcohol; 1-Phenyl-3-hydroxy-1-propene; 1-Phenylprop-1-en-3-ol; 3-Hydroxy-1-phenylprop-1-ene; 3-Phenyl-2-propenol; 3-Phenylallyl alcohol; Cinnamic alcohol; NSC 623440; NSC 8775; Styrene; Styryl alcohol; Styryl carbinol; γ-Phenylallyl alcohol	

Current regulation: Annex III, part 1, n° 69

Clinical data:

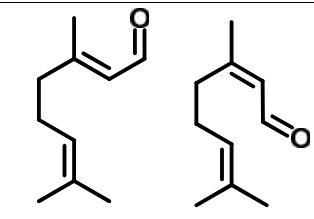
In the “background information” section of the previous opinion (33), cinnamyl alcohol, one of the 8 constituents of the FM I, is classified as frequent allergen, causing allergic reactions in a notable persons with eczema from cosmetic products (33).

Since the last SCCNFP-opinion of 1999, the IVDK 2007 study yielded 0.6% (95% CI: 0.3 – 1.1%) positive reactions in 2063 consecutively PTed patients (4). In the Groningen 2009 study, 2.5% (95% CI: 1.1 – 4.9%) had positive reactions to cinnamyl alcohol, tested at 2% pet., i.e., twice the commonly used concentration (6). As test concentrations of up to 5% are apparently non-irritating (de Groot et al. after (33)), the latter data can be regarded as valid. In the An 2005 study, 13 of 422 consecutive patients, i.e., 3.1%, had positive reaction (13) (test concentration 2%). In the Wöhrl 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded 1.5% positive reactions (22). The IVDK 2010 study, 0.73% (95% CI: 0.17 – 1.30%) of 1214 consecutively tested patients reacted to the compound, while 2.36% (95% CI: 1.89 – 2.83%) of 4502 of patients tested in a more aimed manner, partly as break-down testing to the FM I, had a positive PT reaction (7). In a study from Alicante, Spain, 86 selected patients were patch tested with an extended fragrance series; n=12 reacted positively to cinnamyl alcohol (48).

Additional information:

In a recent experimental study protein-cinnamal adducts were detected in skin homogenates treated with cinnamal and cinnamyl alcohol but not with alpha-amyl cinnamal. This suggests that there is a common hapten involved in cinnamal and cinnamyl alcohol sensitization, in line with the observation of a marked concordance upon patch testing (7, 79), and that metabolic activation (to cinnamal) is involved in the latter. Conversely, there does not appear to be a common hapten for cinnamal and alpha-amyl cinnamal (80), again in line with the observations in the IVDK 2010 study (7).

A RIFM review is available (81)

CITRAL	
CAS # 5392-40-5	
EC # 226-394-6	
3,7-Dimethyl-2,6-octadienal	
3,7-Dimethyl-2,6-octadien-1-al; Citral; Citral PQ Extra; Lemarome N; Lemsyn GB; NSC 6170	

Citral = isomeric mixture of Geranial and Neral

Current regulation: Annex III, part 1, n° 70

Clinical data:

In the “background information” section of the previous opinion (33), citral is classified as frequent allergen, causing about 1% allergic reactions in consecutive PT patients, and being a proven cause of contact allergic reactions in 2.6% patients with eczema from cosmetic products (33).

Since the last SCCNFP-opinion of 1999, the Frosch 2002 a study yielded 1.1% positive (and 1.3% doubtful) reactions among the 1855 consecutive patients tested (16). In a study on 586 consecutive patients with hand eczema it has been noted that citral (2% pet.) not only caused (mostly weak) positive PT reactions, but far more often irritant reactions (n=82 vs. n=28). It was hypothesised that this very property could contribute to citral’s sensitising potential (82). In the EU 2005 study, 12 of 1701 patients (0.7%, 95% CI: 0.4 – 1.2%) reacted positively to 2% citral in pet. (10). The IVDK 2007 study yielded 0.6% (95% CI: 0.3 – 1.1%) positive reactions in 2021 consecutively PTed patients; 10 of 13 citral positive patients also reacted positively to geraniol (4). In the Groningen 2009 study, 0.6% (95% CI: 0.1 – 2.2%) had positive reactions to this allergen (6). In the deGroot 2000 multicentre study, 19 of 1825 consecutive patients tested positively to citral (2% pet.), 4 of whom did not react positively to the FM I (12). In the An 2005 study, 5 of 422 consecutive patients, i.e., 1.2%, had positive reaction (13) (test concentration 2%). In the Malten 1984 study, neral at 1% in pet. yielded 2.6% positive reactions in 182 patients (24). In a study from Alicante, Spain, 86 selected patients were tested with citral, yielding 2 positive reactions (48).

Citral in a lip salve has been reported to have caused longstanding, recurrent allergic contact cheilitis in a 30 year old female patient, diagnosed by a strong positive reaction to the FM II, followed by a strong positive reaction to citral (83).

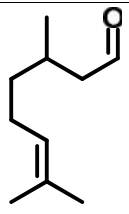
Additional information:

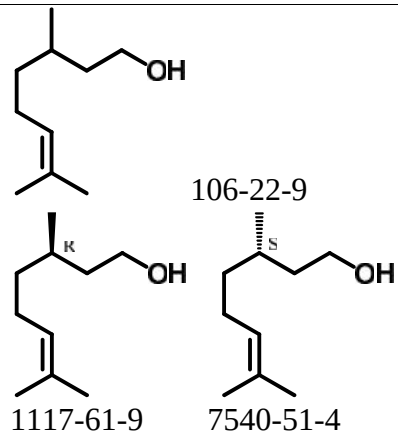
Citral is the mixture of two isomers: cis-citral (neral) and trans-citral (geranial).

Geranial forms oxidation product with increased sensitizing capacity both via spontaneous autoxidization at air exposure and via metabolic oxidation (Hagvall L. Thesis 2009: <http://hdl.handle.net/2077/18951>).

Geranial and neral have been identified as secondary oxidation products when geraniol autoxidizes (84). They have also been identified as metabolites of geraniol (85). This explains the simultaneous reactions to geraniol and citral seen by (4).

It is a “top 100” substance and classified as R43 (IFRA, pers. comm.2010).

CITRONELLAL	
CAS # 106-23-0	
EC # 203-376-6	
3,7-Dimethyl-6-octenal	
(±)-Citronellal; 2,3-Dihydrocitral; 3,7-Dimethyloct-6-en-1-al; Citronellal; NSC 46106; Rhodinal; dl-Citronellal; β-Citronellal	
Current regulation: /	
Clinical data: /	
Additional information: A compound of essential oils of citrus fruits, namely grapefruit, but also contained in “citronella oil” and oil of Melissa.	

CITRONELLOL	
CAS # 106-22-9 / 1117-61-9 / 7540-51-4	
EC # 247-737-6 / 214-250-5 / 231-415-7	
3,7-Dimethyl-6-octen-1-ol (106-22-9); (3R)-3,7-Dimethyl-6-octen-1-ol (1117-61-9); (3S)-3,7-Dimethyl-6-octen-1-ol (7540-51-4)	
106-22-9: (±)-3,7-Dimethyl-6-octen-1-ol; (±)-Citronellol; (±)-β-Citronellol; 2,3-Dihydrogeraniol; 2,6-Dimethyl-2-octen-8-ol; Cephrol; Citronellol; Citronellol 950; DL-Citronellol; Dihydrogeraniol; NSC 8779; Rodinol; dl-Citronellol; β-Citronellol 1117-61-9: (R)-3,7-Dimethyl-6-octen-1-ol; (R)-(+)-3,7-Dimethyl-6-octen-1-ol; (+)-(R)-Citronellol; (+)-Citronellol; (+)-β-Citronellol; (3R)-(+)-β-Citronellol; (R)-(+)-Citronellol; (R)-(+)-β-Citronellol; (R)-Citronellol; (R)-β-Citronellol; D-Citronellol; d-Citronellol 7540-51-4: (-)-3,7-dimethyl-6-octen-1-ol; (-)-(S)-Citronellol; (-)-Citronellol; (-)-β-Citronellol; (S)-(-)-Citronellol; (S)-(-)-β-Citronellol; (S)-3,7-Dimethyl-6-octen-1-ol; (S)-Citronellol; (S)-β-Citronellol; L-Citronellol; l-Citronellol	

Current regulation: Annex III, part 1, n° 86

Clinical data:

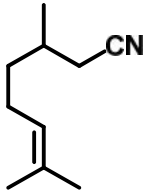
In the “background information” section of the 1999 opinion, citronellol is classified as “less frequently reported allergen”; with few cases of contact allergy reported in the literature (33). Since the last SCCNFP-opinion of 1999, in the Larsen 2002 c study, „DL citronellol“ (5% in pet.) elicited positive PT reactions in 8.7% of the patients (1). In 1855 consecutive patients of the Frosch 2002 a study, 0.4% positive reactions were noted (16). In the EU 2005 study, 4 of 1701 patients (0.2%, 95% CI: 0.06 – 0.6%) reacted positively to 1% citronellol in pet.; at the same concentration, n=23 doubtful or irritant reactions were observed (10). The IVDK 2007 study yielded 0.5% (95% CI: 0.2 – 0.9%) positive reactions in 2003 patients consecutively PTed (4). In the Groningen 2009 study, n=1, i.e. 0.3% (95% CI: 0.01 – 1.7%) had positive reactions to this allergen, tested at only 2% pet. (6). The Larsen 2001 study yielded 5.6% positive reactions to l-citronellol (5% pet.) in 178 patients with known contact allergy to fragrance ingredients (19).

Additional information:

Citronellol autoxidizes spontaneously in contact with air in the same way as linalool forming

allergenic primary oxidation products, hydroperoxides (AT Karlberg, personal communication, 2011).

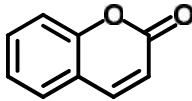
RIFM reviews have been published regarding L-citronellol (86), D-citronellol (87) and DL-citronellol (88). Another review is available by Hostynek and Maibach (89). It is a “top 100” substance and classified as R43 (IFRA, pers. comm.2010).

CITRONELLYL NITRILE	
CAS # 51566-62-2	
EC # 257-288-8	
3,7-Dimethyl-6-octenenitrile	
3,7-Dimethyl-6-octenenitrile(REACH, EINECS, INCI); Agrunitril; Agrunitrile; Citronellyl nitrile	

Current regulation: /

Clinical data: /

Additional information: It is a “top 100” substance (IFRA, pers. comm.2010)

COUMARIN	
CAS # 91-64-5	
EC # 202-086-7	
2H-1-Benzopyran-2-one	
1,2-Benzopyrone; 2-Chromenone; 2-Propenoic acid, 3-(2-hydroxyphenyl)-, δ-lactone; 5,6-Benzo-2-pyrone; Benzo-α-pyrone; Coumarinic anhydride; NSC 8774; Rattex; Tonka bean camphor; cis-o-Coumarinic acid lactone; o-Hydroxycinnamic acid lactone	

Current regulation: Annex III, part1, n° 77

Clinical data:

In the “background information” section of the previous opinion (33), coumarin is classified as frequent allergen, causing allergic reactions in about 0.4 – 0.8% in consecutive PT patients, and causing contact allergic reactions in 0.8-10% of patients with eczema from cosmetic products (33).

Since the last SCCNFP-opinion of 1999, in the Frosch 2002 a study, 0.3% positive PT reactions to consecutive patients were noted (16). In the EU 2005 study, none of the 1701 patients reacted positively to 5% coumarin in pet., while 7 doubtful or irritant reactions were observed (10). The IVDK 2007 study yielded 0.4% (95% CI: 0.2 – 0.8%) positive reactions in 2020 consecutively PTed patients (4). In the Groningen 2009 study, 0.6% (95% CI: 0.1 – 2.2%) had positive reactions to this allergen (6). In the deGroot 2000 study, 13 of 1825 consecutive patients reacted positively to coumarin (5% pet.) (12).

V. Mutterer et al. present the case of a 44 year old patient in whom coumarin was identified as culprit allergen by controlled ROAT testing with 1%, after having caused dermatitis by the use of a deodorant containing coumarin at 0.23% and an EdT (90).

Additional information:

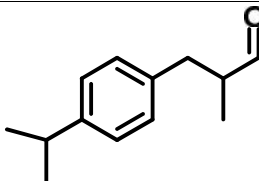
Coumarin is found in several plant families, including *Melilotus* and *Galium*, e.g., *Galium odoratum* (sweet woodruff), however, also in oil of lavender, lovage and others (53).

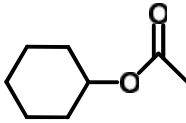
Researchers from INSERM and “Rhodia Organique, Lyon , France” observed that pure coumarin is not an allergen in the LLNA, however, commercially available materials, containing “contaminants” (3,4-dihydrocoumarin, 6-chlorocoumarin and 6,12-epoxy-

6H,12H-dibenzo[b,f][1,5] dioxocin, were identified as weak and moderate sensitisers, resp. (91).

Coumarin is a “top 100” substance and classified as R43 (IFRA, pers. comm.2010).

CUMINALDEHYDE	
CAS # 122-03-2	
EC # 204-516-9	
4-(1-Methylethyl)-benzaldehyde	
4-Isopropylbenzaldehyde; p-Isopropylbenzaldehyde; 4-(Propan-2-yl)benzaldehyde; 4-Isopropylphenylcarboxaldehyde; Cumaldehyde; Cumic aldehyde; Cuminal; Cuminaldehyde; Cuminic aldehyde; Cuminyaldehyde; NSC 4886; p-Cumic aldehyde; p-Isopropylbenzaldehyde; p-Isopropylbenzenecarboxaldehyde	
Current regulation: /	
Clinical data:	
The DeGroot 1985 study identified 3 (1.7%) positive reactions among 179 patients using a 15% PT preparation of cuminaldehyde (25).	
Additional information: ...	

CYCLAMEN ALDEHYDE	
CAS # 103-95-7	
EC # 203-161-7	
α-Methyl-4-(1-methylethyl)-benzenepropanal	
p-Isopropyl-α-methyl-hydrocinnamaldehyde; 2-Methyl-3-(4-isopropylphenyl)propionaldehyde; 2-Methyl-3-(p-isopropylphenyl)propionaldehyde; 3-(4-Isopropylphenyl)-2-methylpropanal; 3-(p-Isopropylphenyl)-2-methylpropionaldehyde; 3-p-Cumenyl-2-methylpropionaldehyde(REACH, EINECS); 4-Isopropyl-α-methylhydrocinnamic aldehyde; Cyclamal; Cyclamen aldehyde; Cyclosal; Cyclosal perfume; Cymal; p-Isopropyl-α-methylhydrocinnamaldehyde; α-Methyl-4-(1-methylethyl)benzenepropanal; α-Methyl-p-isopropylhydrocinnamaldehyde	
Current regulation: ...	
Clinical data:	
/	
Additional information: It is a “top 100” substance and classified as R43 (IFRA, pers. comm.2010).	

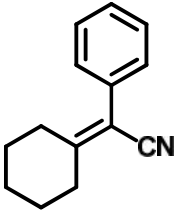
CYCLOHEXYL ACETATE	
CAS # 622-45-7	
EC # 210-736-6	
Cyclohexyletanoat	
Acetic acid cyclohexanyl ester; Acetoxycyclohexane; Cyclohexyl acetate; NSC 8772	

Current regulation: /

Clinical data:

In the Larsen 2002 c study, 0.5% positive reactions among 218 patients with know contact allergy to fragrance ingredients were observed (1).

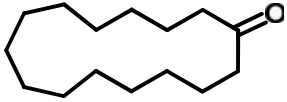
Additional information: A RIFM review is available (92).

<i>alpha-CYCLOHEXYLIDENE BENZENEACETONITRILE</i>	
CAS # 10461-98-0	
EC # 423-740-1	
<i>α-Cyclohexylidenebenzeneacetonitrile</i>	
alpha-cyclohexylidene-benzeneacetonitrile (REACH); Δ1α-Phenyl-α-Cyclohexaneacetonitrile; 2-cyclohexylidene-2-phenylacetonitrile; NSC 408284; Peonile (REACH)	

Current regulation: /

Clinical data: /

Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).

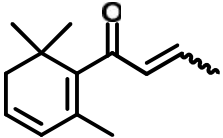
<i>CYCLOPENTADECANONE</i>	
CAS # 502-72-7	
EC # 207-951-2	
<i>Cyclopentadecanone</i>	
CPE 218; Exaltone; NSC 63900; Normuscon; Normuscone	

Current regulation: /

Clinical data:

In the Larsen 2001 study, n=3, i.e., 1.7% positive reactions were observed to the compound, tested 5% pet., in 178 pateints with known contact allergy to fragrance ingredients (19).

Additional information: ...

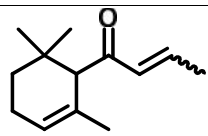
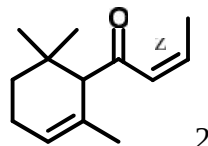
<i>DAMASCENONE</i>	
<i>ROSE KETONE-4</i> (← Not officially an INCI Name but Perfuming Name; Damascenone as such is not listed in CosIng)	
CAS # 23696-85-7	
EC # 245-833-2	
<i>1-(2,6,6-Trimethyl-1,3-cyclohexadien-1-yl)-2-buten-1-one</i>	
1-(2,6,6-Trimethyl-1,3-cyclohexadienyl)-2-buten-1-one; 1-Crotonoyl-2,6,6-trimethyl-1,3-cyclohexadiene; 2,6,6-Trimethyl-1-(2-butenoyl)-1,3-cyclohexadiene; 2,6,6-Trimethyl-1-crotonyl-1,3-cyclohexadiene; Rose ketone # 4	

Current regulation: Annex III, part1, n° 160 (max. conc. 0.02%)

Clinical data: /

Additional information:

RIFM reviews are available (93, 94), quoting 1 negative, and 2 positive (2 of 37, 1 of 50 volunteers) HRIPTs with damascenone based on 2 LLNA, the EC3 values were calculated as 1.24% and 1.22%, respectively (94).

<i>alpha-DAMASCONE (TMCHB)</i>	 43052-87-5  23726-94-5
CAS # 43052-87-5 / 23726-94-5	
EC # x / 245-845-8	
1-(2,6,6-Trimethylcyclohex-2-en-1-yl)but-2-enone (43052-87-5); (2Z)-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one (23726-94-5)	
43052-87-5: 2,6,6-Trimethyl-1-crotonyl-2-cyclohexene; α -Damascone 23726-94-5: (Z)-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one; (Z)- α -Damascone; cis- α -Damascone	
Current regulation: Annex III, part1, n° 157 (max. conc. 0.02%)	

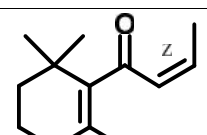
Clinical data:

In the Frosch 2002 b study, n=8 (0.5%) mostly strong positive PT reactions to consecutive patients were noted using a mixture of alpha and beta damascone, 0.1% pet. each (17). In human sensitisation experiments, after epicutaneous induction with 30% 1-(2,6,6-trimethylcyclohex-2-en-1-yl)but-2-enone (TMCHB, CAS # 43052-87-5) with adjuvant, to enhance response to this weak sensitiser, 8 of 30 patients were elicited by a challenge with 3% TMCHB 2 weeks later (95).

Additional information:

The former CAS # refers to alpha-Damascone or 1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-2-Buten-1-one. The latter CAS # refers to the identified ingredient cis-alpha-Damascone or (Z)-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one, the content of which is restricted (SCCS-opinion 0392/00).

A RIFM review is available on alpha-damascone (96), quoting a number of partly positive HRIPT and other human studies, as well as different animal experiments. In 1 LLNA reported, an EC3 value of 3.3% was found. Another RIFM review is available for cis-alpha-damascone (97), supplying, however, no data on sensitisation.

<i>cis-beta-DAMASCONE</i>	 Z
CAS # 23726-92-3	
EC # 245-843-7	
(2Z)-1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-buten-1-one	
(Z)-1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-buten-1-one; (Z)- β -Damascone	

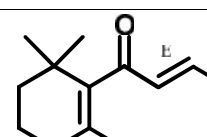
Current regulation: Annex III, part 1, n° 162 (max. conc. 0.02%)

Clinical data:

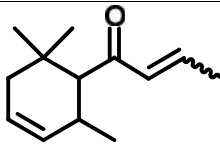
Regarding results of the Frosch 2002 b study, see under alpha-damascone.

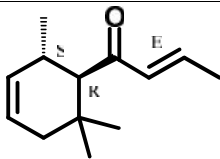
Additional information:

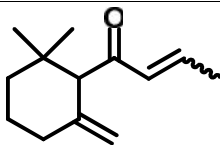
A RIFM review is available (98), citing several negative and one positive HRIPTs, and a number of – mostly positive – animal experiments.

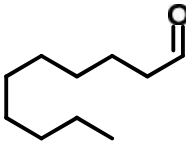
<i>trans-beta-DAMASCONE</i>	 E
CAS # 23726-91-2	
EC # 245-842-1	
(2E)-1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-buten-1-one	
(E)-1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-buten-1-one; (E)- β -Damascone; Damascone beta; trans-2,6,6-Trimethyl-1-	

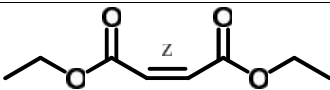
crotonylcyclohex-1-ene; trans- β -Damascone; β -Damascone	
Current regulation: Annex III, part 1, n° 158 (max. conc. 0.02%)	
Clinical data: /	
Additional information:	
A RIFM review is available (99), citing 2 negative HRIPT and 1 negative maximisation test, and a number of positive animal experiments (the EC3 value, based on 1 LLNA, was found to be 2.4%).	

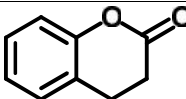
<i>delta-DAMASCONE</i>	
CAS # 57378-68-4	
EC # 260-709-8	
1-(2,6,6-Trimethyl-3-cyclohexen-1-yl)-2-buten-1-one	
δ -Damascone	
Current regulation: Annex III, part 1, n° 161 (max. conc. 0.02%)	
Clinical data: /	
Additional information:	
A RIFM review is available (100), citing several positive HRIPT and 1 negative HRIPT.	
Cross sensitisation to alpha- and beta-damascone was demonstrated in 3 sensitised subjects. 2	
LLNA studies are reported on, yielding EC3 values of 5.19% and 9.6%, resp.	

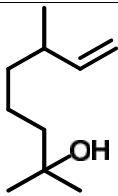
<i>trans-trans-delta-DAMASCONE</i>	
CAS # 71048-82-3	
EC # 275-156-8	
(2E)-rel-1-[(1R,2S)-2,6,6-trimethyl-3-cyclohexen-1-yl]- 2-buten-1-one	
[1 α (E),2 β]-1-(2,6,6-trimethyl-3-cyclohexen-1-yl)-2-buten-1-one; trans- δ -Damascone; δ -Damascone; trans, trans- δ -Damascone	
Current regulation: Annex III, part 1, n° 165 (max. conc. 0.02%)	
Clinical data: /	
Additional information:	
A RIFM review is available (101), citing 1 positive HRIPT (2/15 with 1%).	

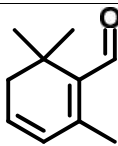
<i>gamma-DAMASCONE</i>	
CAS # 35087-49-1	
EC # 481-910-9	
1-(2,2-Dimethyl-6-methylenecyclohexyl)-2-buten-1-one	
γ -Damascone	
Current regulation: /	
Clinical data: /	
Additional information:	
A RIFM review is available (102), citing 1 positive Buehler test and 1 LLNA study yielding an EC3 value of 4.6%	

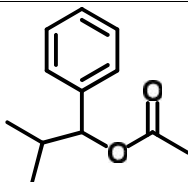
DECANAL	
CAS # 112-31-2	
EC # 203-957-4	
n-Decanal	
Capraldehyde; Capric aldehyde; Caprinaldehyde; Caprinic aldehyde; Decaldehyde; Decanaldehyde; Decyl aldehyde; Decylic aldehyde; NSC 6087; n-Decaldehyde; n-Decyl aldehyde	
Current regulation: /	
Clinical data: /	
Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).	

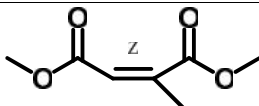
DIETHYL MALEATE	
CAS # 141-05-9	
EC # 205-451-9	
(2Z)-Diethyl but-2-enedioate	
2-Butenedioic acid (2Z)-, diethyl ester; 2-Butenedioic acid (Z)-, diethyl ester; Maleic acid, diethyl ester; (2Z)-2-Butenedioic acid diethyl ester; Diethyl (Z)-2-butenedioate; Ethyl maleate; Staflex DEM	
Current regulation: Annex II, n° 426	
Clinical data:	
In the Malten 1984 study, 3.2% of 182 patients displayed a positive PT reaction to diethyl maleate 0.1% pet. (24). In this study, it has been noted that “in the max. test and clinically this is a strong sensitiser having caused patch test sensitisation (42%)”	
Additional information: /	

DIHYDROCOUMARIN	
CAS # 119-84-6	
EC # 204-354-9	
3,4-Dihydro-2H-1-benzopyran-2-one	
Other names: Hydrocoumarin; Hydrocinnamic acid, o-hydroxy-, δ-lactone; 2-Chromanone; 3,4-Dihydro-1H-benzopyran-2-one; 3,4-Dihydrocoumarin; Dihydrocoumarin; Melilotin; Melilotin (coumarin); Melilotol	
Current regulation: Annex II, n° 427	
Clinical data:	
In the Malten 1984 study, 3.7% of 182 patients displayed a positive PT reaction to dihydrocoumarine 5% pet. (24).	
Additional information: /	

DIHYDROMYRCENOL	
CAS # 18479-58-8	
EC # 242-362-4	
(±)-2,6-Dimethyloct-7-en-2-ol	
1,1,5-Trimethyl-6-heptenol; 2,6-Dimethyl-7-octen-2-ol; 3,7-Dimethyl-1-octen-7-ol; 2,6-dimethyl-7-octen-2-ol (INCI)	
Current regulation: /	
Clinical data: /	
Additional information:	
A RIFM review is available (103), listing 2 negative HRIPTs and 1 negative human maximisation test.	
It is a “top 100” substance (IFRA, pers. comm.2010).	

2,3-DIHYDRO-2,2,6-TRIMETHYLBENZALDEHYDE	
CAS # 116-26-7	
EC # 204-133-7	
2,6,6-Trimethyl-1,3-cyclohexadiene-1-carboxaldehyde	
2,2,6-Trimethyl-4,6-cyclohexadien-1-aldehyde; 2,6,6-Trimethyl-1,3-cyclohexadiene-1-aldehyde; Safranal	
Current regulation: /	
Clinical data: /	
Additional information:	
A RIFM review quotes one positive HRIPT (5 of 53) and one negative HRIPT (0 of 54) (93).	

<i>DIMETHYLBENZYL CARBINYL ACETATE (DMBCA)</i>	
CAS # 151-05-3	
EC # 205-781-3	
2-Methyl-1-phenylpropyl acetate	
Benzeneethanol, α,α-dimethyl-, acetate; Phenethyl alcohol, α,α-dimethyl-, acetate; 1,1-Dimethyl-2-phenylethyl acetate; 2-Methyl-1-phenyl-2-propyl acetate; 2-Methyl-1-phenylpropan-2-yl acetate; Benzyl dimethylcarbinol acetate; Benzyl dimethylcarbinyl acetate; Dimethylbenzylcarbinol acetate; Dimethylbenzylcarbonyl acetate; NSC 46123; α,α-Dimethylphenethyl acetate	
Current regulation: /	
Clinical data:	
In the Frosch 2002 a study, 0.2% positive PT reactions to consecutive patients were noted (16). In the Frosch 1995 dose-finding pilot study, no positive reaction to 1% and one to 5% DMBCA in pet., tested in 313 consecutive patients in Bordeaux and London, were observed (15).	
Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).	

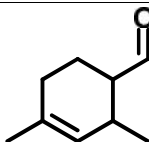
<i>DIMETHYL CITRACONATE</i>	
CAS # 617-54-9	
EC #	
(2Z)-Diethyl-2-metyl-but-2-enedioate	
(2Z)-2-methyl-2-Butenedioic acid, dimethyl ester; 2-Butenedioic acid, 2-methyl-, dimethyl ester, (Z)-; Citraconic acid, dimethyl ester; Dimethyl methylmaleate; Methylmaleic acid, dimethyl ester	

Current regulation: Annex II, n° 431

Clinical data:

In the Malten 1984 study, 3.7% of 182 patients displayed a positive PT reaction to dimethylcitraconate 12% pet. (24). In this paper, a human maximisation test positive in “4/44” is quoted.

Additional information: ...

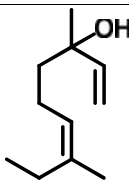
2,4-DIMETHYL-3-CYCLOHEXEN-1-CARBOXALDEHYDE	
CAS # 68039-49-6	
EC # 268-264-1	
2,4-Dimethyl-cyclohex-3-ene-1-carboxaldehyde	
(Z)-Vertocitral C; 2,4-Dimethyl-3-cyclohexene-1-carboxaldehyde; 2,4-Dimethyl-3-cyclohexenecarboxaldehyde; 2,4-Dimethyl-3-cyclohexenylcarbaldehyde; Cyclal C; Ligustral; Tricyclal; Triplal; Tripral; Zestover	

Current regulation: /

Clinical data: /

Additional information:

It is a “top 100” substance and classified as R43 (IFRA, pers. comm.2010).

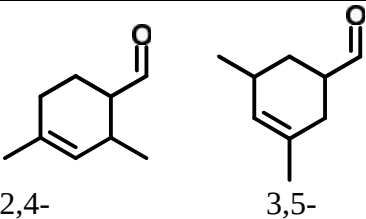
3,7-DIMETHYL-1,6-NONADIEN-3-OL	
CAS # 10339-55-6	
EC # 233-732-6	
(7Z)-3,7-Dimethyl-1,6-nonadien-3-ol	
Ethyl linalool; Methyl linalool	

Current regulation: /

Clinical data: /

Additional information:

It is a “top 100” substance (IFRA, pers. comm.2010). A RIFM review is available (104), citing 1 negative human maximisation test (n=25).

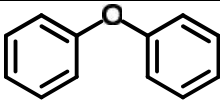
<i>DIMETHYLTETRAHYDRO BENZALDEHYDE</i>	
CAS # 68737-61-1	
EC # 272-113-5	
2,4-Dimethyl-cyclohex-3-ene-1-carboxaldehyde 3,5-Dimethyl-cyclohex-3-ene-1-carboxaldehyde	
Hivertal; Vertocitral	

Current regulation: /

Clinical data:

In the Larsen 2001 study, 2.3% positive PT reactions were observed with the isomer mixture, tested 5% pet., in 178 patients with known contact allergy to fragrance ingredients (19).

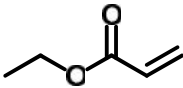
Additional information: /

<i>DIPHENYL ETHER</i>	
CAS # 101-84-8	
EC # 202-981-2	
Phenyl ether	
1,1'-oxybis-Benzene; Barrel Therm 330; Benzene, phenoxy-; Biphenyl oxide; Chemcryn JK-EB; Diphenyl ether; Diphenyl oxide; NSC 19311; Oxybisbenzene; Phenoxybenzene; Phenyl oxide	

Current regulation: /

Clinical data: /

Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).

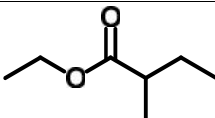
<i>ETHYL ACRYLATE</i>	
CAS # 140-88-5	
EC # 205-438-8	
Ethyl 2-propenoate	
Acrylic acid ethyl ester (6CI,8CI); 2-Propenoic acid ethyl ester; Ethyl 2-propenoate; Ethyl acrylate; Ethyl acrylic ester; Ethyl propenoate; NSC 8263	

Current regulation: Annex II, n° 435

Clinical data:

In the Malten 1984 study, n=1 (0.5%) of 182 patients displayed a positive PT reaction to ethyl acrylate 1% pet. (24). In the NACDG 2009 multicentre study, 0.9% of consecutive patients (n=4428) had a positive PT reaction (21).

Additional information: /

<i>ETHYL 2-METHYLBUTYRATE</i>	
CAS # 7452-79-1	
EC # 231-225-4	
Ethyl 2-methylbutyrate	
Butyric acid, 2-methyl-, ethyl ester (6CI,7CI,8CI); (±)-Ethyl 2-methylbutanoate; 2-Methylbutanoic acid ethyl ester; 2-Methylbutyric acid ethyl ester; Ethyl 2-methylbutanoate; Ethyl	

2-methylbutyrate; Ethyl α -methylbutyrate; NSC 1103	
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Current regulation: /	
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Clinical data: /	
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Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).	
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ETHYLENE DODECANEDIOATE	
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CAS # 54982-83-1	
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EC # 259-423-6	
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1,4-dioxacyclohexadecane-5,16-dione	
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Cyclic ethylene dodecanedioate; Ethylene dodecanedioate; Musk 144; Musk C-14	
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Current regulation: /	
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Clinical data:	
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In the Larsen 2002 c study on 218 patients with known contact allergy to fragrance ingredients, this compound caused 0.9% positive PT reactions at 5% pet. (1).	
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Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).	
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6-ETHYLIDENEOCTAHYDRO-5,8-METHANO-2H-BENZO-1-PYRAN	
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CAS # 93939-86-7	
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EC # 300-376-9	
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6-Ethylideneoctahydro-5,8-methano-2H-1-benzopyran	
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Current regulation: /	
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Clinical data:	
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In the Larsen 2001 study, no positive PT reactions were observed with this compound, tested 5% pet., in 178 patients with known contact allergy to fragrance ingredients (19).	
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Additional information: /	
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2-ETHYL-4-(2,2,3-TRIMETHYL-3-CYCLOPENTEN-1-YL)-2-BUTEN-1-OL	
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CAS # 28219-61-6	
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EC # 248-908-8	
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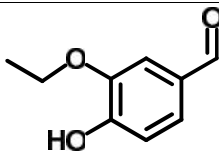
2-Ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol	
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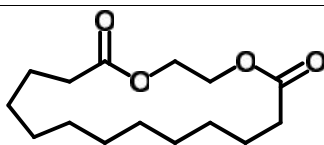
2-Ethyl-4-(2,2,3-trimethyl-3-cyclopenten-1-yl)-2-buten-1-ol; 2-Ethyl-4-(2',2',3-trimethylcyclopent-3'-enyl)but-2-enol; Bacdanol; Bangalol; Dartanol; Finanol; Levosandol; Radjanol; Sanjinol	
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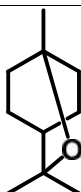
Current regulation: /	
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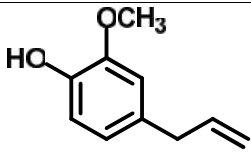
Clinical data: /	
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Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).	
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ETHYL VANILLIN	
CAS # 121-32-4	
EC # 204-464-7	
3-Ethoxy-4-hydroxybenzaldehyde	
2-Ethoxy-4-formylphenol; 3-Ethoxy-4-hydroxybenzaldehyde; 3-Ethylvanillin; 4-Hydroxy-3-ethoxybenzaldehyde; Arovanillon; Bourbonal; Ethavan; Ethovan; Ethylprotal; Ethylvanillin; NSC 1803; NSC 67240; Protocatechuic aldehyde ethyl ether; Quantrovanil; Rhodiarome; Vanillal; Vanirom	
Current regulation: /	
Clinical data:	
The case of a 28-year-old metal grinder with allergic contact dermatitis to a “cutting oil reodorant” has been reported, who tested positively not only to the cutting fluid, the reodorant, but also to several ingredients of the latter product, including “Vanillal S 10026”, 5% pet. (105).	
Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).	

ETHYLENE BRASSYLATE	
CAS # 105-95-3	
EC # 203-347-8	
1,4-Dioxacycloheptadecane-5,17-dione	
Tridecanedioic acid, cyclic ethylene ester; Ethylene glycol, cyclic tridecanedioate; Astratone; Cyclic ethylene glycol tridecanedioate; Cyclic ethylene tridecanedioate; Emeressence 1150; Ethylene brassylate; Musk T; NSC 46155	
Current regulation: /	
Clinical data: /	
Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).	

EUCALYPTOL	
CAS # 470-82-6	
EC # 207-431-5	
1,3,3-trimethyl-2-Oxabicyclo[2.2.2]octane	
1,8-Epoxy-p-menthane; 1,3,3-Trimethyl-2-oxabicyclo[2.2.2]octane; 1,8-Cineol; 1,8-Cineole; 1,8-Epoxy-p-menthane; 2-Oxa-1,3,3-trimethylbicyclo[2.2.2]octane; Cajeputol; Cineol; Cineole; Eucalyptol; Eucalyptole; Eucalytol; Eucapur; Eukalyptol; NSC 6171; Terpan; p-Cineole	
Current regulation: /	
Clinical data: /	
Additional information:	
It is a “top 100” substance (IFRA, pers. comm.2010).	
See also EUCALYPTUS SPP. LEAF OIL ; eucalyptol is the major ingredient there (up to 85%), but found in significant quantities also in a number of other essential oils (see 3.2).	

EUGENOL	
CAS # 97-53-0	
EC # 202-589-1	
2-Methoxy-4-(2-propen-1-yl)-phenol	
Other names: 4-allyl-2-methoxy-phenol; 1-Allyl-4-hydroxy-3-methoxybenzene; 2-Hydroxy-5-allylanisole; 2-Methoxy-1-hydroxy-4-allylbenzene; 2-Methoxy-4-(2-propenyl)phenol; 2-Methoxy-4-(2'-propenyl)phenol; 2-Methoxy-4-[2-allyl]phenol; 2-Methoxy-4-allylphenol; 3-(3-Methoxy-4-hydroxyphenyl)propene; 3-(4-Hydroxy-3-methoxyphenyl)-1-propene; 4-Allyl-1-hydroxy-2-methoxybenzene; 4-Allyl-2-methoxyphenol; 4-Allylguaiacol; 4-Hydroxy-3-methoxyallylbenzene; Allylguaiacol; Bioxeda; Caryophyllic acid; Dentogum; Eugenol; Eugenic acid; Eugenol; NSC 209525; NSC 8895; p-Allylguaiacol; p-Eugenol	

Current regulation: Annex III, part 1, n° 71

Clinical data:

In the “background information” section of the previous opinion (33), eugenol, one of the 8 components of the FM I, is classified as frequent allergen, causing allergic reactions in about 1.2% in consecutive PT patients and accounting for 4 to 16% of reactions to the FM I. Allergic reactions had been observed in 0.7 – 20% of patients with eczema from cosmetic products (33).

Since the last SCCNFP-opinion of 1999, the IVDK 2007 study yielded 0.5% (95% CI: 0.3 – 1.0%) positive reactions in 2065 consecutively PTed patients (4). In the Groningen 2009 study, 1.3% (95% CI: 0.3 – 3.2%) had positive reactions to eugenol, tested at 2% pet., i.e., twice the commonly used concentration (6). F. Giusti et al. examined 1754 consecutive patients tested with eugenol 1% pet. in addition to the baseline series, 09/1998 - 01/2000. 21 patients (1.2%) reacted positively to eugenol (106). In the An 2005 study, 8 of 422 consecutive patients, i.e., 1.9%, had positive reaction (13) (test concentration 2%). In the Wöhr 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded 2.5% positive reactions (22). The IVDK 2010 study, 0.44% (95% CI: 0.04 – 0.84%) of 1214 consecutively tested patients reacted to the compound, while 1.57% (95% CI: 1.19 – 1.95%) of 4801 of patients tested in a more aimed manner, partly as break-down testing to the FM I, had a positive PT reaction (7). In a study from Alicante, Spain, 86 selected patients were patch tested with an extended fragrance series; n=12 reacted positively to eugenol (48). Moreover, eugenol is capable of inducing immediate type reactions of the airways, as illustrated by the well-documented case of a 30 year old hairdresser who developed severe occupational bronchial asthma due to eugenol (107). A case of urticaria after dental treatment with eugenol-containing material was reported from India (108); however, occasional cases are also reported from Europe (109). Occupational exposure to eugenol / zinc oxide type dental restorative material, which is apparently less frequently used nowadays, may lead to occupational sensitisation to eugenol, as illustrated by a case report (110).

Additional information:

Eugenol is the main component (80-95%) of clove oil, but also found in citronella oil, pimento leaf oil and cinnamon bark oil (see section 3.2).

It is a “top 100” substance and classified as R43 (IFRA, pers. comm.2010).

FARNESOL

CAS # 4602-84-0

EC # 225-004-1

3,7,11-Trimethyl-2,6,10-Dodecatrien-1-ol

Farnesol; 3,7,11-Trimethyl-2,6,10-dodecen-1-ol; FCI 119a;

Farnesyl alcohol; NSC 60597; Nikkosome

Current regulation: Annex III, part 1, n° 82

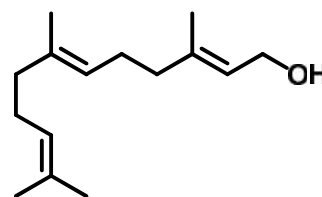
Clinical data:

In the “background information” section of the 1999 opinion, farnesol is classified as “less frequently reported allergen”; in 1 study of patients with cosmetic dermatitis 2 cases with contact allergy to farnesol had been reported; in other studies, positive reactions were seen in patients with positive PT reactions to MPR (33).

Since the last SCCNFP-opinion of 1999, farnesol is used not only for its scent, but also for its (slight) antimicrobial activity, useful, for instance, in deodorants. Thus, axillary dermatitis is a relatively typical presentation (111). In a multicentre study based on 1997/98 PT data, 0.5% positive reactions in consecutive patients were noted (Frosch 2002 a (16)). Farnesol is included in the FM II. In the original publication on single constituents of the FM II, 6 of 1701 consecutive patients reacted positively to farnesol 5%, ie., 0.35% (95% CI: 0.13 – 0.77%) (10). In a study on consecutive patients tested in 2003, 38 of 4238 patients had positive reactions to farnesol 5% pet. (0.9%, 95% CI: 0.6 – 1.2%) (4)(IVDK 2007). (A paper on farnesol previously published by the IVDK (112) presents results included in this later analysis.) In a series from Nagoya, Japan, 1.1% positive reactions in 1483 patients with suspected cosmetic dermatitis were observed (tested at 5% pet.) (14). In the Groningen 2009 study, 0.9% (95% CI: 0.2 – 2.7%) had positive reactions (6).

Additional information:

“Farnesol is an acyclic primary sesquiterpene alcohol found in essential oils such as lemongrass, citronella, tuberose blossom, sandalwood and orange blossom” (23). A RIFM review is available (113).

**GERANIOL**

CAS # 106-24-1

EC # 203-377-1

(2E)-3,7-Dimethyl-2,6-octadien-1-ol

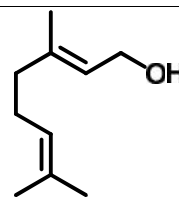
(E)-3,7-Dimethyl-2,6-octadien-1-ol; (E)-Geraniol; (E)-Nerol; 3,7-Dimethyl-trans-2,6-octadien-1-ol; Geraniol; Geranyl alcohol; Lemonol; MosquitoSafe; NSC 9279; trans-3,7-Dimethyl-2,6-octadien-1-ol; trans-Geraniol; β-Geraniol

Current regulation: Annex III, part 1, n° 78

Clinical data:

In the “background information” section of the previous opinion (33), geraniol, one of the 8 components of the FM I, is classified as frequent allergen, causing allergic reactions in about 0.4% in consecutive PT patients and accounting for 3 to 7% of reactions to the FM I. Allergic reactions had been observed in 1.2 – 30% of patients with eczema from cosmetic products (33).

Since the last SCCNFP-opinion of 1999, the IVDK 2007 study yielded 0.5% (95% CI: 0.2 – 0.9%) positive reactions in 2063 consecutively PTed patients (4). In the Groningen 2009 study, 0.6% (95% CI: 0.1 – 2.2%) had positive reactions to this allergen, tested at 2%, i.e. twice the usual concentration (6). In a series from Nagoya, Japan, 0.3% positive reactions in 1483 patients with suspected cosmetic dermatitis were observed (tested at the unusually high



concentration of 5% pet.) (14). In the Wöhrle 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded n=7 (0.9%) positive reactions (22). The IVDK 2010 study, 0.39% (95% CI: 0.10 – 0.69%) of 1214 consecutively tested patients reacted to the compound, while 0.87% (95% CI: 0.63 – 1.10%) of 5695 of patients tested in a more aimed manner, partly as break-down testing to the FM I, had a positive PT reaction (7). In a study from Alicante, Spain, 86 selected patients were patch tested with an extended fragrance series; n=17 reacted positively to geraniol (48).

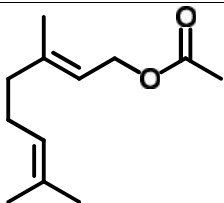
The fact that geraniol also occurs in food flavourings, and can elicit signs and symptoms of manifest contact sensitisation, is illustrated by the case of a 19 year old Japanese woman with cheilitis due to geraniol, improving after avoidance of respective foodstuff (114). A 20 year old Japanese woman with urticaria at the site of application of cosmetics with generalisation (contact urticaria syndrome grade 2), which A. Yamamoto et al. diagnosed as immediate type hypersensitivity to geraniol (without CA) (115).

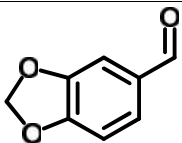
Additional information:

Geraniol is a component of Palmarosa oil (CYMBOPOGON MARTINI see below), geranium oil (about 40%), citronella oil (30-40%), rose oil, lavender oil, and jasmine oil. It is sensitive to heat which induces autooxidation and isomeric with linalool (53).

Geraniol forms oxidation product with increased sensitizing capacity both via spontaneous autooxidation at air exposure and via metabolic oxidation. Geraniol and neral together with hydroperoxide have been identified as oxidation products when geraniol autoxidizes (84). Geraniol and neral were also identified as metabolites of geraniol (85). This explains the simultaneous reactions to geraniol and citral seen by (4).

A review is available by Hostynek and Maibach (116) and by RIFM (117). It is a “top 100” substance and classified as R43 (IFRA, pers. comm.2010).

GERANYL ACETATE	
CAS # 105-87-3	
EC # 203-341-5	
(2E)-1-Acetate-3,7-dimethyl-2,6-octadien-1-ol	
(E)-Acetat-3,7-dimethyl-2,6-Octadien-1-ol; Geraniol acetate; (E)-3,7-Dimethyl-2,6-octadien-1-ol acetate; (E)-3,7-Dimethyl-2,6-octadienyl acetate; Acetic acid (2E)-3,7-dimethyl-2,6-octadienyl ester; Acetic acid geraniol ester; Bay pine (oyster) oil; Geranyl acetate; Geranyl ethanoate; NSC 2584; trans-1-Acetoxy-3,7-dimethyl-2,6-octadiene; trans-3,7-Dimethyl-2,6-octadien-1-yl acetate; trans-Geranyl acetate; β-Geranyl acetate	
Current regulation: /	
Clinical data: /	
Additional information:	
It is a “top 100” substance (IFRA, pers. comm.2010).	

HELIOTROPINE	
CAS # 120-57-0	
EC # 204-409-7	
1,3-Benzodioxole-5-carboxaldehyde	
Piperonal; 2H-Benzo[3,4-d]-1,3-dioxolan-5-ylformaldehyde; 3,4-(Methylenedioxy)benzaldehyde; 3,4-Dihydroxybenzaldehyde methylene ketal; 3,4-Dimethylenedioxybenzaldehyde; 5-Formyl-1,3-benzodioxolane;	

5-Formyl-1,3-benzodioxole; 5-Formylbenzodioxole;
Benzo[1,3]dioxole-5-carbaldehyde; Benzo[d][1,3]dioxole-5-
carboxaldehyde; Geliotropin; Heliotropin; Heliotropine; NSC
26826; Piperonaldehyde; Piperonylaldehyde; Protocatechuic
aldehyde methylene ether

Current regulation: /

Clinical data:

In the Frosch 2002 b study, n=2 (0.2%) positive reactions to “piperonal” (1% pet.) and n=6 (0.4%) to “piperonal” (5% pet.), respectively, in 1606 consecutive were observed (17). In the Frosch 1995 dose-finding pilot study, no positive reaction to 1% and 5% heliotropine in pet., tested in 106 consecutive patients in Barcelona, were observed (15).

Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).

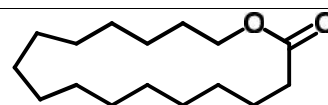
HEXADECANOLACTONE

CAS # 109-29-5

EC # 203-662-0

Oxacycloheptadecan-2-one

o-lactone-16-hydroxy-hexadecanoic acid; 1,16-Hexadecanolide;
16-Hexadecanolactone; Cyclohexadecanolide;
Dihydroambrettolide; Hexadecanoic acid, 16-hydroxy-, o-
lactone; Hexadecanolactone; Hexadecanolide; Juniperic acid
lactone; NSC 33546



Current regulation: /

Clinical data:

In the Larsen 2001 study, 1 of 178 patients with previously diagnosed contact allergy to fragrance ingredients had a positive PT reaction to this compound, tested 5% pet. (19). In the An 2005 study, 6 of 422 consecutive patients, i.e., 1.4%, had positive reactions to 5% “hexadecanolide” (13).

Additional information: /

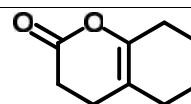
HEXAHYDROCUMARIN

CAS # 700-82-3

EC # 211-851-4

3,4,5,6,7,8-Hexahydro-2H-1-benzopyran-2-one

3,4,5,6,7,8-Hexahydro-coumarin; δ -Lactone-2-hydroxy-1-
cyclohexene-1-propanoic acid; 3,4,5,6,7,8-Hexahydrocoumarin;
Hexahydrocoumarin; Δ -1,6-2-Oxabicyclo(4.4.0)decen-3-one



Current regulation: Annex II, n° 1135

Clinical data: /

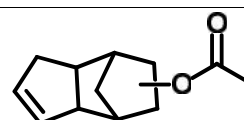
Additional information:

A RIFM review is available (93), p. S115 ff, citing a number of positive human sensitisation experiments.

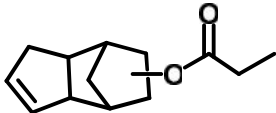
3 α ,4,5,6,7,7 α -HEXAHYDRO-4,7-METHANO-1H-INDEN-5(OR 6)-YL ACETATE

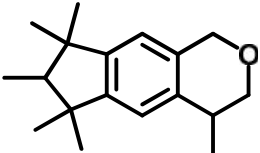
CAS # 54830-99-8

EC # 259-367-2



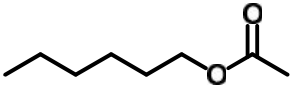
3α,4,5,6,7,7α-hexahydro-4,7-methano-1H-indenol Acetate	
Acetoxydihydrodicyclopentadiene; Cyclacet; Dicyclopentenyl acetate; Dicylat; Tricyclo[5.2.1.0 ^{2,6}]dec-3-enyl acetate; Tricyclodecenyl acetate	
Current regulation: /	
Clinical data:	
In the Frosch 1995 dose-finding pilot study, no positive reaction to 1% and 1 to 5% “Cyclacet ®” in pet., tested in 313 consecutive patients in Bordeaux and London, were observed (15).	
Additional information:	
Produced by IFF under the brand name “Cyclacet”	
(http://www.iff.com/Ingredients.nsf/0/1C9F2CB39EB1EF6480256993002FBC14 , last accessed 2010-07-08).	

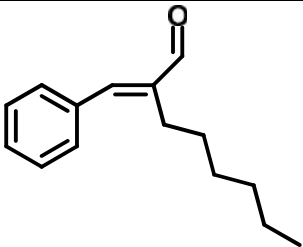
HEXAHYDRO-METHANOINDENYL PROPIONATE	
CAS # 68912-13-0	
EC # 272-805-7	
3α,4,5,6,7,7α-hexahydro-4,7-methano-1H-indenol propanoate	
3 α ,4,5,6,7,7 α -Hexahydro-4,7-methano-1H-indenyl propionate (Mixture of Isomers); dicyclopentadiene propionate; tricyclodecenyl propionate; tricyclo[5.2.1.0 ^{2,6}]dec-3-enyl propionate; verdyl propionate	
Current regulation: /	
Clinical data: /	
Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).	

HEXAMETHYLINDANOPYRAN	
CAS # 1222-05-5	
EC # 214-946-9	
1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethyl-cyclopenta[γ]-2-benzopyran	
1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[γ]-2-benzopyrane; 1,3,4,6,7,8-Hexahydro-4,6,6,8,8,8-hexamethylcyclopenta-2-benzopyran; Abbalide; Galaxolide; Galaxolide 50; Galaxolide 50BB; Galaxolide 50IPM; Galaxolide White; HHCB; Pearlide	
Current regulation: /	
Clinical data:	
In the Frosch 2002 a study, n=3 (0.2%) had positive reactions to the compound, tested 10% in isopropyl myristate (with 1 patient reacting positively to the diluent) (16). The Larsen 2001 study, testing with HHCB 7% pet., found 3.4% positive reactions in 178 patients with known contact allergy to fragrance ingredients (19). In the An 2005 study, 5 of 422 consecutive patients, i.e., 1.2%, had a positive reaction to “Galaxolide 50”, tested at 5% (13) (test concentration 2% pet.). The DeGroot 1985 study identified 3 (1.7%) positive reactions among 179 patients using a 25% PT preparation of HHCB (25). In the Frosch 1995 dose-finding pilot study, no positive reaction to 1% and 5% “Galaxolide 50 ®” in pet., tested in 100 consecutive patients in Stockholm, were observed (15).	

Additional information:

[0403/00 - Opinion concerning Hexahydro-hexamethyl-cyclopenta\(y\)-2-benzopyran \(HHCB\)](#)
[0610/02 - Opinion on Hexahydro-hexamethyl-Cyclopenta \(y\)-2-Benzopyran \(HHCB\)](#) (no restrictions) It is a “top 100” substance (IFRA, pers. comm.2010).

HEXYL ACETATE	
CAS # 142-92-7	
EC # 205-572-7	
Hexyl ethanoate	
Acetic acid, hexyl ester, Hexyl alcohol, acetate; 1-Hexyl acetate; Exceed 600; Hexyl acetate; Hexyl ester acetic acid;; NSC 7323; n-Hexyl acetate; n-Hexyl ethanoate	
Current regulation: /	
Clinical data: /	
Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).	

HEXYL CINNAMAL	
CAS # 101-86-0	
EC # 202-983-3	
α -Hexyl-cinnamaldehyde	
2-(Phenylmethylene)octanal; 2-Hexyl-3-phenyl-2-propenal; 2-Hexylcinnamaldehyde; Hexyl cinnamic aldehyde; NSC 406799; NSC 46150; α -Hexylcinnamaldehyde; α -Hexylcinnamic aldehyde; α -Hexylcinnamyl aldehyde; α -n-Hexyl- β -phenylacrolein; α -n-Hexylcinnamaldehyde	
Current regulation: Annex III, part 1, n° 87	
Clinical data:	

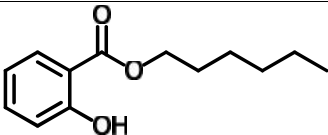
In the “background information” section of the 1999 opinion, hexyl cinnamal (synonymous: alpha-hexyl cinnamal, AHCA) is classified as “less frequently reported allergen”; 2 studies with 1 case and 1 study with 7 cases of contact allergy to this compound in patients with eczema from cosmetic products were found (33).

Since the last SCCNFP-opinion of 1999, in the Frosch 2002 a study, 0.3% positive PT reactions to consecutive patients were noted (16). In the subsequent EU 2005 study, 2 of 1701 patients had positive reactions to AHCA, and n=16 doubtful or irritant to AHCA at 10% in pet. (10). The IVDK 2007 study yielded n=3, i.e. 0.2% (95% CI: 0.03 – 0.4%) positive reactions in 2019 consecutively PTed patients, using 10% pet. as test concentration (4). In the Groningen 2009 study, 0.6% (95% CI: 0.1 – 2.2%) had positive reactions to this allergen, using a lower test concentration of 5% pet. (6).

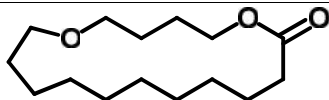
Additional information:

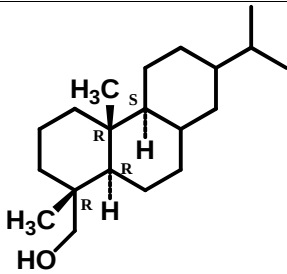
It is a “top 100” substance and classified as R43 (IFRA, pers. comm.2010).

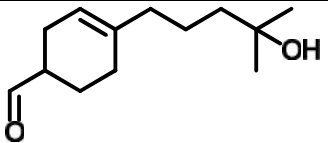
Hexyl cinnamal is regarded as “a recommended positive control for skin sensitization testing”, e.g., in the context of the LLNA (118).

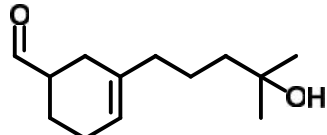
HEXYL SALICYLATE	
CAS # 6259-76-3	
EC # 228-408-6	
Hexyl-2-hydroxybenzoate	

Salicylic acid, hexyl ester; 1-Hexyl salicylate; Hexyl salicylate; n-Hexyl salicylate	
Current regulation: /	
Clinical data:	
None of the 218 patients with known contact allergy to fragrance ingredients reacted positively to this compound (tested at 5% in pet.) in the Larsen 2002 c study (1).	
Additional information:	
In a RIFM review, 2 human sensitisation experiments are mentioned which yielded no evidence of sensitising potential (HRIPT, n=103, maximisation test, n=22) (119). It is a “top 100” substance and classified as R43 (IFRA, pers. comm.2010).	

HIBISCOLIDE	
CAS # 6707-60-4	
EC # 229-755-6	
1,6-Dioxacycloheptadecan-7-one	
Undecanoic acid, 11-(4-hydroxybutoxy)-, o-lactone; 12-Oxa-1,16-hexadecanolide; Cervolide; Musk 781; NSC 34741; 12-Oxahexadecan-16-olide	
Current regulation: /	
Clinical data:	
None of the 178 patients with known contact allergy to fragrance ingredients reacted positively to "12-oxahexadecanolide" (tested at 5% in pet.) in the Larsen 2001 study (19).	
Additional information: /	

HYDROABIETYL ALCOHOL, when used as a fragrance ingredient	
CAS # 13393-93-6	
EC # 236-476-3	
(1R,4αR,4βS,10αR)-Tetradecahydro-1,4α-dimethyl-7-(1-methylethyl)-1-Phenanthrenemethanol	
Tetradecahydro-1,4a-dimethyl-7-(1-methylethyl)- 1-phenanthrenemethanol; Tetrahydroabietyl alcohol	
Current regulation: AnnexII, n° 440	
Clinical data:	
In the deGroot 2000 study, 17 of 1825 consecutively tested patients had positive reactions to hydroabietyl alcohol (10% pet.) (12).	
Additional information:	
Commercial hydroabietyl alcohol consists of di- and tetrahydroabietyl alcohol together with non-modified colophony (120)	

HYDROXYISOHEXYL 3-CYCLOHEXENE CARBOXALDEHYDE (HICC) regioisomers	
CAS # 31906-04-4 / 51414-25-6	
EC # 250-863-4 / 257-187-9	
4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde (31906-04-4)	
3-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-	
	31906-04-4

carboxaldehyde (51414-25-6)	
31906-04-4: 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexenecarboxaldehyde; 4-(4-Methyl-4-hydroxyamyl)cyclohex-3-ene carboxaldehyde; Liral	

51414-25-6

Current regulation: Annex III, part 1, n° 79

Clinical data:

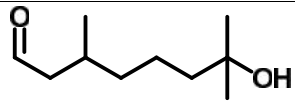
In the “background information” section of the previous opinion (33) HICC is classified as frequent allergen, causing allergic reactions in about 2.8% in consecutive PT patients, two thirds of these being relevant (33).

Since the last SCCNFP-opinion of 1999, in the Frosch 2002 a study, 2.7% of the 1855 consecutive patients reacted positively to HICC (5% pet.) (16). In the EU 2005 study, 28 of 1701 patients (1.7%, 95% CI: 1.1 – 2.4%) reacted positively to 5% HICC in pet. (10). In 21325 patients PTed consecutively in the IVDK 2007 study, 2.4% (95% CI: 2.2 – 2.6%) positive reactions were noted to 5% HICC in pet. (4). Similar to other studies, HICC was the most common single fragrance allergen among 320 patients tested in the Groningen 2009 study, with 3.1% (95% CI: 1.5 – 5.7%) positive reactions despite testing with a lower concentration of 2% pet. (6). In the An 2005 study, 7 of 422 consecutive patients, i.e., 1.7%, had positive reaction (13). The Belsito 2006 study (20) yielded a relatively low prevalence of 0.4% (7 of 1603; exact 95% CI (recalculated): 0.17 – 0.90%) positive reactions with 5% HICC in pet. and even less with lower test concentrations; possible reasons for the much lower prevalence were discussed. The IVDK 2010 study, 2.36% (95% CI: 2.19 - 2.53%) of 37270 consecutively tested patients reacted to HICC (7). In a study from Alicante, Spain, 86 selected patients were patch tested with an extended fragrance series; n=8 reacted positively to HICC (48).

Further clinical data with a focus on quantitative dose-response (see also section 4.3), is discussed in (121).

Among the early case reports, S.A. Hendriks reported the case of a 20 year old patient developing axillary dermatitis after 5 months use of a deodorant containing HICC (122).

Additional information: /

<i>HYDROXYCITRONELLAL</i>	
CAS # 107-75-5	
EC # 203-518-7	
7-Hydroxy-3,7-dimethyl-octanal	
(±)-Hydroxycitronellal; 3,7-Dimethyl-7-hydroxyoctanal; 7-Hydroxy-3,7-dimethyloctanal; 7-Hydroxycitronellal; Citronellal hydrate; Citronellal, hydroxy-; Cyclalia; Cyclosia; Cyclosia base; Fixol; Hydroxycitronellal; Laurine; Lilyl aldehyde; Muguet synthetic; Muguetine principle; NSC 406740; Phixia	

Current regulation: Annex III, part 1, n° 72

Clinical data:

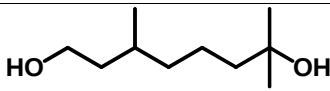
In the “background information” section of the previous opinion (33), hydroxycitronellal, one of the 8 components of the FM I, is classified as frequent allergen, causing allergic reactions in about 0.75% in consecutive PT patients and accounting for 6 to 16% of reactions to the FM I. Allergic reactions had been observed in 10 – 45% of patients with eczema from cosmetic products (33).

Since the last SCCNFP-opinion of 1999, the IVDK 2007 study yielded 1.3% (95% CI: 0.9 – 1.9%) positive reactions in 2063 consecutively PTed patients (4). In the Groningen 2009 study, 2.2% (95% CI: 0.9 – 4.5%) had positive reactions to this compound, tested at 2% pet.,

i.e., twice the commonly used concentration (6). The Sugiura 2000 study observed 1% positive PT reactions (test concentration 5% pet.) in 1483 patients tested for suspected cosmetic dermatitis (14). In the Wöhrle 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded 1.5% positive reactions (22). The IVDK 2010 study, 1.17% (95% CI: 0.48 – 1.85%) of 1214 consecutively tested patients reacted to the compound, while 2.95% (95% CI: 2.43 – 3.47%) of 4359 of patients tested in a more aimed manner, partly as break-down testing to the FM I, had a positive PT reaction (7). In a study from Alicante, Spain, 86 selected patients were tested with hydroxycitronellal, yielding 6 positive reactions (48).

Additional information:

Hydroxycitronellal is a synthetic fragrance, which only recently has been found in a few essential oils, e.g., of a *Narcissus* species and in essential oils of pepper (53)

HYDROXYCITRONELLOL	
CAS # 107-74-4	
EC # 203-517-1	
3,7-dimethyl-7-octanediol	
2,6-Dimethyl-2,8-octanediol; 3,7-Dimethyl-1,7-octanediol; 3,7-Dimethyloctan-1,7-diol; Citronellol, hydroxy-; Hydroxyciol; Hydroxycitronellol; NSC 406140; NSC 67886	

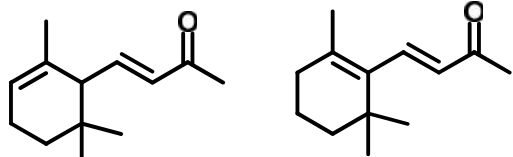
Current regulation: /

Clinical data:

This compound elicited 6.0% positive PT reactions in 218 fragrance sensitive individuals (Larsen 2002 c, (1)).

Additional information:

A RIFM review is available, reporting results of a human induction study (maximisation test) in 25 volunteers, yielding no evidence of sensitisation (123).

IONONE isomeric mixture	
CAS # 8013-90-9	
EC # 232-396-8	
Ionone	
Irisone, mixture of alpha- and beta ionone	

Current regulation: /

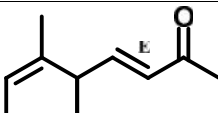
Clinical data: / (see single isomers)

Additional information:

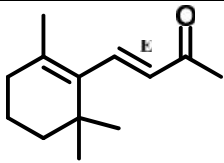
It is a “top 100” substance, further specified with “mixed isomers” (IFRA, pers. comm.2010).

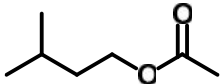
INCI: “MIXED IONONES”, with CAS # 14901-07-6 / 6901-97-9 / 8013-90-9 (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=35383>, last accessed 2010-07-13).

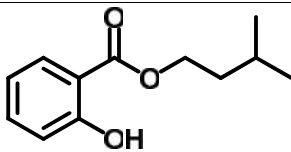
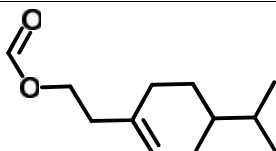
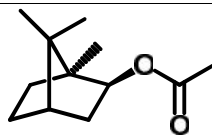
A RIFM review is available on “ionone” (124), quoting negative human and experimental results.

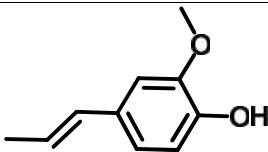
alpha-IONONE	
CAS # 127-41-3	
EC # 204-841-6	

(3E)-4-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-3-Buten-2-one	
(E)-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-Buten-2-one; (5E)-Ionone; (E)-4-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-3-buten-2-one; (E)- α -Ionone; ($\pm$)-trans- α -Ionone; ($\pm$)- α -Ionone; 4-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-3-buten-2-one; 4-(2,6,6-Trimethyl-2-cyclohexenyl)-3-buten-2-one; trans- α -Ionone; α -Cyclocitrylideneacetone; α -Ionone	
Current regulation: /	
Clinical data:	
In the Frosch 1995 dose-finding pilot study, no positive reaction to 1% and 5% alpha-ionone in pet., tested in 205 consecutive patients, were observed (15).	
Additional information: A RIFM review is available (125).	

beta-IONONE	
CAS # 79-77-6	
EC # 201-224-3	
(3E)-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-Buten-2-one	
(E)-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-Buten-2-one; (E)- β -Ionone; Ionone beta; trans- β -Ionone; β -Ionone	
Current regulation: /	
Clinical data:	
In the Frosch 1995 dose finding pilot study, no positive reaction to 1% and 5% beta-ionone in pet., tested in 205 consecutive patients, were observed (15).	
Additional information:	
It is a “top 100” substance (IFRA, pers. comm.2010). A RIFM review is available (126).	

ISOAMYL ACETATE	
CAS # 123-92-2	
EC # 204-662-3	
3-Methylbutyl acetate	
1-Butanol, 3-methyl-, acetate; Acetic acid, isoamyl ester; Isopentyl alcohol, acetate; 3-Methyl-1-butanol acetate; 3-Methyl-1-butyl acetate; 3-Methylbutyl acetate; 3-Methylbutyl ethanoate; Acetic acid 3-methyl-1-butyl ester; Acetic acid 3-methylbutyl ester; Acetic acid isopentyl ester; Banana oil; Isoamyl acetate; Isoamyl alcohol acetate; Isoamyl ethanoate; Isopentyl acetate; Isopentyl ethanoate; NSC 9260; Pear oil; i-Amyl acetate; iso-Amyl acetate; iso-Pentyl acetate	

ISOAMYL SALICYLATE	
CAS # 87-20-7	
EC # 201-730-4	
3-Methylbutyl-2hydroxybenzoate	
Isopentyl 2-Hydroxybenzoate; isopentyl salicylate; Salicylic acid, isopentyl ester (6CI,8CI); Isopentyl alcohol, salicylate; 3-Methylbutyl salicylate; Isoamyl o-hydroxybenzoate; Isoamyl salicylate; Isopentyl salicylate; NSC 7952	
Current regulation: /	
Clinical data:	
The DeGroot 1985 study identified 1 (0.6%) positive reactions among 179 patients using a 50% PT preparation of this compound – this reaction may have been due to an “excited back syndrome” and is thus a limited evidence (25). In the Frosch 1995 dose finding pilot study, no positive reaction to 1% and 5% isoamyl salicylate in pet., tested in 95 consecutive patients, were observed (15).	
Additional information: A RIFM review is available (127).	
ISOBERGAMATE	
CAS # 68683-20-5	
EC # 272-066-0	
4-(isopropyl)cyclohexadiene-1-ethyl formate	
Structure is incompletely defined 4-(1-methylethyl)-1,?-Cyclohexadiene-1-ethyl formate 4-(Isopropyl)cyclohexadiene-1-ethyl methanoate; menthadienyl formate; Menthadiene-7-methyl formate	
Current regulation: Annex III, part 1, n° 170	
Clinical data: /	
Additional information: A RIFM review is available (128).	
ISOBORNYL ACETATE	
CAS # 125-12-2	
EC # 204-727-6	
(1R,2R,4R)-1,7,7-trimethyl-Bicyclo[2.2.1]hept-2-yl acetate	
Bicyclo[2.2.1]heptan-2-ol, 1,7,7-trimethyl-, acetate, (1R,2R,4R)-rel- ; Bicyclo[2.2.1]heptan-2-ol, 1,7,7-trimethyl-, acetate, exo-; Isoborneol, acetate; (±)-Isobornyl acetate; Isobornyl acetate; NSC 62486; Pichtosin; Pichtosine; exo-Bornyl acetate	
Current regulation: /	
Clinical data:	
In the Frosch 1995 dose-finding pilot study, no positive reaction to 1% and 5% isobornyl acetate in pet., tested in 107 consecutive patients in High Wycombe, were observed (15).	
Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).	

ISOEUGENOL	
CAS # 97-54-1	
EC # 202-590-7	
2-Methoxy-4-(1-propen-1-yl)-phenol	
Phenol, 2-methoxy-4-(1-propenyl)- ; Phenol, 2-methoxy-4-propenyl-; 1-(3-Methoxy-4-hydroxyphenyl)-1-propene; 2-Methoxy-4-(1-propenyl)phenol; 2-Methoxy-4-propenylphenol; 3-Methoxy-4-hydroxy-1-propenylbenzene; 4-Hydroxy-3-methoxy-1-propenylbenzene; 4-Hydroxy-3-methoxy-β-methylstyrene; 4-Propenylguaiacol; Isoeugenol; NSC 6769	

Current regulation: Annex III, part 1, n° 73

Clinical data:

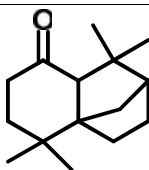
In the “background information” section of the previous opinion (33), isoeugenol, one of the 8 components of the FM I, is classified as frequent allergen, causing allergic reactions in about 1.9% in consecutive PT patients and accounting for 6 to 22% of reactions to the FM I. Allergic reactions had been observed in 2 – 25% of patients with eczema from cosmetic products (33).

Since the last SCCNFP-opinion of 1999, the IVDK 2007 study yielded 1.3% (95% CI: 0.8 – 1.8%) positive reactions in 2063 consecutively PTed patients (4). In the Groningen 2009 study, 1.3% (95% CI: 0.3 – 3.2%) had positive reactions to isoeugenol, tested at 2% pet., i.e., twice the commonly used concentration (6). In the Wöhrle 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded 5.4% positive reactions (22). At St Johns Institute of Dermatology in London 3636 subjects were patch tested with isoeugenol 2001-2005, 97 of whom were positive. Year-on-year incidence showed an increasing trend, with an overall incidence of 2.67% (129). The IVDK 2010 study, 1.62% (95% CI: 0.87 – 2.38%) of 1214 consecutively tested patients reacted to the compound, while 3.41% (95% CI: 2.90 – 3.92%) of 5747 of patients tested in a more aimed manner, partly as break-down testing to the FM I, had a positive PT reaction (7). In a study from Alicante, Spain, 86 selected patients were patch tested with an extended fragrance series; n=11 reacted positively to isoeugenol (48).

Additional information:

Isoeugenol occurs in a cis- (CAS 5912-86-7) and a trans-isomers (CAS 5932-68-3), the latter dominating in trade products (82-88%) (53).

Isoeugenyl methyl ether caused 7.3% positive reactions in the Larsen 2002 c study (1). A number of derivatives of isoeugenol, such as isoeugenyl acetate, transisoeugenol, isoeugenyl benzoate, isoeugenyl phenylacetate, isoeugenyl methyl ether and benzyl isoeugenyl have been examined in 2261 consecutive patients; a varying proportion of positive patch test reactions and a varying proportion of concomitant reactions with isoeugenol have been observed (130). In an earlier study, 5 of 7 patients positive to isoeugenol also displayed positive reactions to isoeugenol acetate (1.2% eth.) (131) (see also section 5 and 6).

ISOLONGIFOLENEKETONE	
CAS # 33407-62-4	
EC # 245-890-3	
1,3,4,6,7,8a-Hexahydro-1,1,5,5-tetramethyl-2H-2,4a-methanonaphthalen-8(5H)-one	
Hexahydro-1,1,5,5-tetramethyl-2H-2,4a-methanonaphthalen-8(5H)-one	

Current regulation: /

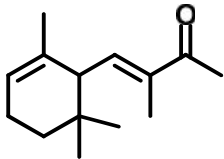
Clinical data:

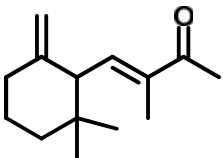
The Larsen 2001 study identified 1 in 178 patients with known contact allergy to fragrance ingredients who reacted positively in the PT (5% pet.) (19).

Additional information:

Not listed in CosIng under this CAS #. Other CAS # reported in RIFM review ³:

- 29461-14-1 CosIng: INCI name “ISOLONGIFOLENE KETONE EXO”;
- 23787-90-8 CosIng: INCI name “ISOLONGIFOLANONE”;
- 29461-13-0: CosIng: INCI name “HEXAHYDRO-TETRAMETHYLMETHANONAPHTHALEN-8-ONE”.

<i>alpha-ISOMETHYL IONONE</i>	
CAS 127-51-5	
EC 204-846-3	
3-Methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one	
4-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-3-methyl-3-buten-2-one; Cetone Alpha; Isomethyl- α -ionone; NSC 66432; α -Cetone	
Current regulation: Annex III, part 1, n° 90	

<i>gamma-Methylionone</i>	
CAS 7388-22-9	
EC /	

According to CosIng, “alpha-ISOMETHYL IONONE” (CAS # 127-51-5) and “gamma-Methylionone” (CAS # 7388-22-99) are synonyms, with one CAS number, and one preferred chemical name. The substance(s) are accordingly treated in the 1999 opinion (33) as one. As this treatment is also found in the literature, both substances are reviewed together.

Clinical data:

In the “background information” section of the 1999 opinion, “gamma-methylionone” is classified as “less frequently reported allergen”; 1 study with 2 cases and 2 studies with 1 case were found among patients with eczema from cosmetic products (33).

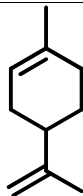
The IVDK 2007 study yielded n=1, i.e. 0.1% (95% CI: 0.00 – 0.2%) positive reactions in 2004 consecutively PTed patients (4). In the subsequent period (2005-2008), n=986 patients were tested in the IVDK 2010 study, with no positive reactions (7). In the Groningen 2009 study, n=2, i.e. 0.6% (95% CI: 0.1 – 2.2%) had positive reactions to this allergen, tested at only 1% pet. (6). In a Korean study with 422 consecutive patients, 2.1% reacted positively to “alpha isomethyl ionone (gamma-methylionone), CAS # 127-51-5”, tested 5% pet. (13)

Additional information:

It is a “top 100” substance (IFRA, pers. comm.2010) under the label of “alpha-ISOMETHYL IONONE (CAS # 127-51-5)”.

A RIFM review is available, listing 4 human sensitisation experiments employing different study protocols – all yielding negative results (132). Another review is available by Hostynek and Maibach (133), both referring to “alpha-ISOMETHYL IONONE (CAS # 127-51-5)”.

³ Opdyke, D. L. J.; Letizia, C. **Monographs on fragrance raw materials. Isolongifolanone.** Food and Chemical Toxicology (1983), 21(6), 859

(DL)-LIMONENE	
CAS # 138-86-3	
EC # 231-732-0	
1-Methyl-4-(1-methylethenyl)-cyclohexene	
p-Mentha-1,8-diene; (±)-Dipentene; (±)-Limonene; (±)-α-Limonene; 1,8-p-Menthadiene; 1-Methyl-4-(1-methylethenyl)cyclohexene; 1-Methyl-4-isopropenyl-1-cyclohexene; 1-Methyl-4-isopropenylcyclohexene; 1-Methyl-p-isopropenyl-1-cyclohexene; 4-Isopropenyl-1-methyl-1-cyclohexene; 4-Isopropenyl-1-methylcyclohexene; Cajeputen; Cajeputene; Cinen; Cinene; DL-Limonene; Dipenten; Dipentene; Eulimen; Flavor orange; Goldflush II; Kautschin; Limonen; Limonene; NSC 21446; NSC 844; Nesol; Orange X; Orange flavor; PC 560; Roti-Histol; SF 001; dl-Limonene; α-Limonene	
Current regulation: Annex III, part1, n° 88, 167, 168	

Clinical data:

In the “background information” section of the 1999 opinion, d-limonene (CAS 5989-27-5) is classified as “less frequently reported allergen in relation to cosmetic exposure”; with contact allergy to oxidised limonene not infrequently reported in the literature (33).

Since 1999, several studies have been performed using limonene where the oxidation state is not given, but intended to be low. In one study, 0.6% positive reactions to limonene (3% pet.) were observed in 1606 consecutive patients (17). The IVDK 2007 study yielded n=3, i.e. 0.1% (95% CI: 0.03 – 0.4%) positive reactions in 2396 patients consecutively PTed with limonene (2% pet.) (4). The IVDK 2010 study, 0.28% (95% CI: 0 – 0.57%; percentages standardised for age and sex) of 1241 patients PTed with dipentene reacted to the compound (7). In the Groningen 2009 study, no positive reactions to this allergen, tested at 2% pet., were observed in 320 patients (6).

Regarding selected case reports, a case of a 40 year old citrus fruit picker with work related hand dermatitis and bronchial asthma has been described, who tested extreme positive to DL-limonene (2% pet.), and, less extremely, to citronellol and to the biocide dichlorophene (134). Moreover, limonene is used as a solvent in technical applications and cleaning and can lead to allergic contact dermatitis (e.g., a histopathology technicians (135, 136) or a painter and decorator (137)). In “water-free” hand cleansers it is reported to be used in concentrations around 10 – 20% (137). Wax polishes may contain dipentene and have caused one reported case of occupational ACD in a car mechanic (138). Another case of occupational ACD from dipentene in honing oil has been reported (139). In a case series from Sweden, 2 of 105 car mechanics patch tested for occupational contact dermatitis had positive reactions to oxidised d-limonene (5% pet.) (140).

Additional information:

Limonene is a monocyclic monoterpene existing in two enantiomers: (R)-(+)-limonene (CAS 5989-27-5) and (S)-(-)-limonene (CAS 5989-54-8). Racemic limonene is known as dipentene.

The allergenicity of limonene is closely related to oxidation (71, 72, 141, 142). It has been demonstrated that both enantiomers, R-(+)- and S-(-)-limonene spontaneously autoxidize, and that the primary oxidation products formed, the hydroperoxides, are strong and clinically relevant contact allergens. Among 2411 consecutive patients in a multi-centre European study, 63 (2.6 % [95%CI: 2.0-3.3]) reacted to oxidised (R)-(+)-and/or (S)-(-)-limonene (3.0% pet.) (72). In other multi-studies also, a considerable proportion of patients showed positive patch test reactions to oxidised R-(+)- limonene, e.g.,

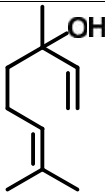
- between 0.3% and 5.1% of subgroups of 2800 patients in Stockholm and Leuven, depending on test concentration, oxidation state and department(141),
- between 0.3% and 6.5% in 4 different departments in altogether 2273 patients (72, 143).

The primary oxidation products are the major allergens forming specific antigens (Bråred-Christensson J, Matura M, Bäcktorp C, Börje A, Nilsson JLG, Karlberg A-T. Hydroperoxides form specific antigens in contact allergy. Contact Dermatitis 2006; 55: 230-237.).

Current IFRA standards emphasise “a peroxide value of less than 20 millimoles peroxides per litre, determined according to the FMA method”

(<http://www.ifraorg.org/Home/Code,+Standards+Compliance/IFRA+Standards/page.aspx/56>, last accessed 2009-11-11). For a more general discussion see section 5.

There is no scientific rationale for the difference in peroxide value allowed for limonene (20 ppm) compared to linalool (10 ppm). Specific values for hydroperoxides, which are allergens, would be desirable.

LINALOOL	
CAS # 78-70-6 (isomeric mixture)	
EC # 201-134-4; 245-083-6 See: http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=27933	
3,7-Dimethyl-1,6-octadien-3-ol	
(±)-Linalool; 2,6-Dimethyl-2,7-octadien-6-ol; 2-Methyl-1-prenyl-3-buten-2-ol; 3,7-Dimethyl-1,6-octadiene-3-ol; 3,7-Dimethyl-3-hydroxy-1,6-octadiene; L 260-2; Linalol; Linalool; Linalyl alcohol; Linanool; NSC 3789; dl-Linalool; β-Linalool	
Current regulation: Annex III, part 1, n° 84	

Clinical data:

In the “background information” section of the 1999 opinion, linalool in non-oxidized form is classified as “less frequently reported allergen”; with 4 cases of contact allergy reported in 2 studies on patients with eczema from cosmetic products (33).

Since the last SCCNFP-opinion of 1999, studies have been performed on contact allergy to linalool, oxidation state not given, but intended to be low. In the Larsen 2002 c study, none of the 218 patients with known contact allergy to fragrance ingredients had a positive reaction to linalool 5% pet., as prepared specially for this study (1). The IVDK 2007 study yielded 0.3% (95% CI: 0.1 – 0.6%) positive reactions in 2401 patients consecutively tested with stabilised linalool (10% pet.) (4). The IVDK 2010 study, 1 patient had a weak, and another a ++ reaction among the n=985 patients tested with 10% linalool (stabilised) in pet. (7). In the Groningen 2009 study, n=2, i.e. 0.6% (95% CI: 0.1 – 2.2%) had positive reactions to this allergen (6). The deGroot 2000 study with 1825 consecutively tested patients yielded 3 positive reactions to linalool (12). The DeGroot 1985 study found no positive reactions among 179 patients using a 30 % PT preparation of linalool (25).

Additional information:

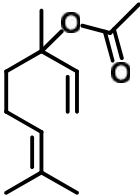
The allergenicity of linalool is closely related to oxidation and the primary oxidation products, the hydroperoxides, are the main allergens (144). In a clinical study 2002-2003 in 6 European centres including 1511 consecutive patients, 1.3% showed a positive reaction to oxidized linalool (2.0% pet.) and 1.1% to the hydroperoxide fraction (65). A recent dose-response study in Sweden including 3400 patients in two test centres showed a positive reaction in 5.3% of the 1725 patients tested with oxidized linalool 6% pet. (145).

A review by RIFM is available both regarding linalool (146) and linalool “and related esters”

(147). Another review is available by Hostynek and Maibach (148).

It is a “top 100” substance (IFRA, pers. comm.2010).

Additional CAS numbers exist for the single isomers: CAS # 126-90-9 (S-isomer), CAS # 126-91-0 (R-isomer); however, in the studies reviewed the isomeric mixture has been used throughout.

LINALYL ACETATE	
CAS # 115-95-7	
EC # 204-116-4	
3,7-Dimethyl-1,6-octadien-3-yl acetat	
1,6-Octadien-3-ol, 3,7-dimethyl-, acetate; Linalool acetate K; (±)-Linaloyl acetate; (±)-Linalyl acetate; 1,5-Dimethyl-1-vinyl-4-hexenyl acetate; 3,7-Dimethyl-1,6-octadien-3-yl acetate; 3-Acetoxy-3,7-dimethyl-1,6-octadiene; Acetic acid linalool ester; Bergamiol; Bergamol; Bergamot mint oil; Linalyl acetate; NSC 2138; dl-Linalool acetate	

Current regulation: /

Clinical data:

In 100 patients tested in Odense, DK, in the early 90s, no positive reactions were observed with 1 and 5% linalyl acetate in pet. (15). In the Frosch 2002 a study, testing with linalyl acetate (10% pet.), 0.2% positive PT reactions to consecutive patients were noted (16). Similarly, the RIFM review mentioned quotes a number of studies where no allergic reactions to this compound had been observed, with the exception of one positive reaction in a Dutch study in 1988(149).

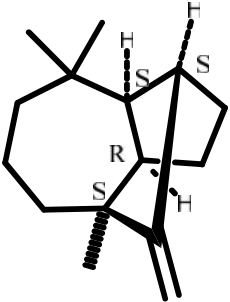
Additional information:

This is the main component of lavender oil (30%), also part of bergamot oil, neroli oil, peppermint oil, lemon oil and jasmine oil (53).

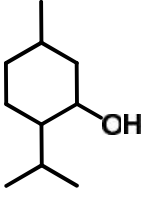
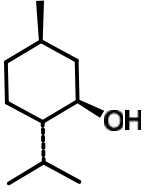
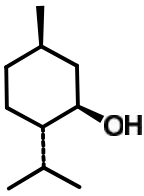
Linalyl acetate autoxidizes spontaneously at air exposure and the major allergens, the hydroperoxides, are the primary oxidation products (150). The pattern of autoxidation is similar to that for linalool and as the acetate can be metabolically hydrolysed to the corresponding alcohol cross reactions to allergens from oxidized linalool should be possible. This was indicated in a study of lavender oil and oxidised linalyl acetate which elicited positive PT reactions in some patients with known contact allergy to oxidised linalool (n=3) (151).

A RIFM review is available reporting 7 human sensitisation experiments yielding few or no cases of sensitisation (152).

It is a “top 100” substance (IFRA, pers. comm.2010).

Longifolene	
CAS # 475-20-7	
EC # 207-491-2	
(1S,3aR,4S,8aS)-Decahydro-4,8,8-trimethyl-9-methylene-1,4-methanoazulene	
1,4-Methanoazulene, decahydro-4,8,8-trimethyl-9-methylene-, (1S,3aR,4S,8aS)-(+)-; 1,4-Methanoazulene, decahydro-4,8,8-trimethyl-9-methylene-, [1S-(1α,3aβ,4α,8aβ)]-; (+)-Longifolene; Junipen; Junipene; Kuromatsuen; Kuromatsuene; Longifolen; NSC 150808; d-Longifolene; α-	

Longifolene	
Current regulation: /	
Clinical data: /	
Additional information:	
It is a “top 200” substance and classified as R43 (IFRA, pers. comm.2010)	
http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details_v2&id=77412	
This substance is listed in the Register of Flavouring Substances pursuant to Article 3(1) of Regulation EC No. 2232/96 (28 Oct 1996) that lays down a procedure for flavouring substances used or intended for use in or on foodstuffs. Adopted February 23, 1999.	
A RIFM review is available citing one negative human maximisation test (n=25) with 10% pet. (153).	

MENTHOL	 1490-04-6
CAS # 1490-04-6 / 89-78-1 / 2216-51-5	
EC # 216-074-4 / 239-388-3 / 218-690-9	
5-Methyl-2-(1-methylethyl)-cyclohexanol (1490-04-6) (1R,2S,5R)-rel-5-Methyl-2-(1-methylethyl)-cyclohexanol (89-78-1) (1R,2S,5R)-5-Methyl-2-(1-methylethyl)-cyclohexanol (2216-51-5)	
Other names: 1490-04-6: Menthol; 1-Methyl-4-isopropyl-3-cyclohexanol; 2-Isopropyl-5-methylcyclohexan-1-ol; 2-Isopropyl-5-methylcyclohexanol; 3-Hydroxy-p-menthane; 5-Methyl-2-(1-methylethyl)cyclohexanol; 5-Methyl-2-isopropylcyclohexanol; Menthyl alcohol; p-Menthan-3-ol 89-78-1: (1 α ,2 β ,5 α)-5-methyl-2-(1-methylethyl)-Cyclohexanol; cis-1,3,trans-1,4-Menthol; dl-Menthol; (1R,2S,5R)-rel-5-Methyl-2-(1-methylethyl)cyclohexanol; ($\pm$)-Menthol; DL-Menthol; Fisherman's Friend Lozenges; Hexahydrothymol; Menthacamphor; Menthol; Menthomenthol; NSC 2603; Peppermint camphor; Racementhol; Therapeutic Mineral Ice; Thymomenthol; rac-Menthol 2216-51-5: (1R,2S,5R)-5-methyl-2-(1-methylethyl)-Cyclohexanol; [1R-(1 α ,2 β ,5 α)]-5-methyl-2-(1-methylethyl)-Cyclohexanol; (1R,3R,4S)-(-)-Menthol; (-)-Menthol; (-)-Menthyl alcohol; (-)-trans-p-Methan-cis-3-ol; (1R)-(-)-Menthol; (1R,2S,5R)-(-)-Menthol; (1R,2S,5R)-2-Isopropyl-5-methylcyclohexan-1-ol; (1R,2S,5R)-2-Isopropyl-5-methylcyclohexanol; (R)-(-)-Menthol; 1R-Menthol; L-Menthol; L-Mentholum; Levomenthol; NSC 62788; l-(-)-Menthol; l-Menthol	 89-78-1  2216-51-5
Current regulation: /	
Clinical data:	

Among 512 patients referred from a dental department for diagnostic work-up of various intraoral symptoms and complaints within 4 years, 10 patients had positive (+ to +++) PT reactions to menthol 5% pet. at D4, mostly reporting dramatic improvement after cessation of use of peppermint-containing oral products (154). In 63 patients positive to the FM I, 1 had a positive PT reaction to menthol, 5% pet., in the Santucci 1987 study (28). The IVDK 2010

study, 1 of 1147 patients tested with 1% menthol in pet. had a weak positive reaction to menthol (7).

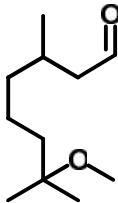
A case of contact allergy to “peppermint and menthol” in a transdermal therapeutic system with flurbiprofen for lumbar pain has been described (155). Moreover, a case of rhinitis caused by different menthol-containing products, diagnostically proven by repeatedly positive urticarial reactions after application of 2% menthol in pet. or 5% peppermint oil in pet., has been reported (156). “A case of asthma due to menthol is reported in a 40-year-old woman with no history of asthma or any other allergy. During the last two years, the patient had presented dyspnoea, wheezing and nasal symptoms when exposed to mentholated products such as toothpaste and candies. The aetiology was suggested by the history of exposure and diagnosis was established by skin tests and bronchial challenge with menthol. The patient achieved control of symptoms by avoiding menthol and its derivatives.” (157).

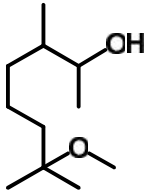
Additional information:

Menthol is an ingredient of several essential oils, like peppermint oil, and has been identified as causative allergen in case reports listed above.

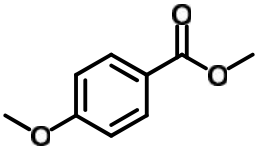
Four stereoisomeric forms are known. Natural menthol occurs as L-form (CAS 2216-51-5), trade products are DL-menthol (CAS 1490-04-6). D-form: CAS 89-78-1, racemic: CAS 15356-70-4. Sensitive to light, air and heat (53).

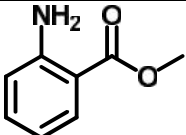
L-menthol and menthol (isomer not specified) are “top 100” substances (IFRA, pers. comm.2010). RIFM reviews are available regarding “menthol” (158), D-menthol (159), L-menthol (160), DL-menthol (161) and menthol, racemic (162). A CIR expert panel review is available (163).

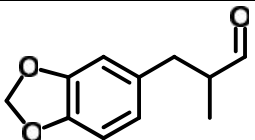
METHOXYCITRONELLAL	
CAS # 3613-30-7	
EC # 222-784-5	
7-Methoxy-3,7-dimethyl-octanal	
7-Methoxy-3,7-dimethyloctanal; 7-Methoxy-6,7-dihydrocitronellal; 7-Methoxycitronellal; Methoxycitronellal; Methoxydihydrocitronellal	
Current regulation: /	
Clinical data:	
Nakayama et al. found 1974 (after (29)) 12 “strong positive” and 10 “weak positive” reactions to methoxycitronellal (unknown test concentration), with cross-reactions to hydroxycitronellal (proportion not given), in 183 patients.	
Additional information: /	

METHOXYTRIMETHYLHEPTANOL	
CAS # 41890-92-0	
EC # 255-574-7	
7-Methoxy-3,7-dimethyl-2-octanol	
3,7-Dimethyl-7-methoxy-2-octanol; Dihydromethoxyelgenol; Elesant; Oxyrol	
Current regulation: /	
Clinical data:	
In the Larsen 2002 c study, 0.9% of the patients with known contact allergy to fragrance ingredients had a positive PT reaction to this ingredient not reported as allergen previously (1).	
Additional information:	

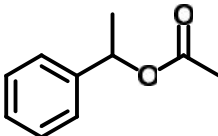
A RIFM review is available (128) citing 1 negative maximisation test (n=27).

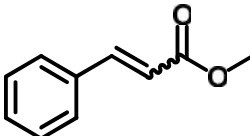
METHYL <i>p</i>-ANISATE	
CAS # 121-98-2	
EC # 204-513-2	
Methyl-4-methoxybenzoate	
p-Anisic acid, methyl ester; 4-(Methoxycarbonyl)anisole; 4-Methoxybenzoic acid methyl ester; Methyl p-anisate; Methyl p-methoxybenzoate; NSC 7324; p-Methoxybenzoic acid methyl ester	
Current regulation: /	
Clinical data:	
In the Malten 1984 study, n=1 (0.5%) of 182 patients displayed a positive PT reaction to methyl anisate 4% pet. (24).	
Additional information: /	

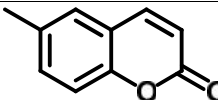
METHYL ANTHRANILATE	
CAS # 134-20-3	
EC # 205-132-4	
Methyl 2-aminobenzoate	
Anthranilic acid, methyl ester; 2-(Methoxycarbonyl)aniline; 2-Aminobenzoic acid methyl ester; 2-Carbomethoxyaniline; Bird Shield; Grain 96-1; Methyl 2-aminobenzoate; Methyl 6-aminobenzoate; Methyl anthranilate; Methyl o-aminobenzoate; NSC 3109; ReJex-iT; ReJex-iT AP 50; ReJex-iT TP 40; Sunarome UVA; [2-(Methoxycarbonyl)phenyl]amine; o-(Methoxycarbonyl)aniline; o-Aminobenzoic acid methyl ester; o-Carbomethoxyaniline	
Current regulation: /	
Clinical data:	
In 91 Israeli patients with a positive or doubtful reaction to FM I or MP methyl anthranilate was tested (conc. not given), with a negative result (164).	
Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).	

METHYLENEDIOXYPHENYL METHYLPROPANAL	
CAS # 1205-17-0	
EC # 214-881-6	
3-(1,3-Benzodioxol-5-yl)-2-methylpropanal	
Hydrocinnamaldehyde, α-methyl-3,4-(methylenedioxy)-; 2-Methyl-3-(3,4-methylenedioxyphenyl)propanal; 2-Methyl-3-(3,4-methylenedioxyphenyl)propionaldehyde; 3-(3,4-Methylenedioxyphenyl)-2-methylpropanal; Heliobouquet; Heliofresh; Heliogan; Helional; Helipropanal; NSC 22282; Tropional; α-Methyl-1,3-benzodioxole-5-propanal; α-Methyl-3,4-(methylenedioxy)hydrocinnamaldehyde	
Current regulation: /	
Clinical data: /	

Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).

METHYLBENZYL ACETATE	
CAS # 93-92-5	
EC # 202-288-5	
1-Phenylethyl acetate	
Benzenemethanol, α-methyl-, acetate ; Benzyl alcohol, α-methyl-, acetate ; (±)-Styryllyl acetate; (±)-α-Methylbenzyl acetate; (±)-α-Phenethyl acetate; 1-Acetoxy-1-phenylethane; 1-Phenylethyl acetate; Gardeniol II; Gardenol; Methyl phenyl carbinyl acetate; Methylphenylcarbinol acetate; NSC 2397; Styryllyl acetate; Styrylallyl acetate; dl-1-Phenylethyl acetate; sec-Phenethyl acetate; sec-Phenylethyl acetate; α-Methylbenzenemethanol acetate; α-Methylbenzyl acetate; α-Methylbenzyl alcohol, acetate; α-Phenethyl acetate; α-Phenylethyl acetate	
Current regulation: /	
Clinical data: /	
Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).	

METHYL CINNAMATE	
CAS # 103-26-4	
EC # 203-093-8	
Methyl 3-phenylprop-2-enoate	
3-Phenyl-2-propenoic acid methyl ester; Cinnamic acid, methyl ester; 3-Phenyl-2-propenoic acid methyl ester; 3-Phenylacrylic acid methyl ester; Methyl 3-phenyl-2-propenoate; Methyl 3-phenylacrylate; Methyl 3-phenylpropenoate; Methyl cinnamate; Methyl cinnamylate; NSC 9411; SemaSORB 9815	
Current regulation: /	
Clinical data:	
Patch tests with some components of Peru balsam were carried out at 8 worldwide centers in 142 patients who had previously reacted to 25% MP. Reactions to methyl cinnamate (dose and vehicle not reported) were observed in 6 of 142 patients (no further details reported) (165).	
Additional information:	
A RIFM review is available (166), reviewing, e.g., a number of animal studies with conflicting results. See also under Myroxylon pereirae.	

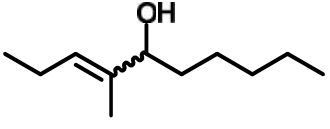
6-METHYL COUMARIN	
CAS # 92-48-8	
EC # 202-158-8	
6-Methylchromen-2-one	
Coumarin, 6-methyl-; 6-MC; 6-Methyl-2H-1-benzopyran-2-one; 6-Methyl-2H-chromen-2-one; 6-Methylbenzopyrone; 6-Methylcoumarin; 6-Methylcoumarinic anhydride; NSC 5870; Toncarine	

Current regulation: Annex III, part 1, n° 46

Clinical data:

Two of 24 white volunteers developed a photoallergic reaction after single epicutaneous exposure with 5% methyl coumarin in ethanol and UV-A radiation (16 J/cm²). After a photomaximisation test, 6 of 10 subjects developed photocontact allergic reactions (167). Cardoso et al. report on 2 photoallergic patch test reactions to this substance, which were apparently clinically relevant, in 83 Portuguese patients tested (168). Similar results (2 of 76 patients with positive photopatchtest) were reported from New York (169).

Additional information: /

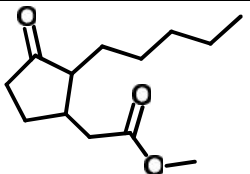
METHYL DECENOL	
CAS # 81782-77-6	
EC # 279-815-0	
4-Methyl-3-decen-5-ol	

Current regulation: /

Clinical data: /

Additional information:

A RIFM review is available (170), reporting 1 negative HRIPT (n=50). It is a “top 100” substance (IFRA, pers. comm.2010).

METHYL DIHYDROJASMONATE	
CAS # 24851-98-7	
EC # 246-495-9	
Methyl 2-(3-oxo-2-pentylcyclopentyl)acetate	

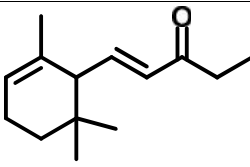
Current regulation: /

Clinical data:

In the Frosch 2002 b study, 3 of 1606 consecutive patients (0.2%) showed positive reactions to hedione (5% pet.) (17). In the Frosch 1995 dose-finding pilot study, no positive reaction to 1% and 5% hedione in pet., tested in 100 consecutive patients in Belfast, were observed (15).

Additional information:

It is a “top 100” substance (IFRA, pers. comm.2010). An older RIFM review exists (128) citing 1 negative human maximisation test (n=25).

METHYL IONONE (mixture of isomers)	
CAS # 1335-46-2	
EC # 215-635-0	
1-(2,6,6-trimethyl-1-cyclohex-2-enyl)pent-1-en-3-one	

6-Methylionone

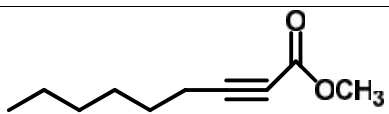
Current regulation: /

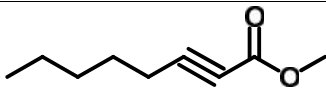
Clinical data:

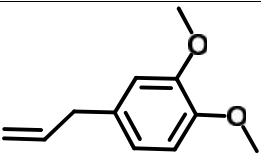
See METHYLIONANTHEME for one clinical case report. Regarding methyl ionone gamma, the Frosch 1995 dose-finding pilot study found no positive reaction to 1% and 5% of this substance in pet., tested in 100 consecutive patients in Belfast (15).

Additional information:

It is a “top 100” substance (IFRA, pers. comm.2010). A RIFM review is available (171).

METHYL OCTINE CARBONATE	
CAS # 111-80-8	
EC #	
Methyl 2-octynoate	
Methyl 2-Nonynoate, MOC	
Current regulation: Annex III, part 1, n°173	
Clinical data:	
English and Rycroft reported a case of a 19-year-old laboratory technician working in the fragrance industry, who developed hand dermatitis after contact with methyl heptine and methyl octane carbonates; patch testing was strongly positive to both compounds at 1% in MEK (172).	
Additional information: /	

METHYL 2-OCTYNOATE	
CAS # 111-12-6	
EC # 203-836-6	
Methyl oct-2-ynoate	
M2O; Methyl heptin carbonate; Folione; Methyl hept-1-yne-1-carboxylate; Methyl pentylacetylenecarboxylate; NSC 72098; Vert de violette artificiel	
Current regulation: Annex III, part 1, n° 89	
Clinical data:	
In the “background information” section of the 1999 opinion, methyl 2-octynoate is classified as “less frequently reported allergen”; with only single cases of reported contact allergy, but the observation of this compound being a strong sensitizer according to IFRA (33), as also reported by Hostynek and Maibach (173) Since the last SCCNFP-opinion of 1999, the IVDK 2007 study yielded 0.3% (95% CI: 0.1 – 0.49%) positive reactions in 2401 consecutively PTed patients (1% pet.) (4). The IVDK 2010 study, n=1 weak positive reaction was observed in 988 patients tested with the compound (7). In the Groningen 2009 study, n=1, i.e. 0.3% (95% CI: 0.01 – 1.7%) had positive reactions to this allergen, tested at only 2% pet. (6). In a previous case report of a fragrance laboratory assistant with work-related ACD both methyl heptin and methyl octin carbonate had been found sensitisers – probably due to their very similar chemical structure (172). In a recent bi-centric study with 350 eczema patients who were consecutively tested with 1% and 2% M2O in pet.; 0.8% positive reactions were observed. However, in 3 additional cases active sensitisation, with first reactions appearing 2 to 4 weeks after the patch test, and prompt reactions in the 2 cases repeat-patch tested, was observed (174). Additional information: /	

METHYL EUGENOL	
CAS # 93-15-2	
EC # 202-223-0	
1,2-Dimethoxy-4-(prop-2-enyl)benzene	

4-Allylveratrole; Eugenyl methyl ether extra; 1,2-Dimethoxy-4-allylbenzene; 1,3,4-Eugenol methyl ether; 1-(3,4-Dimethoxyphenyl)-2-propene; 1-Allyl-3,4-dimethoxybenzene; 3,4-Dimethoxy-1-(2-propenyl)benzene; 3,4-Dimethoxyallylbenzene; 3-(3,4-Dimethoxyphenyl)propene; 4-Allyl-1,2-dimethoxybenzene; Benzene, 4-allyl-1,2-dimethoxy-; Chavibetol methyl ether; Ent 21040; Eugenol methyl ether; Eugenyl methyl ether; Methyl eugenol ether; Methyl eugenyl ether; Methylchavibetol; NSC 209528; NSC 8900; O-Methyleugenol; Veratrole methyl ether; Veratrole, 4-allyl-

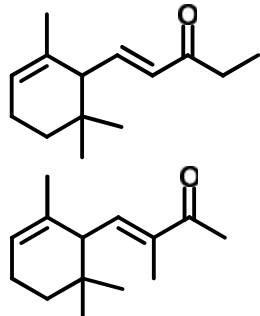
Current regulation: Annex II, 451

Clinical data:

In a previous study by Larsen et al (2002 c), 1.8% of patients with contact allergy to fragrance ingredients reacted positively to this compound (1).

Additional information:

Quote from the SCCS-opinion [0373/00](#): “Methyleugenol should not be intentionally added as a cosmetic ingredient. However, when fragrance compounds containing methyleugenol naturally present in essential oils are used as components in cosmetic products, the highest concentration of methyleugenol in the finished products must not exceed 0.01 % in fine fragrance, 0.004 % in eau de toilette, 0.002 % in a fragrance cream, 0.0002 % in other leave-on products and in oral hygiene products, and 0.001% in rinse-off products.” (The reason is genotoxicity and carcinogenicity).

METHYLIONANTHEME	
CAS # 55599-63-8	
EC #	
(1E)-2-Methyl-1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-1-penten-3-one mixt. with (3E)-3-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one	
8-Methyl- α -ionone-10-methyl- α -ionone mixt.; Iralia Mixture	

Current regulation: ...

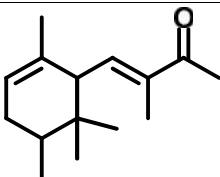
Clinical data:

One case of ACD has been reported, caused by an E.d.C. (175).

Additional information:

Patented by GIVAUDAN SA 1933, is composed of isomeric n-methylionones and isomethylionones. Methylionone has CAS # 1335-94-0 (not in CosIng) and 1335-46-2 (METHYL α -IONONE ISOMERS); other names: Methyl- α -cyclocitrilydenacetone; Iralia; Isoaldeine

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=41456>, last accessed 2010-07-14).

5-METHYL-α-IONONE	
CAS # 79-69-6	
EC # 201-219-6	
4-(2,5,6,6-Tetramethyl-2-cyclohexen-1-yl)-3-buten-2-one	
Methyl- α -Ionone; 6-Methyl- α -ionone; α -Irone	

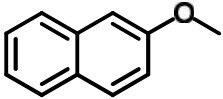
Current regulation: /

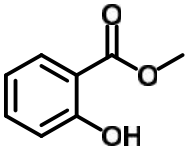
Clinical data:

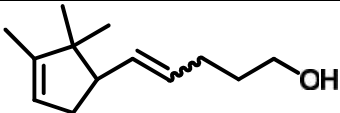
In the Frosch 2002 b study, 5 of 1606 consecutive patients (0.3%) showed positive reactions to alpha-irone (10% pet.) (17).

Additional information:

A RIFM review is available (176), citing a (negative) human maximisation test and the study results quoted.

METHYL beta-NAPHTHYL ETHER	
CAS # 93-04-9	
EC # 202-213-6	
2-Methoxynaphthalene	
beta-Naphthyl methyl ether; methyl 2-naphthyl ether; Nerolin (old); NSC 4171; Yara yara; β-Methoxynaphthalene; β-Naphthol methyl ether; β-Naphthyl methyl ether; 2-Methoxynaphthalene; Methyl β-naphthyl ether; 2-Naphthol methyl ether; 2-Naphthyl methyl ether; 6-Methoxy-2-naphthalene	
Current regulation: /	
Clinical data: /	
Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).	

METHYL SALICYLATE	
CAS # 119-36-8	
EC # 204-317-7	
Methyl 2-hydroxybenzoate	
Other names: Salicylic acid, methyl ester; 2-(Methoxycarbonyl)phenol; 2-Carbomethoxyphenol; 2-Hydroxybenzoic acid methyl ester; Analgit; Anthrapole ND; Ben Gay; Exagien; Flucarmit; Methyl ester of 2-hydroxy benzoic acid; Methyl o-hydroxybenzoate; Methyl salicylate; NSC 8204; Wintergreen oil; o-Hydroxybenzoic acid methyl ester; “Oil of wintergreen”	
Current regulation: /	
Clinical data:	
The deGroot 2000 study yielded 7 positive reactions to methyl salicylate (2% pet.) in 1825 consecutive patients (12).	
A case of ACD following the application of a compress bandage containing methyl salicylate has been reported, using 2% “o.o.” as PT concentration; the dose per area of methyl salicylate in the occlusive bandage was not reported (177). A similar case was reported in 1977, positive to 2% methyl salicylate in olive oil, with elicitation of pruritus and erythema after oral ingestion of acetyl salicylic acid (178).	
Additional information:	
A RIFM review is available (179) providing an overview on 3 human sensitisation experiments (e.g., the HRIPT) which were all negative, and clinical data. In a number of older PT studies, positive test results were seen in 6 of 4600, 3 of 183, 3 of 241, 17 of 585, 1 of 70, all employing a test concentration of 2%, usually in pet., according to above review. Methyl salicylate may occur in topical analgesic (OTC) medications, in Germany, for instance, in “Camphopin® Salbe“ („Rote Liste 2010“).	

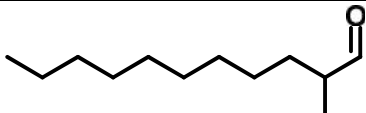
3-METHYL-5-(2,2,3-TRIMETHYL-3-CYCLOPENTENYL)PENT-4-EN-2-OL	
CAS # 67801-20-1	
EC # 267-140-4	
3-Methyl-5-(2,2,3-trimethyl-1-cyclopent-3-enyl)pent-4-en-2-ol	
3-Methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol; 3-Methyl-5-(2,2,3-trimethylcyclopent-3-enyl)pent-4-en-2-ol; Ebanol	

Current regulation: /

Clinical data:

In the Larsen 2001 study, 1 of 178 patients with known contact allergy to fragrance ingredients exhibited a positive PT reaction to "MTCP", tested 5% pet. (19). In the An 2005 study, 12 of 422 consecutive patients, i.e., 2.8%, had positive reactions to "ebanol", tested at 5% (13).

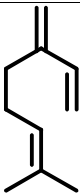
Additional information: /

METHYLUNDECANAL	
CAS # 110-41-8	
EC # 203-765-0	
2-Methylundecanal	
Aldehyde c-12 mna; undecenal, 2-methyl-; 2-Methyl-1-undecanal; Aldehyde M.N.A.; Methyl n-nonyl acetaldehyde; Methylnonylacetaldehyde; NSC 46127	

Current regulation: /

Clinical data: /

Additional information: It is a "top 100" substance (IFRA, pers. comm.2010).

MYRCENE	
CAS # 123-35-3	
EC # 204-622-5	
7-Methyl-3-methylideneocta-1,6-diene	
2-Methyl-6-methylene-2,7-octadiene; 7-Methyl-3-methylene-1,6-octadiene; NSC 406264; β -Geraniolene; β -Myrcene	

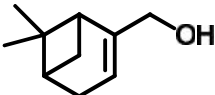
Current regulation: /

Clinical data:

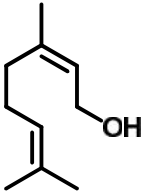
In a clinical study in 6 European centres, including 1511 consecutive patients, 1 patient had a positive reaction to oxidized myrcene (65).

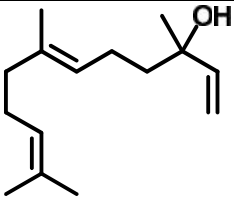
Additional information:

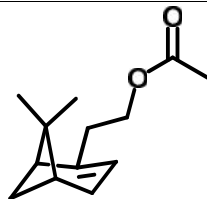
Myrcene autoxidizes spontaneously and rapidly at air exposure. In experimental studies on beta-myrcene an EC3 value of 4.3% was seen for a sample air-exposed 10 weeks (Sköld M. Contact allergy to autoxidized fragrance terpenes (180).

MYRTENOL	
CAS # 515-00-4	
EC # 208-193-5	

(7,7-dimethyl-4-bicyclo[3.1.1]hept-3-enyl)methanol
(-)-Pin-2-ene-10-ol; 2-Pinen-10-ol; (6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)methanol; (±)-Myrtenol; 6,6-Dimethyl-2-(hydroxymethyl)bicyclo[3.1.1]hept-2-ene; NSC 408846; α-Pinene-10-ol
Current regulation: /
Clinical data: /
Additional information: A RIFM review exists (181), citing 2 of 3 HRIPT studies with 1 case of sensitisation to myrtenol each.

NEROL	
CAS # 106-25-2	
EC # 203-378-7	
(2Z)-3,7-dimethylocta-2,6-dien-1-ol	
2,6-Octadien-1-ol, 3,7-dimethyl-, (Z)-; (Z)-3,7-Dimethyl-2,6-octadien-1-ol; (Z)-Geraniol; (Z)-Nerol; 2-cis-3,7-Dimethyl-2,6-octadien-1-ol; 3,7-Dimethyl-cis-2,6-octadien-1-ol; Nerol 900; Neryl alcohol; cis-3,7-Dimethyl-2,6-octadien-1-ol; cis-Geraniol; β-Nerol; cis-geraniol – i.e., isomeric to geraniol	
Current regulation: /	
Clinical data: In the Larsen 2002 c study, 6.0% of the fragrance sensitive patients reacted positively to 5% in pet. (1).	
Additional information: A RIFM review is available (182) citing (negative) human sensitisation experiments, an older study from Japan and the Larsen 2002 c study (see above). Regarding autoxidation studies – see geraniol.	

Nerolidol (isomer not specified)	
CAS # 7212-44-4	
EC # 230-597-5	
3,7,11-Trimethyl-1,6,10-odecatrien-3-ol	
Nerolidol; (±)-Nerolidol; FCI 119b; Nerodilol	
Current regulation: /	
Clinical data: /	
Additional information: RIFM review is available (183) citing the occurrence of “3 positive reactions in 2273 patients”. Another RIFM review is available on cis-nerolidol (184), mentioning that no data on this compound are available.	

NOPYL ACETATE	
CAS # 128-51-8	
EC # 204-891-9	
2-(7,7-dimethyl-4-bicyclo[3.1.1]hept-3-enyl)ethyl acetate	
2-Norpinene-2-ethanol, 6,6-dimethyl-, acetate; Bicyclo[3.1.1]hept-2-ene-2-ethanol, 6,6-dimethyl-, acetate; 2-	

(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethyl acetate; 7,7-Dimethylbicyclo[3.1.1]hept-2-ene-2-ethanol acetate; Citroviol; NSC 1286; NSC 404963; Nopol acetate; Nopyl acetate

Current regulation: /

Clinical data:

The DeGroot 1985 study identified 2 (1.1%) positive reactions among 179 patients using a 25% PT preparation of this compound – reactions may have at least partly been due to an “excited back syndrome” and thus a limited evidence (25).

Additional information: /

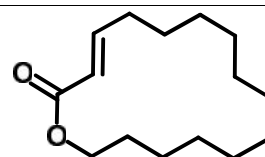
OXACYCLOHEXADECENONE

CAS # 34902-57-3

EC # 609-040-9

(3E)-oxacyclohexadec-3-en-2-one

Globalide; Oxacyclohexadecen-2-one



Current regulation: /

Clinical data: /

Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).

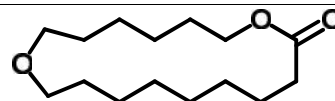
OXALIDE

CAS # 1725-01-5

EC # 217-033-3

1,8-Dioxacycloheptadecan-9-one

Nonanoic acid, 9-[(6-hydroxyhexyl)oxy]-, o-lactone; 10-Oxa-16-hexadecanolide; Oxalide; Oxalide T



Current regulation: /

Clinical data:

In the Larsen 2001 study, none of 178 patients with known contact allergy to fragrance ingredients exhibited a positive PT reaction to "10-oxahexadecanolide", tested 5% pet. (19).

Additional information:

A RIFM review is available (128), citing a negative maximisation test (n=29).

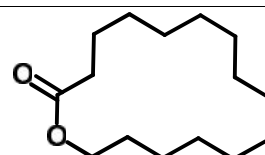
PENTADECALACTONE

CAS # 106-02-5

EC # 203-354-6

1-Oxacyclohexadecan-2-one

Pentadecanoic acid, 15-hydroxy-, ξ-lactone; 1,15-Pentadecanolide; 15-Hydroxypentadecanoic acid lactone; 15-Pentadecanolide; 15-Pentadodecanolactone; 2-Pentadecalone; CPE 215; Cyclopentadecanolide; Exaltolide; Macrolide Supra; Muskalactone; NSC 36763; Pentadecalactone; Pentadecanolactone; Pentadecanolide; Pentalide; Thibetolide; cpd Supra; ω-Pentadecalactone; angelica lactone; hexaltolide



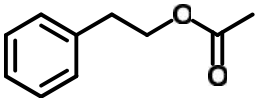
Current regulation: /

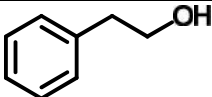
Clinical data: /

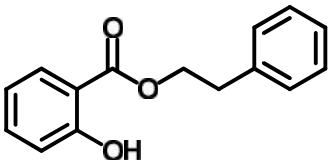
Additional information:

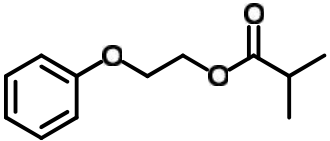
It is a “top 100” substance (IFRA, pers. comm.2010). The substance has been used for

clinical olfactory testing in the 60ies under the name of exaltolide.

PHENETHYL ACETATE	
CAS # 103-45-7	
EC # 203-113-5	
2-Phenylethyl acetate	
Acetic acid, phenethyl ester ; Phenethyl alcohol, acetate; 2-Phenethyl acetate; 2-Phenylethyl acetate; Benzylcarbinyl acetate; NSC 71927; Phenethyl acetate; Phenylethyl ethanoate; β -Phenethyl acetate; β -Phenylethanol acetate; β -Phenylethyl acetate	
Current regulation: /	
Clinical data: /	
Additional information:	
It is a “top 100” substance (IFRA, pers. comm.2010). Exposure via plants (<i>Tanacetum parthenium</i>) is possible (185).	

PHENETHYL ALCOHOL	
CAS # 60-12-8	
EC # 200-456-2	
2-Phenylethanol	
Phenethyl alcohol; (2-Hydroxyethyl)benzene; 2-Phenethanol; 2-Phenethyl alcohol; 2-Phenyl-1-ethanol; 2-Phenylethyl alcohol; Benzyl carbinol; Ethanol, 2-phenyl-; NSC 406252; PEA; Phenethanol; Phenethylol; Phenylethanol; Phenylethyl alcohol; β -(Hydroxyethyl)benzene; β -PEA; β -Phenethanol; β -Phenethyl alcohol; β -Phenethylol; β -Phenylethanol; β -Phenylethyl alcohol	
Current regulation: /	
Clinical data:	
The DeGroot 1985 study identified 1 (0.6%) positive reactions among 179 patients using a 25% PT preparation of phenylethyl alcohol (25). In the Frosch 1995 dose-finding pilot study, no positive reaction to this compound, tested 1% pet. in 100 consecutive patients in Odense, DK, was observed (15).	
Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).	

PHENETHYL SALICYLATE	
CAS # 87-22-9	
EC # 201-732-5	
2-Phenylethyl 2-hydroxybenzoate	
Salicylic acid, phenethyl ester; 2-Phenylethyl salicylate; Benzylcarbinyl salicylate; NSC 72035; Phenethyl salicylate	
Current regulation: /	
Clinical data: /	
Additional information:	
A RIFM review exists (186), quoting a negative human maximisation test and a number of animal experiments, including cross-sensitisation experiments with benzyl salicylate. One LLNA study is reported yielding an EC3 value of 2.1%.	

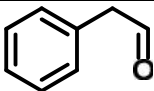
<i>PHENOXYETHYL ISOBUTYRATE</i>	
CAS # 103-60-6	
EC # 203-127-1	
2-Phenoxyethyl 2-methylpropanoate	
Isobutyric acid, 2-phenoxyethyl ester; Ethanol, 2-phenoxy-, isobutyrate; 2-Phenoxyethyl isobutyrate; NSC 227210; NSC 406209; Phenoxyethyl isobutyrate; β-Phenoxyethyl isobutyrate	

Current regulation: /

Clinical data: /

Additional information:

It is a “top 100” substance (IFRA, pers. comm.2010).

<i>PHENYLACETALDEHYDE</i>	
CAS # 122-78-1	
EC # 204-574-5	
2-Phenylacetaldehyde	
Benzylcarboxaldehyde; Hyacinthin; NSC 406309; Phenacetaldehyde; Phenylacetaldehyde; Phenylacetic aldehyde; Phenylethanal; α-Phenylacetaldehyde; α-Tolualdehyde; α-Toluic aldehyde	

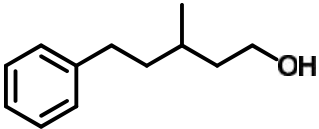
Current regulation: /

Clinical data:

In the Malten 1984 study, 1.1% of 182 patients displayed a positive PT reaction to phenylacetaldehyde 2% pet. (24). In a case report, Sanchez-Politta et al. describe a 26-year-old worker in a perfume factory, who suffered from a spill of pure phenylacetaldehyde and became sensitised, as proven by positive patch tests with 0.5%, 1% and 2% (10 healthy controls negative) (187).

Additional information:

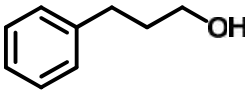
SCCS opinion: [1153/08 - Opinion on "Dermal Sensitization Quantitative Risk Assessment" \(QRA: Citral, farnesol and phenylacetaldehyde\)](#)

<i>PHENYLISOHEXANOL</i>	
CAS # 55066-48-3	
EC # 259-461-3	
3-Methyl-5-phenylpentan-1-ol	
3-Methyl-5-phenyl-1-pentanol; 3-Methyl-5-phenylpentanol; 5-Phenyl-3-methylpentanol; Mefrosol; Phenoxanol	

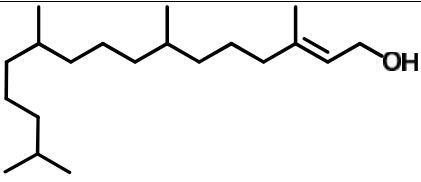
Current regulation: /

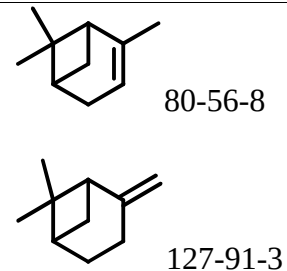
Clinical data: /

Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).

<i>PHENYLPROPANOL</i>	
CAS # 122-97-4	
EC # 204-587-6	

3-Phenylpropan-1-ol	
(3-Hydroxypropyl)benzene; 1-Hydroxy-3-phenylpropane; 3-Benzenepropanol; 3-Hydroxy-1-phenylpropane; 3-Phenyl-1-propanol; 3-Phenyl-n-propanol; 3-Phenylpropanol; 3-Phenylpropyl alcohol; Dihydrocinnamyl alcohol; Hydrocinnamic alcohol; Hydrocinnamyl alcohol; NSC 16942; γ -Phenylpropanol; γ -Phenylpropyl alcohol; Phenethyl Carbinol	
Current regulation: /	
Clinical data:	
The Larsen 2002 c study yielded 0.9% positive reactions in 218 patients with contact allergy to fragrance ingredients (1).	
Additional information: ...	

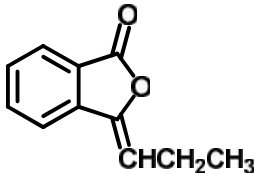
PHYTOL	
CAS # 150-86-7	
EC # 205-776-6	
(E,7R,11R)-3,7,11,15-tetramethylhexadec-2-en-1-ol	
Phytol; (7R,11R,2E)-Phytol; (E)-Phytol; (E,R,R)-Phytol; 3,7,11,15-Tetramethylhexadec-2-en-1-ol; trans-Phytol	
Current regulation: /	
Clinical data:	
/	
Additional information:	
Phytol is a main constituent of Jasmin abs. with 7.4% reported content (17). In a human maximization study involving 25 subjects, there was one case of contact sensitization to 10% phytol (6900 μ g/cm ²), applied in petrolatum, as reported in a RIFM review (188).	

<i>alpha-PINENE and beta-PINENE</i>	
CAS # 80-56-8 (alpha-Pinene); CAS # 127-91-3 (beta-Pinene)	
EC # 201-291-9 (alpha-Pinene; according to CAS service: 219-445-9); EC # 204-872-5 (beta-Pinene; according to CAS service: 245-424-9)	
2,6,6-Trimethylbicyclo[3.1.1]hept-2-ene (80-56-8) 6,6-dimethyl- 2-methylenebicyclo[3.1.1]heptane (127-91-3)	
80-56-8: 2-Pinene; ($\pm$)-2-Pinene; ($\pm$)- α -Pinene; Acintene A; NSC 7727; PC 500; PC 500 (terpene); Sylvapine A; α -Pinene 127-91-3: 2(10)-Pinene ; ($\pm$)-2(10)-Pinene; ($\pm$)-6,6-Dimethyl-2-methylenebicyclo[3.1.1]heptane; ($\pm$)- β -Pinene; 6,6-Dimethyl-2-methylenebicyclo[3.1.1]heptane; NSC 21447; NSC 406265; NSC 59190; Nopinene; Nopinene; PC 600; PC 600 (pesticide); Pseudopinene; Pseudopinene; Terebenthene; β -Pinene	
Current regulation: Annex III, part 1, n° 130 (Peroxide value less than 10 mmoles/L in substance)	
Clinical data:	
In 63 patients positive to the FM I, 2 had a positive PT reaction to beta-pinene (and none to alpha-pinene 5% pet.), 1% pet., in the Santucci 1987 study (28). A clinical series from Portugal, addressing contact allergy to oil of turpentine diagnosed in 30 patients, used a	

series with pure terpenes. A total of 17 of 30 patients reacted positively to alpha-pinene, and 2 to beta-pinene (189). In a series of 24 patients with occupational contact dermatitis from the pottery industry, Lear at al. found 14 to be sensitised to “Indonesian oil of turpentine” and 8 to alpha-pinene (190).

A case report from Zacher and Ippen on 2 patients with allergic contact dermatitis due to bergamot oil (191) describes positive patch test reactions to alpha-pinene and beta-pinene in one, a worker in a perfume factory.

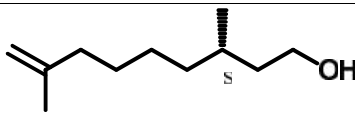
Additional information: /

PROPYLIDENE PHTHALIDE	
CAS # 17369-59-4	
EC # 241-402-8	
3-Propylidene-2-benzofuran-1-one	
3-Propylidene-1(3H)-isobenzofuranone; 3-Propylidenephthalide; Celeriax; Propylidenephthalide	
Current regulation: Annex III, part 1, n° 175	

Clinical data:

In the Malten 1984 study, 2.6% of 182 patients displayed a positive PT reaction to ethyl acrylate 1% pet. (24). In this paper, “3/25” positive results in human maximisation tests are listed.

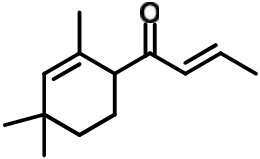
Additional information: /

<i>RHODINOL</i>	
CAS # 6812-78-8	
EC # 229-887-4	
(3S)-3,7-Dimethyloct-7-en-1-ol	
Rhodinol; (-)-Rhodinol; α-citronellol; (-)-α-Citronellol; (S)-α-Citronellol	

Clinical data: / (see below)

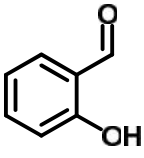
Additional information:

A RIFM review exists citing a positive HRIPT with several cases of sensitisation, 5 of these proven upon re-challenge, and a negative human maximisation test (192). In a previous RIFM review (128), a Japanese clinical study (source not accessible) is cited: “In patch tests using cosmetics ingredients and fragrance materials on patients with eczema and dermatitis, 5% rhodinol (vehicle not specified) produced one sensitization reaction in 202 patients (Itoh et al., 1988⁴)”

trans-ROSE KETONE-5	
CAS # 39872-57-6	
EC # 254-663-8	
(2E)-1-(2,4,4-Trimethylcyclohex-2-en-1-yl)but-2-en-1-one	
alpha-Isodamascone; trans-2,4,4-Trimethyl-1-crotonyl-2-cyclohexene; (E)-1-(2,4,4-Trimethyl-2-cyclohexen-1-yl)-2-	

⁴ Itoh M., Hosono K., Kantoh H., Kinoshita M., Yamada K., Kurosaka R. and Nishimura M. (1988) Patch test results with cosmetic ingredients conducted between 1978-1986. *Nippon Koshohen Kagakkaishi* 12 (1), 27-41.

buten-1-one	
Current regulation: Annex III, part 1, n° 159 (max. conc. 0.02%)	
Clinical data: /	
Additional information:	
A RIFM review is available (193) quoting 2 HRIPT studies: one with 0.2% concentration in DEP in 103 volunteers, and negative result, one with 2% concentration, sensitising 2 of 22 volunteers.	

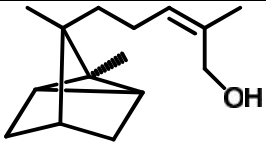
SALICYLALDEHYDE	
CAS # 90-02-8	
EC # 201-961-0	
2-Hydroxybenzaldehyde	
Salicylaldehyde; 2-Formylphenol; NSC 112278; NSC 49178; NSC 83559; NSC 83560; NSC 83561; NSC 83562; NSC 97202; Salicylal; Salicylic aldehyde; o-Formylphenol; o-Hydroxybenzaldehyde	

Current regulation: /

Clinical data:

In a series of 40 of 744 consecutive patients PTed with an extended fragrance series (Sheffield 1999), 1 positive reaction to salicylaldehyde was observed (3). In the Wöhrle 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded n=1 (0.1%) positive reaction to salicylaldehyde 2% pet. (22). The IVDK 2010 study, 0.48% (95% CI: 0.18 – 0.79%; percentages standardised for age and sex) of 2729 patients PTed reacted to the compound (7). An earlier study by Bruze and Zimerson points to possible cross-reactivity between salicylaldehyde and “simple methylol phenols” occurring in synthetic resins based on phenol and formaldehyde (194). Among 24 patients sensitised to resorcinol by application of a wart remover, 2 positive reactions to salicylaldehyde were observed (195).

Additional information: Along with other derivatives of salicylic acid, salicylaldehyde is found in the bark of several trees, such as willow or aspen, and can cause allergic contact dermatitis by this exposure (196).

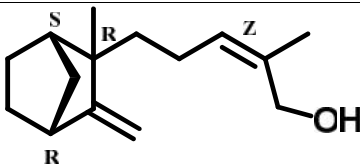
alpha-SANTALOL	
CAS # 115-71-9	
EC # 204-102-8	
(R Z)- 5-(2,3-dimethyltricyclo[2.2.1.0^{2,6}]hept-3-yl)-2-methylPent-2-en-1-ol	
2-Penten-1-ol, 5-(2,3-dimethyltricyclo[2.2.1.0 ^{2,6}]hept-3-yl)-2-methyl-, [R(Z)]-; 2-Penten-1-ol, 5-(2,3-dimethyltricyclo[2.2.1.0 ^{2,6}]hept-3-yl)-2-methyl-, stereoisomer; α-Santalol; Tricyclo[2.2.1.0 ^{2,6}]heptane, 2-penten-1-ol deriv.; (+)-(Z)-α-Santalol; (+)-α-Santalol; (Z)-α-Santalol; Sandal; Santalol a; cis-α-Santalol; d-α-Santalol	

Current regulation: /

Clinical data: / (see beta-santalol)

Additional information:

Following a precautionary principle, both isoforms – often not differentiated in reports – are considered as one and considered as established contact allergen in humans.

<i>beta</i>-SANTALOL	
CAS # 77-42-9	
EC # 201-027-2	
(2Z)-2-methyl-5-[(1S,2R,4R)-2-methyl-3-methylenebicyclo[2.2.1]hept-2-yl]Pent-2-en-1-ol	
2-methyl-5-(2-methyl-3-methylene-2-norbornyl)-2-Penten-1-ol; [1S-[1α,2α(Z),4α]]-2-methyl-5-(2-methyl-3-methylenebicyclo[2.2.1]hept-2-yl)-2-Penten-1-ol; β-Santalol; (-)-(Z)-β-Santalol; (-)-β-Santalol; Santalol b; cis-β-Santalol	

Current regulation: /

Clinical data:

A RIFM review is available for alpha-santalol (197) and on “santalol” (CAS # 11031-45-1 (198). The former review cites a Japanese study: “Between April 1979 and August 1990, a total of 3123 male and female patients were patch tested to 2% santalol (.alpha. or .beta. not specified) in petrolatum. Reactions were observed in 47/3123 (1.5%) of the patients. The incidence of positive reactions from 1979 to 1990 was 1.5%. The rate of reactions observed was higher during the earlier period of the patch testing than the later stage (Utsumi et al., 1992)⁵.” In another Japanese study cited by the RIFM review “... patch tests were conducted with 0.05–0.5% santalol (specified as santalol 1) in a base cream or in 99% ethanol. Patches consisted of a piece of 1 cm² lint with a 2 cm² cellophane disc placed on the lint and then covered with a 4 cm² plaster. Patches were applied to the back, the forearm, and the inside of the upper arm for 24–48 h. Reactions were observed in 15 patients and questionable reactions were observed in 10 patients out of the total 427 participating. A second sample of santalol (specified as santalol 2) was tested on 214 patients. Reactions were observed in three patients and questionable reactions were observed in six patients (Takenaka et al., 1986)⁶.” Moreover, “The Mid-Japan Contact Dermatitis Research group (MJCDRG) conducted a 6-year (1976–1981) patch test study on facial dermatoses patients with various fragrance materials. During the year 1979, a total of 327 patients were tested with a mixture of .alpha. and .beta. santalol at concentrations of 10%, 2%, and 1% in white petrolatum. Reactions were observed in 1.5%, 0.6% and 0.6% of the 327 patients tested at concentrations 10%, 2%, and 1%, respectively (MJCDRG, 1984)⁷.”

The Goossens 1997 study found 5 of 111 patients positive to “santalol 10% pet.” (isoform not specified) – all sensitised to other fragrance allergens as well (23). In the Larsen 2001 study, patch testing with “2-methyl-5-(2,3-dimethyltricyclo[2.2.1.0(2,6)]hept-3-yl-2-pentenol(.alpha.-form) and 2-methyl-5-(2-methyl-3-methylenebicyclo[2.2.1]hept-3-yl-2-penten-1-ol(beta-form) 5% pet.” (no CAS numbers given) yielded a total of 2 positive reactions among the 178 patients with known contact allergy to fragrance ingredients (19).

Additional information: “There is no one CAS number for the mixture. The alpha form

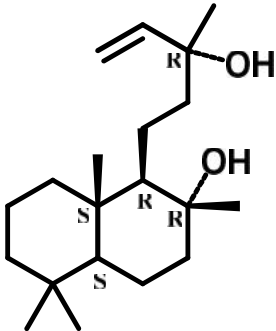
⁵ Utsumi, M., Sugai, T., Shoji, A., Watanabe, K., Asoh, S., Hashimoto, Y., 1992. Incidence of positive reactions to sandalwood oil and its related fragrance materials in patch tests and a case of contact allergy to natural and synthetic sandalwood oil in a museum worker. *Skin Research* 34, 209–213

⁶ Takenaka, T., Hasegawa, E., Takenaka, U., Saito, F., Odaka, T., 1986. Fundamental studies of safe compound perfumes for cosmetics Part 1. The primary irritation of compound materials to the skin. *Unknown Source*, 313–329.

⁷ Mid-Japan Contact Dermatitis Research Group, 1984. Determination of suitable concentrations for patch testing of various fragrance materials. A summary of group study conducted over a 6-year period. *Journal of Dermatology*, 11(1), 31–35.

has a CAS No. 115-71-9 and the beta form is 37172-32-0 (this # is trans-.beta.-santalol). There was no reported use of these materials in the last two IFRA Surveys (8 years total)” (A.M. Api, pers. comm., 2010).

Following a precautionary principle, both isoforms – often not differentiated in reports – are considered as one and considered as established contact allergen in humans

SCLAREOL	
CAS # 515-03-7	
EC # 208-194-0	
(1R,2R,8aS)-1-[(3R)-3-hydroxy-3-methylpent-4-enyl]-2,5,5,8a-tetramethyl-3,4,4a,6,7,8-hexahydro-1H-naphthalen-2-ol	
(αR,1R,2R,4aS,8aS)-α-Ethenyldecahydro-2-hydroxy-α,2,5,5,8a-pentamethyl-1-naphthalenepropanol; [1R-[1α(R*),2β,4aβ,8aα]] - α-ethenyldecahydro-2-hydroxy-α,2,5,5,8a-pentamethyl-1-Naphthalenepropanol; (13R)- Labd-14-ene-8,13-diol; Sclareol; (-)-Sclareol; [1R-[1.alpha.(R*),2.beta.,4a.beta.,8a.alpha.]]-2-hydroxy-.alpha.,2,5,5,8a-pentamethyl-.alpha.-vinyldecahydronaphthalene-1-propan-1-ol	

Current regulation: /

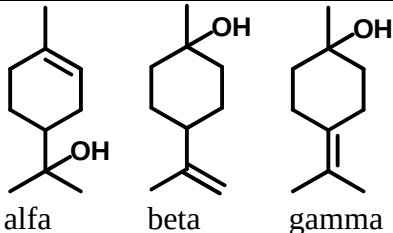
Clinical data: /

Additional information:

An older RIFM review exists (128), reporting several human maximisation tests with different samples of sclareol, yielding partly positive, partly negative results. A more recent RIFM review is available (199), citing no clinical data, but several maximisation studies, one of which was positive in a few volunteers, which was apparently due to an impurity.

[0986/06 - Opinion on Sclareol \(sensitisation only\)](#)

(http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_056.pdf)

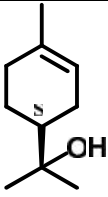
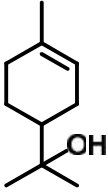
TERPINEOL	
CAS # 8000-41-7	
EC # 232-268-1	
Mixtures of isomers	
Terpineol 318, mixture of terpineol isomers alfa, beta, gamma	

Current regulation: /

Clinical data:

A RIFM review is available (200), citing negative human induction studies and one clinical study “Takenaka 1986”, finding 4 of 312 patients with 0.05% to 0.5% terpineol in a cream base and in ethanol, resp., and 2 negative clinical studies of limited size. In the Frosch 1995 dose-finding pilot study, no positive reaction to 1% and 5% terpineol in pet., tested in 100 consecutive patients in Belfast, were observed (15).

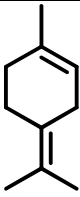
Additional information: It is a “top 100” substance (IFRA, pers. comm. 2010).

<i>alpha-TERPINEOL</i>	 10482-56-1  98-55-5
CAS # 10482-56-1 / 98-55-5	
EC # 233-986-8 / 202-680-6	
2-[(1S)-4-methyl-1-cyclohex-3-enyl]propan-2-ol (10482-56-1) 2-(4-Methyl- 1-cyclohex-3-enyl)propan-2-ol (98-55-5)	
10482-56-1: (S)-(-)-p-Menth-1-en-8-ol;(-)- α -Terpineol; (S)-(-)-Terpineol; (S)-(-)- α -Terpineol; (S)- α -Terpineol; l- α -Terpineol 98-55-5: p-Menth-1-en-8-ol; ($\pm$)- α -Terpineol; 1,1-Dimethyl-1-(4-methylcyclohex-3-enyl)methanol; 1-p-Menthen-8-ol; 2-(4-Methyl-3-cyclohexenyl)-2-propanol; 4-(2-Hydroxy-2-propyl)-1-methylcyclohexene; 8-Hydroxy-p-menth-1-ene; NSC 21449; NSC 403665; PC 593; Pine Oil 593; Terpineol 350; dl- α -Terpineol; $\alpha,\alpha,4$ -Trimethyl-3-cyclohexene-1-methanol; α -Terpineol	
Current regulation: /	

Clinical data:

A RIFM review is available (201) specifically on (-)-alpha-terpineol stating that “no data is available” regarding skin sensitisation. Another RIFM review is available on alpha-terpineol (202). In the Frosch 2002 b study, 1 of 1606 consecutive patients showed a positive reaction, but 11 patients doubtful reactions to alpha-terpineol (5% pet.) (17). The DeGroot 1985 study identified no positive reactions among 179 patients using a 15% PT preparation of terpineol (mixed isomers) (25). In 63 patients positive to the FM I, 2 had a positive PT reaction to alpha terpineol, 5% pet., in the Santucci 1987 study (28). A clinical series from Portugal, addressing contact allergy to oil of turpentine diagnosed in 30 patients, used a series with pure terpenes. A total of 3 of 30 patients reacted positively to alpha-terpineol (189)

Additional information: see also terpineol (mixture of isomers). Comments on turpentine under pinene.

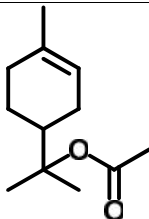
<i>Terpinolene</i>	
CAS # 586-62-9	
EC # 209-578-0	
1-Methyl-4-propan-2-ylidenecyclohexene	
p-Mentha-1,4(8)-diene; 1-Methyl-4-(1-methylethylidene)-cyclohexene; 4-Isopropylidene-1-methylcyclohexene; Isoterpinene; Nofmer TP; Terpinolen; Terpinolene; α -Terpinolene; δ -Terpinene	

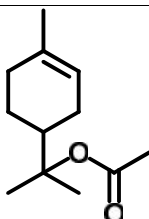
Current regulation: Annex III, part 1, n° 133 (Peroxide value less than 10 mmol/L in substance)

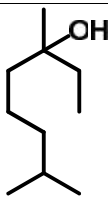
Clinical data:

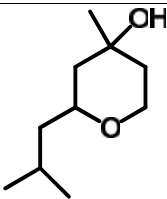
A 49-year-old machine cleaner developed occupational contact dermatitis due to the cleaner, which gave a positive patch test result at 1:10 000 in water. Of the ingredients identified by chromatography, only .delta.-3-carene and terpinolene, tested 5% pet., gave a positive result (negative in 10 controls) (203). Eleven patients sensitised to tea tree oil showed positive reactions to alpha-terpinene, terpinolene and ascaridol (204).

Additional information: It is a “top 100” substance (IFRA, pers. comm. 2010)

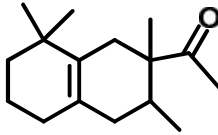
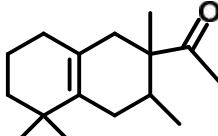
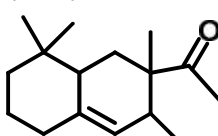
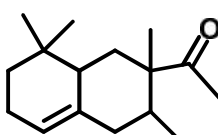
TERPINEOL ACETATE (Isomer mixture)	
CAS # 8007-35-0	
EC # 232-357-5	
4-Methyl-1-propan-2-yl-1-cyclohex-2-enyl acetate	
Terpinyl acetate	
Current regulation: /	
Clinical data:	
In the Frosch 1995 dose-finding pilot study, no positive reaction to 1% and 5% terpinyl acetate in pet., tested in 106 consecutive patients in Barcelona, were observed (15)	
Additional information: It is a “top 100” substance (IFRA, pers. comm. 2010)	

<i>alpha</i>-TERPINYL ACETATE	
CAS # 80-26-2	
EC # 201-265-7	
2-(4-Methyl-1-cyclohex-3-enyl)propan-2-yl acetate	
3-Cyclohexene-1-methanol, $\alpha,\alpha,4$ -trimethyl-, acetate; p-Menth-1-en-8-ol, acetate; ($\pm$)- α -Terpineol acetate; ($\pm$)- α -Terpinyl acetate; 2-(4-Methyl-3-cyclohexen-1-yl)-2-propyl acetate; Terpinyl acetate; α -Terpineol acetate; p-Menth-1-en-8-yl acetate; 1-Methyl-1-(4-methylcyclohex-3-enyl)ethyl ethanoate; ($\pm$)-.alpha.,.alpha.,.4-trimethylcyclohex-3-ene-1-methyl acetate	
Current regulation: /	
Clinical data:	
The DeGroot 1985 study identified no positive reactions among 179 patients using a 10% PT preparation of “terpinyl acetate” (25).	
Additional information: It is a “top 100” substance (IFRA, pers. comm. 2010)	

Tetrahydrolinalool	
CAS # 78-69-3	
EC # 201-133-9	
3,7-Dimethyloctan-3-ol	
2,6-Dimethyl-6-octanol; 3,7-Dimethyloctan-3-ol; Linalool tetrahydride; NSC 128151; Tetrahydrolinalool	
Current regulation: /	
Clinical data:	
/	
Additional information: It is a “top 100” substance (IFRA, pers. comm. 2010). A RIFM review is available (205) quoting 1 negative human maximisation test.	

TETRAHYDRO-METHYL-METHYLPROPYL)-PYRAN-4-OL	
CAS # 63500-71-0	
EC # 405-040-6	
4-Methyl-2-(2-methylpropyl)tetrahydro-2H-4-pyranol 2-(2-Methylpropyl)-4-hydroxy-4-methyltetrahydropyran; 2-	

Isobutyl-4-hydroxy-4-methyltetrahydropyran; 2-Isobutyl-4-methyltetrahydropyran-4-ol; 4-Hydroxy-4-methyl-2-(2-methylpropyl)tetrahydropyran; Florosa; Rozanol	
Current regulation: /	
Clinical data:	
/	
Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).	

TETRAMETHYL ACETYLOCTAHYDRONAPHTHALENES	
CAS # 54464-57-2 / 54464-59-4 / 68155-66-8 / 68155-67-9	
EC # 259-174-3 / 259-175-9 / 268-978-3 / 268-979-9	
1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-ethanone (54464-57-2)	
1-(1,2,3,4,5,6,7,8-octahydro-2,3,5,5-tetramethyl-2-naphthalenyl)-ethanone (54464-59-4)	
1-(1,2,3,5,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-ethanone (68155-66-8)	
1-(1,2,3,4,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-ethanone (68155-67-9)	
54464-57-2: 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone; 1',2',3',4',5',6',7',8'-Octahydro-2',3',8',8'-tetramethyl-2'-acetonephthone; 7-Acetyl-1,2,3,4,5,6,7,8-octahydro-1,1,6,7-tetramethylnaphthalene; Amberonne; Ambralux; Iso Ambois Super; Iso-E Super; Isocyclemon E; OTNE; Orbitone	

Current regulation: /

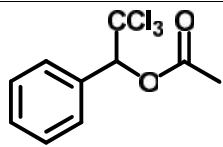
Clinical data:

In the Frosch 2002 a study, 0.2% of 1855 consecutive patients reacted to the compound (brand name mentioned: „Iso E. Super“, 5% pet.) (16). In the Frosch 1995 dose-finding pilot study, 1 positive reaction both to 1% and 5% “Iso E Super ®” in pet., tested in 313 consecutive patients in Bordeaux and London, were observed (15). The Larsen 2001 study yielded 1.7% positive reactions (5% pet.) in 178 patients with known contact allergy to fragrance ingredients (19).

Additional information: According to CosIng: “Mixture of isomers: 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthyl)ethan-1-one; 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,5,5-tetramethyl-2-naphthyl)ethan-1-one; 1-(1,2,3,5,6,7,8,8a-Octahydro-2,3,8,8-tetramethyl-2-naphthyl)ethan-1-one (68155-67-9); 1-(1,2,3,4,6,7,8,8a-Octahydro-2,3,8,8-tetramethyl-2-naphthyl)ethan-1-one (68155-66-8) „

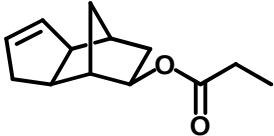
(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=40504>, last accessed 2009-11-11).

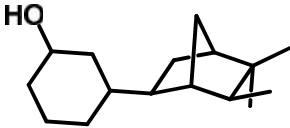
It is a “top 100” substance (IFRA, pers. comm. 2010)

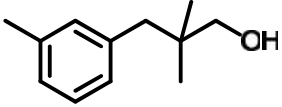
TRICHLOROMETHYL PHENYL CARBINYL ACETATE	
CAS # 90-17-5	
EC # 201-972-0	
2,2,2-Trichloro-1-phenylethyl acetate	

Benzenemethanol, α -(trichloromethyl)-, acetate; Benzyl alcohol, α -(trichloromethyl)-, acetate (Trichloromethyl)phenylcarbinyl acetate; ($\pm$)- α -(Trichloromethyl)benzyl acetate; 2-Acetoxy-1,1,1-trichloro-2-phenylethane; Crystal rose; NSC 165582; Rosacetol; Rosephenone; Rosetone; Rosone; α -(Trichloromethyl)benzyl acetate	
Current regulation: /	
Clinical data: /	
Additional information: It is a “top 100” substance (IFRA, pers. comm. 2010)	

TRICYCLODECENYL PROPIONATE

CAS # 17511-60-3	
EC # 241-514-7	
3α,4,5,6,7,7α-hexahydro-4,7-methano-1H-inden-6-yl propionate	
4,7-Methano-1H-inden-6-ol, 3 α ,4,5,6,7,7 α -hexahydro-, propanoate; 4,7-Methanoinden-6-ol, 3 α ,4,5,6,7,7 α -hexahydro-, propionate; Cyclaprop; Florocyclene; Greenyl propionate; Tricyclo(5.2.1.02,6)dec-3-en-8-yl propionate.	
Current regulation: /	
Clinical data: /	
Additional information: It is a “top 100” substance (IFRA, pers. comm. 2010).	

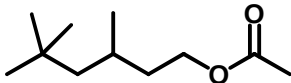
3-(5,5,6-TRIMETHYLBICYCLO[2.2.1]HEPT-2-YL)-CYCLOHEXAN-1-OL	
CAS # 3407-42-9	
EC # 222-294-1	
3-(5,5,6-Trimethyl-6-bicyclo[2.2.1]heptanyl)cyclohexan-1-ol	
3-(5,5,6-Trimethyl-2-norbornyl)-cyclohexanol; 3-(5,5,6-Trimethylbicyclo[2.2.1]hept-2-yl)cyclohexan-1-ol; 3-Hydroxy-1-(5-isocamphyl)cyclohexane; Sandela	
Current regulation: /	
Clinical data: /	
Additional information: part of “synthetic sandalwood oil”.	

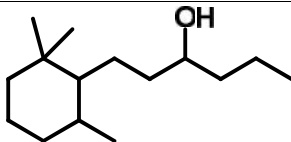
TRIMETHYL-BENZENEPROPANOL (Majantol)	
CAS # 103694-68-4	
EC # 403-140-4	
2,2-Dimethyl-3-(3-methylphenyl)propan-1-ol	
2,2-Dimethyl-3-(3-tolyl)propan-1-ol; 3-(2,2-dimethyl-3-hydroxypropyl)toluene	
Current regulation: /	

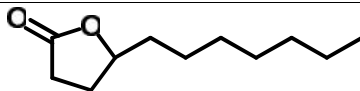
Clinical data:

In the Larsen 2002 c study, majantol (conc. not given, elsewhere reported as 5% pet.) caused positive PT reactions in 3.2% of patients with known contact allergy to fragrance ingredients. In a later study by the IVDK, 0.5% (95% CI: 0.3 – 0.7%) consecutive patients displayed a

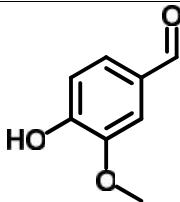
positive reaction to majantol 5% pet. (206). In the IVDK 2010 study, majantol was tested both in n=2189 consecutive patients, yielding 0.36 % (95% CI: 0.12—0.60%) positive reactions, and in the context in a special series, applied in an aimed fashion to n=4972 patients, yielding 0.76% (95% CI: 0.49—1.03%) (standardised) positive reactions (7). In a recent study from Copenhagen, DK, 6 of 722 patients tested with this compound were found positive, 2 of these to material used earlier provided by Symrise, 4 to material by Allmiral/Hermal/Trolab used later instead. There was no significant difference between these proportions obtained with batches of majantol from different production processes (207).
Additional information: /

TRIMETHYLHEXYL ACETATE	
CAS # 58430-94-7	
EC # 261-245-9	
3,5,5-trimethylhexyl acetate	
1-Hexanol, 3,5,5-trimethyl-, acetate; Vanoris; neononyl acetate	
Current regulation: /	
Clinical data: /	
Additional information: It is a “top 100” substance (IFRA, pers. comm. 2010)	

TRIMETHYL-PROPYLCYCLOHEXANEPROPANOL (TMCH)	
CAS # 70788-30-6	
EC # 274-892-7	
1-(2,2,6-trimethylcyclohexyl)hexan-3-ol	
Other names: 2,2,6-Trimethyl-alpha-propylcyclohexanepropanol (REACH, EINECS); .alpha.-Propyl-2,2,6-trimethyl-cyclohexanepropanol; 6-(2,2,6-Trimethylcyclohexyl)-4-hexanol; Finotimber; Timberol	
Current regulation: /	
Clinical data: In the Larsen 2001 study, none of 178 patients with contact allergy to fragrance ingredients reacted positively to this ingredient, PTed at 5% pet. (19).	
Additional information: /	

gamma-UNDECALACTONE	
CAS # 104-67-6	
EC # 203-225-4	
5-Heptyltetrahydrofuran-2-one	
Undecanoic acid, 4-hydroxy-, γ-lactone; (RS)-γ-Undecalactone; (±)-γ-Undecalactone; 4-Hydroxyundecanoic acid lactone; 4-Undecanolide; 5-Heptyldihydro-2(3H)-furanone; NSC 406421; NSC 46118; NSC 76413; Neutralizing agent 350120-1; Peach lactone; Peche Pure; Persicol; γ-(n-Heptyl)-γ-butyrolactone; γ-Heptyl-γ-butyrolactone; γ-Heptylbutyrolactone; γ-Undecalactone; γ-Undecanolactone; γ-Undecanolide; γ-n-Heptylbutyrolactone	
Current regulation: /	

Clinical data: /
 Additional information:
 It is a “top 100” substance (IFRA, pers. comm. 2010)

VANILLIN	
CAS # 121-33-5	
EC # 204-465-2	
4-Hydroxy-3-methoxybenzaldehyde	
2-Methoxy-4-formylphenol; 3-Methoxy-4-hydroxybenzaldehyde; 4-Formyl-2-methoxyphenol; 4-Hydroxy-5-methoxybenzaldehyde; 4-Hydroxy-m-anisaldehyde; H 0264; Lioxin; NSC 15351; NSC 403658; NSC 48383; Rhovanil; Vanillaldehyde; Vanillic aldehyde; Vanillum; m-Methoxy-p-hydroxybenzaldehyde; p-Hydroxy-m-methoxybenzaldehyde; p-Vanillin	

Current regulation: /

Clinical data:

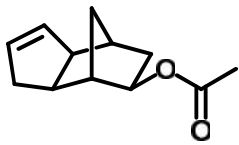
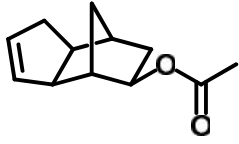
In a series of 40 of 744 consecutive patients PTed with an extended fragrance series (Sheffield 1999), 1 positive reaction to vanillin was observed (3). In the Wöhrle 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded n=1 (0.1%) positive reaction to vanillin 10 % pet. (22). The IVDK 2010 study, n=10, i.e., 0.19% (95% CI: 0.07 – 0.32%; percentages standardised for age and sex) of 4377 patients PTed reacted to the compound, tested 10% pet. (7). In n=102 patients with a positive reaction to MPR, 19 compounds of this natural mixture were tested, among these, vanillin, to which none reacted positively (208). In 21 patients with contact allergy to propolis, 2 also reacted to vanillin (10% pet.) (209).

A 13-year-old girl with recurrent (peri-)cheilitis after application of a vanilla lip salve tested strongly positive to this salve (as is), “Vanilla 10% pet.” (unclear, whether natural extract or vanillin) and MPR (210). Trattner/David identified 1 / 641 consecutive patients with positive reaction to vanillin (31).

Additional information:

Naturally occurring in the fruit of *Vanilla planifolia* after a fermentation process, in styrax, clove oil, potatoes, wood, including Myroxylon pereirae resin, and other material (53).

Nowadays, vanillin is synthesised from eugenol, guajakol and lignin residues from paper production, however, not fully achieving the subtle scent and taste of the natural material (53). It is a “top 100” substance and classified as R43 (IFRA, pers. comm. 2010).

VERDYL ACETATE	
CAS # 2500-83-6/ 5413-60-5	
EC # 219-700-4 / 226-501-6	
3α,4,5,6,7,7α-Hexahydro-4,7-methanoinden-6-yl acetat (2500-83-6)	
3α,4,5,6,7,7α-Hexahydro-4,7-methano-1H-inden-5-yl acetat (5413-60-5)	
2500-83-6: 4,7-Methano-1H-inden-5-ol, 3a,4,5,6,7,7a-hexahydro-, acetate; 4,7-Methanoinden-5-ol, 3a,4,5,6,7,7a-hexahydro-, acetate; NSC 142428; NSC 94573	

5413-60-5: 4,7-Methano-1H-inden-6-ol, 3a,4,5,6,7,7a-hexahydro-, acetate; 4,7-Methanoinden-6-ol, 3a,4,5,6,7,7a-hexahydro-, acetate; 4,7-Methano-3a,4,5,6,7,7a-hexahydroinden-6-yl acetate; 8-Acetoxytricyclo[5.2.1.0 ^{2,6}]dec-3-ene; Greenyl acetate; Herbaflorat; Jasmacyclene; NSC 6598	
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Current regulation: /

Clinical data: /

Additional information:

In CosIng, both above CAS numbers are listed under “verdyl acetate”

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=41289>, last accessed 2010-07-19).

In the CAS, there are 2 separate entries; moreover, there are 2 separate RIFM reviews:

- # 2500-83-6: Other names: Tricyclo[5.2.1.0^{2,6}]dec-4-en-8-yl acetate (REACH, EINECS, INCI Name according to CAS); 3a,4,5,6,7,7a-Hexahydro-4,7-methanoinden-6-yl Acetate; Tricyclodecen-4-yl 8-Acetate. It is a “top 100” substance (IFRA, pers. comm. 2010). A RIFM review is available, stating that “no data is available” regarding the skin sensitising properties of the substance (211).
- # 5413-60-5: Other names: 3a,4,5,6,7,7a-hexahydro-4,7-methanoinden-6-yl acetate (REACH, EINECS, INCI Name according to CAS), 4,7-Methano-3a,4,5,6,7,7a-hexahydroinden-6-yl acetate; 4,7-Methanoinden-6-ol, 3a,4,5,6,7,7a-hexahydro-, acetate; 8-Acetoxytricyclo[5.2.1.0^{2,6}]dec-3-ene; Tricyclodecenyl acetate; Greenyl acetate; Herbaflorat; Jasmacyclene; NSC 6598; Verdyl acetate. It is a “top 100” substance (IFRA, pers. comm. 2010). A RIFM review is available (212), citing 2 negative human maximisation tests and 1 negative HRIPT.

Natural extracts / essential oils

Natural raw materials in terms of extracts are used in the fragrance and flavour industry for various reasons. Most importantly, several naturally occurring mixtures have a very complex composition and sensory nature which cannot (fully) be achieved by synthetic material. Moreover, several compounds cannot be synthesised at a competitive price, and the demand for perfumes based on natural materials is considerable (34).

The three main methods used to concentrate plant fragrance substances as essential oils comprise steam distillation, mechanical processes from the epicarp of Citrus fruits (“pressing”) and dry distillation. An Essential oil is „obtained by steam distillation with addition of water in the still (hydrodistillation) or without addition of water in the still (directly by steam“){Anonymous, 2010 #15047}. Essential oil of fruit juice is „obtained by from a fruit juice during its concentration or during UHT (flash pasteurization) treatment“ {Anonymous, 2010 #15047}. Cold pressed essential oil is „obtained by mechanical processes from the epicarp of the fruit of a Citrus, at ambient temperature“{Anonymous, 2010 #15047}. Citrus peel oils, apart from distilled Citrus oils, are produced with various methods {Schmidt, 2010 #14566}. The oil consists of a high volume of volatile terpenes, mostly monoterpenes but also contains small amounts of non-volatile compounds such as dyes, waxes and furocoumarines.

The method of solvent extraction is generally applied in the separation of heat-labile materials or if an essential oil can only be obtained in very low yield, e.g. from blossoms. It is also used if the non-volatile components are desired for their fixative properties, e.g. in the preparation of resinoids from exudates. The most important extracts are termed: (i) concrete: an extract „obtained from a fresh plant natural raw material by extraction with a solvent“⁸, containing not only volatile, but also a large proportion of non-volatile substances such as waxes; and (ii) absolute: „product, obtained by extraction with ethanol from a concrete, a floral pomade, a resinoid or a supercritical fluid extract. The ethanolic solution is generally cooled down and filtered in order to eliminate the «waxes»; the ethanol is then eliminated by distillation“⁹. Resinoids, used for their fixative properties, are „obtained from a dry plant natural raw material by extraction with a solvent“¹⁰. The products are usually highly viscous and thus might sometimes be diluted, e.g. with phthalates or benzyl benzoate. Oleoresins are extracts „of spice or aromatic herb“ by „treating a natural raw material with a solvent, then, after filtration if necessary, the solvent is eliminated“¹¹.

Regarding clinical data in terms of contact allergy to fragrance ingredients, the main focus of case report or clinical studies regarding essential oils and natural extracts, respectively, is on general dermatological patients with complaints related to use of cosmetics etc. However, series of cases with occupational exposure to essential oils with occupational allergic contact dermatitis have also been reported (e.g., masseurs, physiotherapists (213, 214), aromatherapists (215-219), beauticians doing massages (220); for further details, e.g., PT results with various essential oils, see original case reports. “Current Regulation” refers to the EU Cosmetics Directive only.

⁸ ISO/DIS 9235

⁹ ISO/DIS 9235

¹⁰ ISO/DIS 9235

¹¹ ISO/DIS 9235

Catalogue of natural extracts / essential oils evaluated

ACORUS CALAMUS ROOT OIL *Calamus Oil; "Sweet Flag Oil"*

CAS 84775-39-3; EC 283-869-0
(*Acorus calamus*, ext. = INCI
name)

Current regulation: /

Clinical data:

The Rudzki 1976 study found no positive reaction in 200 patients to “calamus” essential oil, 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=7 (8.1%) positive reactions to “calamus” essential oil 2% pet. (27).

Additional information:

ISO 4720:2009 nomenclature: *Acorus calamus* L. (sweet flag calamus). *Acorus Calamus* Root Oil is an essential oil obtained from the rhizomes of the calamus, *Acorus calamus* L., Araceae. It contains beta-asarone (up to 96%, depending on ploidy, and with this, origin (34)), calamene (about 4%), calamol (about 3%) alpha-asarone (about 1%), camphene (about 1%) and some beta-pinene and asaronaldehyde

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=41330>, last accessed 2010-01-29. Use is restricted due to potential toxicity of beta-asarone (34).

CANANGA ODORATA and Ylang-ylang oil

Ylang-ylang and cananga oils are essential oils that are obtained from two subspecies of the cananga tree (34). In the INCI nomenclature, both are not differentiated.

CANANGA ODORATA FLOWER EXTRACT

CAS 83863-30-3; EC 281-092-1

(ylang-ylang, ext.) INCI name:

CANANGA ODORATA EXTRACT

CANANGA ODORATA FLOWER OIL

CAS 8006-81-3, 68606-83-7; EC / (oils,
ylang-ylang) INCI name: CANANGA
ODORATA OIL

Current regulation: ...

Clinical data:

Ylang-ylang oil

ISO 4720:2009 nomenclature: *Cananga odorata* (Lam.) Hook. f. et Thomson *forma genuina*)

In the Larsen 2002 c study, “synthetic ylang-ylang oil” caused 6.4% positive reactions in 218 patients with known contact allergy to fragrance ingredients (1). In a Japanese study, M. Sugawara et al. noted a significant decline of the proportion of patients reacting positively to “ylang-ylang oil 5% pet.” from 1971 to 1989, the overall number in patients with cosmetic dermatitis amounting to 176 of 1438 (12.2%, 95% CI: 10.6 – 14.0%) (221). In the Frosch 2002 b study, two fractions of Ylang-Ylang oil (I and II) were separately tested, each at 10% pet. Fraction I yielded 2.6%, fraction II 2.5% positive test reactions (no data on concomitant reactivity given) (17). The deGroot 2000 study, with 1825 consecutively tested patients, found 18 positive PT reactions to “ylang-ylang oil”, tested at 4% in pet. (12). The Sugiura 2000 study with 1483 patients with suspected cosmetic dermatitis observed 0.8% positive PT

reactions with ylang-ylang oil (5% pet.) (14). The Coimbra 2000 study found in 67 patients with positive reaction to the FM I who were tested with ylang-ylang oil (2% pet.) 13.4% positive reactions (9). The Belsito 2006 study (20) yielded 0.6% positive reactions to ylang-ylang oil. The subsequent NACDG 2009 study identified 1.5% positive reactions in 4434 patients PTed with 2% “ylang-ylang oil” (21). The IVDK 2010c study found 2.5% positive reactions in 3175 consecutively tested patients, and 3.9% in 2155 patients tested in the context of a special series (30). In a study from Alicante, Spain, 86 selected patients were patch tested with an extended fragrance series; n=12 reacted positively to ylang-ylang oil and 3 to “cananga oil” (48).

Cananga oil

ISO 4720:2009 nomenclature: *Cananga odorata* (Lam.) Hook. f. et Thomson *forma macrophylla*. For Oil of cananga (*Cananga odorata* (Lam.) Hook. f. et Thomson, *forma macrophylla*) an ISO standard exists: ISO 3523:2002. Cananga oil is produced by steam distillation of the flowers of *Cananga odorata* (DC.) Hook f. et Thomson subsp. *macrophylla* (*Annonaceae*). The composition resembles that of “ylang-ylang III”, but with a higher content of caryophyllene (30-40%). Cananga oil originates almost exclusively in Java; annual production about 50 t. The oil is used mainly in perfuming soaps where it is more stable than ylang-ylang oils due to its lower ester content (34).

Sugiura et al. (2000) found 1.1% positive reactions to “cananga oil”, tested 5% pet. (14). Cananga oil (2% pet.) mentioned in the same Portuguese study already cited (9) yielded 10.4% positive reactions. In the An 2005 study, 5 of 422 consecutive patients, i.e., 1.2%, had positive reactions to cananga odorata oil tested at 2% concentration (13).

Studies with both oils

The Goossens 1997 study found 3 of 111 patients positive to “ylang-ylang oil 5% pet.”, and 4 to “cananga oil 15% pet.” – all sensitised to other fragrance allergens (23). The Rudzki 1976 study found 1 positive reaction in 200 patients to “cananga” and 4 to “ylang-ylang” essential oil, both tested 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=10 (11.6%) positive reactions to “cananga” and n=8 (9.3%) to “ylang-ylang” essential oils, each tested at 2% pet. (27). Nakayama et al. found 1974 (after (29)) 11 “strong positive” and 15 “weak positive” reactions to “Cananga oil” and 9 and 16, resp., to “Ylang-ylang oil” (unknown test concentration) in 183 patients.

A number of case reports highlight the possibility of occupational contact and sensitisation, e.g. (220, 222).

Additional information:

Ylang-ylang oil

The composition of this essential oil is defined by a standard: ISO 3063:2004. Ylang-ylang oils are obtained by steam distillation of freshly picked blossoms of *Cananga odorata* (DC.) Hook f. et Thomson subsp. *genuina* (*Annonaceae*). The oil is produced mainly in Madagascar and the Comoro islands. Four fractions are collected at progressively longer distillation times and are known as “extra”, “I”, “II” and “III”. The composition of the various oil fractions depends on the duration of distillation. The first fraction has the highest content of strongly odiferous constituents such as p-cresyl methyl ether (5-16%), methyl benzoate (4-9%), (-)-linalool (7-24%), benzyl acetate (5.5-17.5%), and geranyl acetate (2.5-14%). The other fractions contain increasing amounts of sesquiterpene hydrocarbons such as caryophyllene, germacrene-D, and (E,E)-alpha-farnesene (> 70% in “ylang-ylang III”). Components such as p-cresol, eugenol and isoeugenol are important for odour, although they are present only in low concentration (34). According to (30) the maximum observed concentration in ylang-ylang I and II are (in %): germacrene-D (28); (E,E)-alpha-farnesene (21); caryophyllene (17); linalool (I: 19.0; II: 9.5); benzyl benzoate (8.0); farnesol (4.0); benzyl salicylate (4.0); (E,E)-

farnesyl acetate (3.5); *geraniol* (2.5); *isoeugenol* (0.8); *benzyl alcohol* (0.5); *eugenol* (0.5); *p-cresyl methyl ether* (I: 5.0; II 3.5); *methyl benzoate* (I: 5.5; II: 3.5); *benzyl acetate* (I: 10.0; II: 5.0); *geranyl acetate* (I: 15.0; II: 12.0).

CEDRUS ATLANTICA BARK OIL

CAS 92201-55-3; EC 295-985-9
(*Cedrus atlantica*, ext. = INCI) /
8000-27-9; EC / (Oils, cedarwood)
INCI name: CEDRUS ATLANTICA
OIL

Cedarwood oil

Current regulation: /

Clinical data:

In the Wöhrle 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded n=5 (0.7%) positive reactions to cedarwood oil 10% pet. (22). (The exact origin of “cedarwood oil” in this study is not clear.) The IVDK 2010 c study identified 0.8% positive reactions in 6223 patients tested in the context of a special series with a cedarwood oil tagged with CAS # 8000-27-9 (30).

Additional information:

Cedrus Atlantica Bark Oil is the volatile oil obtained from the bark of *Cedrus atlantica*, *Pinaceae*

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=55309>, last accessed 2010-01-05). The main odiferous component is alpha-atlantone [32207-08-2] (39)

Also used: *Cedrus atlantica* wood oil (*Cedrus atlantica* (Endl.) G.Manetti ex Carrière)¹²

See also *Juniperus virginiana*.

CEDRUS DEODARA WOOD OIL

CAS 91771-47-0; EC 294-939-5
(*Cedrus deodara*, ext.)

Cedarwood oil

Current regulation: /

Clinical data:

The Rudzki 1976 study found 3 positive reactions in 200 patients to “cedarwood” essential oil 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=3 (3.5%) positive reactions to “Himalayan cedarwood” essential oil 2% pet. (27). (The labelling in the latter report points to *Cedrus deodara* as source of “cedarwood oil” in these 2 Polish studies.)

Additional information:

Cedrus Deodara Wood Oil, Himalayan cedarwood oil (*Cedrus deodara* (Roxb. ex D.Don) G. Don)¹³, is the volatile oil obtained by steam distillation of the stumps of the Deodar Cedar, *Cedrus deodara*,

Pinaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=55311>, last accessed 2010-01-29).

Several other conifer species are called cedars, and the corresponding oils vary considerably in composition. These include Cedar leaf oil (*Thuja* oil) produced by steam distillation of

¹² ISO 4720:2009 nomenclature:

¹³ ISO 4720:2009 nomenclature:

fresh leaves and branch ends of *Thuja occidentalis* L. (*Cupressaceae*) from North America, containing a minimum of 60% thujone [8007-20-3] [90131-58-1] (34). Texas cedarwood oil is produced by steam distillation of chopped wood of *Juniperus mexicana* Schiede (*Cupressaceae*), containing alpha-cedrene (15-25%), thujopsene (25-35%), cedrol 20% minimum [8000-27-9] [91722-61-1] (34). Chinese cedarwood oil is similar to Texas cedarwood oil, obtained by steam distillation of *Cupressus funebris* Endl., *Cupressaceae* (*Chamaecyparis funebirs* (Endl.) France), which is a weeping cypress [8000-27-9] [85085-29-6] (34).

CINNAMOMUM CASSIA LEAF OIL

94961-46-6 [invalid] / 8007-80-5;
EC / (Oils, cassia) INCI name:
CINNAMONUM CASSIA OIL

Cassia Oil; Cassia leaf Oil; Cinnamon Oil Chinese

CINNAMOMUM ZEYLANICUM BARK OIL

CAS 84649-98-9; EC 284-635-
0 (Cinnamomum zeylanicum, ext. =
INCI)

Cinnamon Bark Oil Ceylon; Cinnamon Oil Ceylon

Current regulation: /

Clinical data:

The Rudzki 1976 study found 2 positive reactions in 200 patients to "cassia" essential oil, 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=24 (27.9%) positive reactions to "cassia" essential oil 2% pet. (27).

A 32 year old Spanish physiotherapists developed vesicular hand dermatitis after using a "balsam from ash extract" cream. PTing revealed positive reactions to this cream, the FM I, eugenol, and 2 components of the cream: "cinnamon oil" (0.5% pet.) and clove oil (1% pet.) (223).

Additional information:

ISO 4720:2009 nomenclature: *Cinnamomum tsumu* Helms, syn. *Cinnamomum cassia* auct. and *Cinnamomum zeylanicum* Blume syn. *Cinnamomum verum* J. Presl, respectively. Cassia oil (Chinese cinnamon oil) is obtained by steam distillation of the leaves, twigs, and bark of *Cinnamomum aromaticum* Nees (*C. cassia* Blume, *Lauraceae*). In contrast to cinnamon bark oil (see below), cassia oil contains a considerable amount of 2-methoxycinnamal (3-15%), in addition to its main constituent, cinnamal (70-88%). Cassia oil is predominantly used in flavouring soft drinks, with an annual production of a few hundred tons (34). For Oil of cassia, Chinese type (*Cinnamomum aromaticum* Nees, syn. *Cinnamomum cassia* Nees ex Blume) an ISO standard exists: ISO 3216:1997

Cinnamomum Zeylanicum Bark Oil is the volatile oil expressed from the bark of the Ceylon Cinnamon, *Cinnamomum zeylanicum*, *Lauraceae*. It contains mainly cinnamaldehyde (34), e.g. 50-60%, and lesser quantities of eugenol (4-8%), phellandrene (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=75370>, last accessed 2009-11-16). For Oil of cinnamon leaf, Sri Lanka type (*Cinnamomum zeylanicum* Blume) an ISO standard exists: ISO 3524:2003

Cinnamomum Cassia Leaf Oil is the volatile oil obtained by steam distillation from the leaves and twigs of the Chinese Cinnamon, *Cinnamomum cassia* (L.), *Lauraceae*. It contains 80% eugenol

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=75368>, last accessed 2009-11-16). The cinnamon leaf oil produced by steam distillation of the leaves of *Cinnamomum zeylanicum* Blume (*C. verum* J.S. Presl) similarly has a content of 70-83% eugenol (34).

Considering the content of well-known allergenic compounds, the essential oil is considered an Established contact allergen in humans,

CITRUS AURANTIUM AMARA FLOWER OIL	CAS 8016-38-4, 68916-04-1; EC / (Oils, neroli) /
<i>Neroli oil</i>	
CITRUS AURANTIUM AMARA PEEL OIL EXPRESSED	72968-50-4; EC 277-143-2 (Orange, sour, ext.)
<i>"Bitter Orange Oil"</i>	
	INCI names: CITRUS AURANTIUM AMARA ...

Current regulation: /

Clinical data:

The Coimbra 2000 study found in 67 patients with positive reaction to the FM I who were tested with "neroli oil" (2% pet.) 6.6% positive reactions (9). The Rudzki 1976 study found 3 positive reactions in 200 patients to "bitter orange" essential oil 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=2 (2.3%) positive reactions to "bitter orange" essential oil 2% pet. (27). The IVDK 2010 c study identified 0.7% positive reactions in 6220 patients tested in the context of a special series (30)

Additional information:

ISO 4720:2009 nomenclature: *Citrus aurantium* L., syn. *Citrus amara* Link, syn. *Citrus bigaradia* Loisel, syn. *Citrus vulgaris* Risso. For Oil of neroli (*Citrus aurantium* L. spp. *aurantium*, syn. *Citrus aurantium* L. spp. *amara* var. *pumilia*) an ISO standard exists: ISO 3517:2002. *Citrus Aurantium Peel Oil Expressed* is an essential oil expressed from the fresh epicarps of the Sour Orange, *Citrus aurantium*, Rutaceae. It contains D-limonene (about 90%), citral, decanaldehyde, methyl anthranilate, linalool, terpineol (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=41394>, last accessed 2010-01-29). The aldehyde content is lower and the ester content (e.g., linalyl and geranyl acetate) is higher than in sweet orange oil (34). It is predominantly used for flavouring alcoholic beverages. According to (30) the maximum observed concentration in neroli oil are (in %): linalool (44); limonene (18); β -pinene (17); linalyl acetate (15); *trans*- β -ocimene (8); geranyl acetate (5); *trans*-nerolidol (5); (*E,E*)-farnesol (4); myrcene (4); farnesol (4,0); geraniol (3,5); citral (0,3) (30).

CITRUS AURANTIUM AMARA LEAF OIL	72968-50-4; EC 277-143-2 (Orange, sour, ext.)
<i>Petitgrain oil Paraguay / ... bigarade</i>	

Current regulation: /

Clinical data:

The Rudzki 1976 study found 1 positive reaction in 200 patients to "Petitgrain bigarade" and "Petitgrain Paraguay" essential oil each, both tested at 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=7 (8.1%) positive reactions to "Petitgrain bigarade" and n=4 (4.6%) to "Petitgrain Paraguay" essential oil each, both tested at 2% pet. (27).

Additional information:

ISO 4720:2009 nomenclature: *Citrus sinensis* L. Pers. X *Citrus aurantium* L. spp. *amara* var. *pumilia*. Petitgrain oils in general are steam distilled from the leaves of citrus trees. *Citrus*

Aurantium Leaf Oil is an essential oil obtained from the leaves of the Sour Orange, *Citrus aurantium*,

Rutaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=41392>, last accessed 2010-02-10). Petitgrain oil Paraguay is obtained from an acclimatised variety of the bitter orange tree. Main constituents are linalool (15-30%) and linalyl acetate (40-60%). A number of trace constituents contribute essentially to the odour (34). Petitgrain oil bigarade is derived from the same species of tree grown in France, Italy, Spain and North Africa (34). For Oil of bitter orange petitgrain, cultivated (*Citrus aurantium* L.) an ISO standard exists: ISO 8901:2003.

Considering the content of well-known allergenic compounds, the essential oil is regarded as an established contact allergen in humans

CITRUS BERGAMIA PEEL OIL EXPRESSED

CAS 89957-91-5, 8007-75-8; EC 289-612-9 (*Bergamot, ext.*)

Bergamot Oil, Bergamot Orange Oil

INCI: CITRUS AURANTIUM BERGAMIA EXTRACT

Current regulation: /

Clinical data:

The Rudzki 1976 study found 3 positive reactions in 200 patients to “Bergamot” essential oil 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found no positive reaction to “Bergamot” essential oil 2% pet. (27). In 63 patients positive to the FM I, 2 had a positive PT reaction to bergamot oil, 2% pet., in the Santucci 1987 study (28). A case report from Zacher and Ippen describes 2 patients with allergic contact dermatitis due to bergamot oil (191), one a worker in a perfume factory, the other sensitised by non-occupational use of cosmetics.

Additional information:

ISO 4720:2009 nomenclature: *Citrus bergamia* (Risso et Poit.), syn. *Citrus aurantium* L. subsp. *bergamia* (Wight et Arnott) Engler. Citrus Bergamia Peel Oil Expressed is an essential oil expressed from the epicarps of the Bergamot, *Citrus bergamia* risso, Rutaceae. It contains 35-45% L-linalyl acetate, about 6% linalool, D-limonene, DL-limonene and bergaptene (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=41398>, last accessed 2009-11-27). According to Surburg/Panten: linalyl acetate 22-36%, linalool 3-15%, geranial 0.25-0.5%, citral 1%, with a relatively low terpene content of 25-50% (34, 39). Bergaptene content by HPLC is 0.18-0.38% (34). Annual production from Italy, Brazil, Spain and Ivory Coast is 100 to 150 t. For Oil of bergamot [*Citrus aurantium* L. subsp. *bergamia* (Wight et Arnott) Engler], Italian type an ISO standard exists: ISO 3520:1998.

CITRUS LIMONUM PEEL OIL EXPRESSED

CAS 84929-31-7, 8008-56-8; EC 284-515-8 (*Lemon, ext.*)

Lemon oil

INCI names: CITRUS MEDICA LIMONUM ...

Current regulation: /

Clinical data:

The Coimbra 2000 study found in 67 patients with positive reaction to the FM I who were tested with "lemon oil" (2% pet.) 4.5% positive reactions (9). In the Wöhrle 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded n=2 (0.3%)

positive reactions to “lemon oil” 2% pet. (22).

The Rudzki 1976 study found 1 positive reaction in 200 patients to “lemon” essential oil 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=2 (2.3%) positive reactions to “lemon” essential oil 2% pet. (27). The IVDK 2010 c study identified 0.3% positive reactions in 6467 patients tested in the context of a special series (30).

Additional information:

ISO 4720:2009 nomenclature: *Citrus limon* (L.) Burm. f. According to (30) the maximum observed concentration in lemon oil are (in %): limonene (80); β -pinene (16.5); γ -terpinene (12); citral (3.0); geranial (2.0); neral (1.2); β -bisabolene (0.9); geranyl acetate (0.7); neryl acetate (0.6); linalool (0,3); geraniol (0,2) (30). An ISO standard exists for Oil of lemon [*Citrus limon* (L.) Burm. f.], obtained by expression: ISO 855:2003. The composition of lemon oil depends on the variety of lemon and the country of origin, see table from (34).

Table 3. Specifications for qualities of lemon oils of different origins

Parameter	Type	Mediterranean		Equatorial	
	American Origin				
	Coast	Desert	Italy	Spain	Ivory coast, Brazil
α_{20}^{20}	0.851–0.857	0.849–0.854	0.850–0.858	0.849–0.858	0.845–0.854
n_D^{20}	1.4370–1.4760	1.4370–1.4760	1.4370–1.4760	1.4370–1.4760	1.4370–1.4790
α_D^{20}	+57° to +65°6'	+67° to +78°	+57° to +66°	+57° to +66°	+57° to +70°
Composition by GC [area %]					
β -Pinene	9–14	10–13	10–16.5	10–16.5	7–16
Limonene	63–70	70–80	60–68	60–70	59–75
γ -Terpinene	8.3–9.5	6.5–8	8–12	8–128–12	6–12
Neral	0.6–0.9	0.3–0.6	0.6–1.2	0.4–1	0.2–1.2
Geranial	1.0–2	0.5–0.9	0.8–2	0.6–2	0.5–2
Evaporation residue [weight %]					
	1.75–3.9		1.5–3.9	1.5–3.9	1.5–4
Carbonyl value					
	8–14	6.25–12	11–17	11–17	6–17
CD value	min. 0.2	min. 0.2	0.45–0.9	0.4–0.9	0.2–0.96

CITRUS PARADISI PEEL OIL
Grapefruit oil, expressed

CAS 8016-20-4 ; EC /
INCI: CITRUS GRANDIS OIL

Current regulation: II/358 R1

Clinical data: /

Additional information:

Citrus Paradisi Peel Oil is the volatile oil expressed from the peel of the Grapefruit, *Citrus paradisi*, Rutaceae

http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details_v2&id=55434

It is a “top 200” substance and classified as R43 (IFRA, pers. comm.2010)

CITRUS SINENSIS (syn.: *AURANTIUM DULCIS*)
PEEL OIL EXPRESSED

CAS 97766-30-8, 8008-57-9, EC 307-891-8 (*Orange, sweet, Valencia, ext. = INCI*) / 8028-48-6; EC 232-433-8 (*Orange, sweet, ext.*)

(Sweet) Orange oil

INCI names: CITRUS
AURANTIUM DULCIS ...

Current regulation: /

Clinical data:

The Coimbra 2000 study found in 67 patients with positive reaction to the FM I who were tested with "orange oil" (2% pet.) 4.5% positive reactions (9). In the Wöhrle 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded n=1 (0.1%) positive reactions to orange oil 2% pet. (22). The Rudzki 1976 study found 1 positive reaction in 200 patients to "sweet orange" essential oil, 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=3 (3.5%) positive reactions to "sweet orange" essential oil 2% pet. (27). In the Frosch 1995 dose-finding pilot study, neither positive nor irritant reaction to 1% and 5% "orange oil Bras." in pet., tested in 205 consecutive patients in Dortmund and Göttingen, were observed (15). The IVDK 2010 c study identified 0.2% positive reactions in 6246 patients tested in the context of a special series (30).

Additional information:

ISO 4720:2009 nomenclature: *Citrus sinensis* (L.) Osbeck. For Oil of sweet orange (*Citrus sinensis* (L.) Osbeck), CAS 8008-57-9, obtained by mechanical treatment, an ISO norm exists: ISO 3140:2005. The oils have a high terpene hydrocarbon content (> 90%, mainly (+)-limonene. Important for aroma are aldehydes, mainly decanal and citral, and aliphatic and terpenoid esters. The sesquiterpene aldehydes alpha-sinensal [17909-77-2] and beta-sinensal [6066-88-8] contribute particularly to the special sweet aroma (34). According to (30) the maximum observed concentration in sweet orange oil are (in %): *limonene* (95.0); *linalool* (0.7); n-decanal (0.7); *citral* (0.3); alpha-sinensal (0.05); beta-sinensal (0.06) (30). Worldwide production is more than 30000 tons / year. Main uses comprise the flavouring of beverages and confectioneries and perfuming E.d.C, soaps and household products. For the latter uses relevant here, both "Orange peel oil, sweet (*Citrus sinensis* (L.) Osbeck) (8008-57-9)", "Orange peel, sweet, extract (*Citrus sinensis* L. Osbeck) (8028-48-6)" and "Orange, sweet, Valencia, ext. (97766-30-8)" are among the top 100 used fragrance materials and classified as R43 (IFRA, pers. comm. 2010).

ORANGE OIL TERPENES (CAS # 68647-72-3) are a "top 100 mixture of substances and classified as R43 (IFRA, pers. comm.2010). Other names: ORANGE, SWEET, TERPENES (REACH); Terpenes and Terpenoids, sweet orange-oil (REACH). The CAS entry refers to a group of substances "Terpenes and Terpenoids, sweet orange-oil" (REACH).

CITRUS TANGERINA ...
Oil of tangerine

CAS 223748-44-5; EC /
[no info in CAS database]

Current regulation: /

Clinical data:

In a 17 year old girl, the perfume used for 3 months caused ACD due to the ingredient "oil of tangerine", with a strong positive PT reaction (to 2% or 10% in pet.; 50 controls negative) (224).

Additional information:

Citrus Tangerina Peel Oil is the volatile oil expressed from the peel of the ripe fruit the Tangerine, *Citrus Tangerina*,

Rutaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=55441>, last accessed 2010-01-29); (*Citrus tangerina* Tanaka).

CORIANDRUM SATIVUM HERB OIL

Coriander oil

CAS 84775-50-8; EC 283-880-0

(*Coriander, ext.*)

INCI: CORIANDRUM SATIVUM EXTRACT

Current regulation: /

Clinical data:

The Rudzki 1976 study found 2 positive reactions in 200 patients to “coriander” essential oil, 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=3 (3.5%) positive reactions to “coriander” essential oil 2% pet. (27).

Additional information:

Coriander Sativum Herb Oil is an essential oil obtained from the herbs of the Coriander, *Coriandrum sativum* L., Umbelliferae

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=39388>, last accessed 2010-01-29). The main component of coriander oil is linalool (by GC: 65-78%) and mono- and polyunsaturated fatty aldehydes contributing to the particular aroma. In contrast to the seed oil, coriander leaf oil contains these aldehydes as main constituents, e.g. 2-deccanal and 2-dodecanal (34). For Oil of coriander fruits (*Coriandrum sativum* L.) an ISO standard exists: ISO 3516:1997.

CYMBOPOGON OILS

Cymbopogon oils are produced from several aromatic grasses that belong to the genus *Cymbopogon* Speng. (*Poaceae*). The oils are obtained by steam distillation of the aerial parts of the plants (34).

The composition of the essential oil derived from *Cymbopogon flexuosus* (Nees ex Steudel) J.F. Watson is defined by a standard: ISO 4718:2004, as is the oil derived from *Cymbopogon citratus*: 3217:1974.

CYMBOPOGON CITRATUS LEAF OIL

Cymbopogon citratus (DC.) Stapf.¹⁴

Lemon Grass Oil; Indian Verbena Oil; Indian Melissa Oil

CAS 89998-14-1; EC 289-752-0

(*Cymbopogon citratus, ext. = INCI*)

CYMBOPOGON SCHOENANTHUS OIL

Cymbopogon flexuosus (Nees ex Steudel) J.F. Watson¹⁵

CAS 8007-02-1; EC 289-754-1 (oils, lemongrass) / 89998-16-3; EC 289-752-0 (*Cymbopogon Schoenanthus, ext. = INCI*)

Lemon Grass Oil

Current regulation: /

Clinical data:

The Frosch 2002 b study on 1606 consecutive patients reported 1.6% positive reactions to

¹⁴ ISO 4720:2009 nomenclature

¹⁵ ISO 4720:2009 nomenclature

“lemongrass oil (East India), CAS 8007-02-1”, PTed at 2% pet. (17). In a series of 40 of 744 consecutive patients PTed with an extended fragrance series (Sheffield 1999), 3 positive reactions to lemongrass oil were observed (3). In the Wöhrle 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded n=6 (0.8%) positive reactions to lemongrass oil 2% pet. (22). The IVDK 2010 c study identified 0.6% positive reactions in 2435 consecutively tested patients and 2.3% positive reactions in 8445 patients tested in the context of a special series (30).

Additional information:

Cymbopogon Citratus Leaf Oil is an essential oil obtained from the leaves of the Lemon Grass, *Cymbopogon citratus* (DC., ex Nees), *Poaceae*. It contains citral (75-85%), methylheptenone, citronellal, geraniol, limonene

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=39457>, last accessed 2009-11-12). According to Surburg/Panten, by GC: neral (31-40%), geraniol (40-50%) (34).

Indian lemongrass oil is obtained by the so-called Indian variety of lemongrass, *Cymbopogon flexuosus* (Nees ex Steud.) Stapf. Content by GC: 25-35% neral, 35-47% geraniol (34).

Cymbopogon Schoenanthus Oil is the volatile oil obtained by the steam distillation of fresh Lemon Grass, *Cymbopogon schoenanthus* (L.), *Poaceae*

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=75419>, last accessed 2009-11-12). According to (30) the maximum observed concentration in lemongrass oil are (in %): citral (85.0); geraniol (7.0); limonene (4.0); geranyl acetate (2.2); caryophyllene (1.6); trans-isocitral (1.4); 6-methyl 5-hepten-2-one (1.3); caryophyllene oxide (1.2); 4-nonanone (1); citronellol (0.8); eugenol (0.3); linalool (0.2) (also according to (225)) In a LLNA study by RIFM, the lemongrass oil as used was reported to contain 68.8% citral, 6.7% limonene, 6.1% geraniol, 2.2% geranyl acetate, 1.6% caryophyllene, 1.4% trans-isocitral, 1.3% 6-methyl 5-hepten-2-one, 1.2% caryophyllene oxide and 1% 4-nonanone, according to analyses of the supplier. The EC3 value was calculated to be 6.5% (225).

CYMBOPOGON MARTINI HERB EXTRACT

CAS 84649-81-0; EC 283-461-2 (*Cymbopogon Martini*, ext) INCI: CYMBOPOGON MARTINI OIL

Palmarosa oil

Current regulation: /

Clinical data: /

Additional information:

ISO 4720:2009 nomenclature: *Cymbopogon martini* (Roxb.) Will. Watson var. *motia* and var. *sofia*. Cymbopogon Martini Herb Extract is an extract obtained from the herbs of the plant, *Cymbopogon martini*, Gramineae

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=39460>, last accessed 2009-11-24), namely, by steam distillation of wild or cultivated *Cymbopogon martini* (Roxb.) J.F. Wats., collected when in blossom (34). The main constituent is geraniol (72-94%) (34).

In a LLNA study by RIFM, the palmarosa oil as used was reported to contain 79.4% geraniol, 9.4% geranyl acetate and 1.9% caryophyllene, according to analyses of the supplier. The EC3 value was calculated to be 9.6% (225).

CYMBOPOGON NARDUS HERB OIL

CAS 89998-15-2; EC 289-753-

*Citronella Oil (Sri Lanka)***CYMBOPOGON WINTERIANUS HERB OIL***Citronella Oil (Java)*

6 (*Cymbopogon nardus*, ext. = INCI)

CAS 91771-61-8; EC 294-954-

7 (*Cymbopogon Winterianus*, ext. = INCI)

Current regulation: ...

Clinical data:

The Rudzki 1976 study found 5 positive reactions in 200 patients to “citronella” essential oil 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=1 (1.1%) positive reactions to “citronella” essential oil 2% pet. (27).

Additional information:

ISO 4720:2009 nomenclature: *Cymbopogon nardus* (L.) W. Watson var. *lenabatu* Stapf. and *Cymbopogon winterianus* Jowitt, respectively. *Cymbopogon Nardus Herb Oil* is an essential oil obtained from the herbs of the plant, *Cymbopogon* (syn: *Andropogon*) *nardus* (L.), Gramineae. The Ceylon citronella oil contains geraniol (about 60%), citronellal (about 15%), camphene, limonene, linalool, borneol. According to Surburg/Panten, the Sri Lankan oil contains citronellal (3-6%), borneol (4-7%), citronellol (3-8.5%), geraniol 15-23%) and methyl isoeugenol (7.11%) (34).

The Java citronella oil contains 25-50% citronellal, 25-45% geraniol (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=39469>, last accessed 2009-11-24). *Cymbopogon Winterianus Herb Oil* as a synonym for Java citronella oil is obtained from the herbs of the plant, *Cymbopogon winterianus*, Gramineae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=39472>, last accessed 2009-11-24). This oil, produced in Taiwan and Java, contains citronellal (31-40%), geraniol (20-25%), citronellol (8.5-14%), geranyl acetate (2.5-5.5%), citronellyl acetate (2-4%) and many minor components. Annual worldwide production is currently at around 1000 t (34). For Oil of citronella, Sri Lankan type (*Cymbopogon nardus* (L.) W. Watson var. *lenabatu* Stapf.) an ISO standard exists: ISO 3849:2003, for Oil of citronella, Java type the ISO 3848:2001.

In a LLNA study by RIFM, the citronella oil as used was reported to contain 36.6% citronellal, 20.6% geraniol, 4.1% limonene, 3.7% geranyl acetate, 3.0% citronellyl acetate, 2.6% elemol, 2.2% beta-bourbonene, 1.9% delta-cadiene, 1.6% isopugenol I, 1.4% germacrene D and eugenol and linalol at < 1%, according to analyses of the supplier. The EC3 value was calculated as > 50 % (225).

Considering the content of well-known allergenic compounds, this essential oil is regarded as established contact allergen in humans.

EUCALYPTUS SPP. LEAF OIL*Eucalyptus Oil*

CAS 92502-70-0; EC 296-357-7

(*Eucalyptus*, ext. = INCI)

CAS 8000-48-4; EC / (Oils, *eucalyptus*) INCI: **EUCALYPTUS GLOBULUS OIL**

Current regulation: /

Clinical data:

In a study with 218 fragrance sensitive patients, 1.8% reacted positively to 10% eucalyptus oil (pet.) (1). In a series of 40 of 744 consecutive patients PTed with an extended fragrance

series (Sheffield 1999), 1 positive reaction to "eucalyptus oil" was observed (3). In the Wöhrle 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded n=4 (0.6%) positive reactions to eucalyptus oil 2% pet. (22). The Rudzki 1976 study found 3 positive reactions in 200 patients to "eucalyptus" essential oil 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=1 (1.1%) positive reactions to "Eucalyptus" essential oil 2% pet. (27). The IVDK 2010 c study identified 0.2% positive reactions in 6680 patients tested in the context of a special series (30).

In a professional athlete, the use of an "analgesic and anti-inflammatory cream" over 2 years lead to ACD, which was attributed to eucalyptol (eucalyptus oil, 1% pet., 25 controls negative), the sole ingredient of the cream eliciting a positive PT reaction (226)

Additional information:

ISO 4720:2009 nomenclature: *Eucalyptus globulus* Labill. Eucalyptus oils are produced from plants belonging to the genus *Eucalyptus* (Myrtaceae), which includes about 500 species in Australia, the country of origin, alone. At present, few of the oils, which are used to characterise species, are commercially important (34). Some species are rich in 1,8-cineole (80-85% content). Other species contain less cineole, but 10-22% alpha-pinene. *E. citriodora* predominantly contains citronellal (min. 75% by GC), with some citronellol and isopulegol (5-10% each) (34). *E. dives* contains (-)-piperitone and 15-25% alpha-phellandrene (34). According to (30) the maximum observed concentration in eucalyptus oil are (in %): 1,8-cineole (58; 70-80 after rectification); α -pinene (22); limonene (8); para-cymene (5); trans-pinocarveol (5); aromadendrene (10); globulol (2.5) [the latter 2 components only traces after rectification] (30).

For Crude or rectified oils of *Eucalyptus globulus* (*Eucalyptus globulus* Labill.) an ISO standard exists: ISO 770:2002.

It is a "top 100" substance and classified as R43 (IFRA, pers. comm.2010).

EUGENIA CARYOPHYLLUS LEAF / FLOWER OIL <i>Clove oil</i>	CAS 8000-34-8; EC / (Oils, clove) INCI: EUGENIA CARYOPHYLLUS OIL
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Current regulation: /

Clinical data:

In the Larsen 2002 c study, 19.3% of patients with known contact allergy to fragrance ingredients reacted positively to "clove bud oil" (10 % pet.) (1). In a series of 40 of 744 consecutive patients PTed with an extended fragrance series (Sheffield 1999), 2 positive reactions to "clove oil" were observed (3). The Coimbra 2000 study found in 67 patients with positive reaction to the FM I who were tested with clove oil (2% pet.) 13.4% positive reactions (9). In the Wöhrle 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded 1.6% positive reactions 2% pet. (22). The Rudzki 1976 study found 2 positive reactions in 200 patients to "clove" essential oil, 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=12 (13.3%) positive reactions to "clove" essential oil 2% pet. (27). The IVDK 2010 c study identified 1.5% positive reactions 6893 patients tested in the context of a special series (30).

A 32 year old Spanish physiotherapist developed vesicular hand dermatitis after using a "balsam from ash extract" cream. PTing revealed positive reactions to this cream, the FM I, eugenol, and 2 components of the cream: cinnamon oil (0.5% pet.) and clove oil (1% pet.) (223).

Additional information:

ISO 4720:2009 nomenclature: *Syzygium aromaticum* (L.) Merr. & L. M. Perry syn. *Eugenia caryophyllus* (Spreng.) Bullock & S. G. Harrison. Standards regarding the composition of

clove oil are available: ISO 3141:1997, ISO 3142:1997, ISO 3143:1997. Clove oils are produced from the clove tree *Syzygium aromaticum* (L.) Merr. et L.M. Perry [*Eugenia caryophyllus* (Speng.) Bullock ex S.G. Harrison. The content of clove bud, clove leaf and clove stem oil has, with little variation, been determined by GC as 75-92% eugenol, 2-17% caryophyllene and 0.2-15% eugenyl acetate – the latter compound found in particularly high concentration in bud oil (34). According to another source, the following maximum content (%) has been observed regarding the constituents listed: eugenol (92,0); caryophyllene (17); eugenyl acetate (15); isoeugenol (0.5) (30).

In a LLNA study by RIFM, the clove leaf oil as used was reported to contain 85.3% eugenol, 9.9% caryophyllene and 2.2% alpha humulene, according to analyses of the supplier. The EC3 value was calculated to be 7.1% (225).

EVERNIA FURFURACEA LICHEN EXTRACT

CAS 90028-67-4; EC 289-860-8
(*Evernia furfuracea*, ext. = INCI)

Tree moss extract

Current regulation: /

Clinical data:

The Larsen 1977 study in 20 “perfume-sensitive patients” yielded n=6 positive reactions with “treemoss abs. in benzyl benzoate, 5% petrolatum” (18). In the IVDK 2007 study, 2.7% (95% CI: 2.0 – 3.6%) of 1658 consecutive patients had a positive reaction to “tree moss absolute” (4). In the Groningen 2009 study, 2.5% (95% CI: 1.1 – 4.9%) had positive reactions to the allergen, tested at 2%, i.e., twice the commonly used concentration, and not in pet., but in diethylphthalate (6). The IVDK 2010 study, 6.02% (95% CI: 4.90 – 7.14%; percentages standardised for age and sex) of 1947 patients PTed reacted to the compound (7). Additional information:

Syn.: *Pseudoevernia furfuracea* (L.) Zopf (53). The lichen grows on the bark of pine and fir trees. The extraction process with carbohydrate solvents yields a “concrete” (2-5% yield) which, in a next step eliminating waxy compounds, is extracted with warm alcohol and subsequent cooling, yielding an “absolute” (40-60% yield) (53).

EVERNIA PRUNASTRI

CAS 90028-68-5; EC 289-861-3
(*Evernia prunastri*, ext. = INCI)

Oak moss abs.

Current regulation: Annex III, part 1, n° 91

Clinical data:

In the “background information” section of the 1999 opinion, oak moss extract is classified as “most frequently reported allergen”; in consecutive PT patients, about 2.8% positive reactions had been reported (33). The German MAK commission has labelled oak moss extract as ‘sensitising to the skin’ (227).

Since the last SCCNFP-opinion of 1999, a “polymer based method” was developed to reduce the natural content of these two compounds from around 1 - several percent to < 75 ppm for atranol and < 25 ppm for chloratranol. However, PTing 14 subjects with previous positive PT reactions to the “oak moss” allergen preparation with the modified *Evernia prunastri* material still elicited positive reactions in 8/14 subjects; thus, the reduction in allergen content was deemed unsafe for the consumer (228). In a study of 885 consecutive eczema patients tested in Gentofte, Denmark, 3.2% had a positive or follicular patch test response to oak moss absolute. Two types of oak moss absolute were tested, one contaminated by resin acids and

one without any detectable resin acids. There was no difference in reactivity between the two types of oak moss absolute (229). The IVDK 2007 study yielded 2.2% (95% CI: 1.6 – 3.0%) positive reactions in 2063 consecutively tested patients (4). In the Groningen 2009 study, 1.9% (95% CI: 0.7 – 4.0%) had positive reactions to oak moss, tested at 2% pet., i.e., twice the commonly used concentration (6). In the An 2005 study, 6 of 422 consecutive patients, i.e., 1.4%, had positive reaction (13) (test concentration 2% pet.). In the Wöhrle 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded 5.0% positive reactions (22). The IVDK 2010 study, 1.81% (95% CI: 1.07 – 2.56%) of 1213 consecutively tested patients reacted to the compound, while 5.59% (95% CI: 4.90 – 6.27%) of 4482 of patients tested in a more aimed manner, partly as break-down testing to the FM I, had a positive PT reaction (7). In a study from Alicante, Spain, 86 selected patients were tested with *E. prunastri* extract, yielding 2 positive reactions (48).

L. Kanerva et al. report on a 41 year old female hairdresser in whom oak moss abs. contained in a perming solution (concentration in the product unknown) was unequivocally identified as allergen causing (i) occupational hand dermatitis and (ii) scalp dermatitis after application to the own hair (230). Another case of occupational hand dermatitis in a grinding engineer was, at least partly, attributable to contact sensitisation to "oak moss resin" contained in a soluble oil (231).

Additional information:

Source: *Evernia prunastri* (Oak moss) (*Evernia prunastri* var. *prunastri* L. Ach). Oak moss is extracted as described above. Chloratranol and atranol are the degradation products of chloratranorin and atranorin, resp., which are recognised as the main sensitisers in *Evernia prunastri* extracts.

ILLICIUM VERUM FRUIT OIL

CAS 84650-59-9, 8007-70-3; EC 283-518-1

"Anise Oil", *Star anise oil*

(*Star anise, Illicium verum*, ext. = INCI)

Current regulation: /

Clinical data:

In a study involving 100 consecutive patients, Rudzki and Grzywa found (i) a relatively high frequency of active sensitisation to star anise oil (n=5) tested with 0.5, 1 and 2% concentration (most likely in yellow petrolatum, as the other allergens in this series). Later patch testing with constituents of this essential oil (1%) in 3 patients yielded positive results to anethole in 3 cases, and to alpha-pinene and safrole in the 1 case tested to these substances. 34% of the consecutive patients reacted positively to star anise oil at 1%, which was considered as (marginally) non-irritating PT concentration (232).

Additional information:

ISO 4720:2009 nomenclature: *Illicium verum* Hook. f. *Illicium Verum* Fruit Oil is an essential oil distilled from the fruits of the Star Anise, *Illicium verum*, Illiciaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=40297>, last accessed 2010-01-29). The main component is trans-anethole (86-93%), which can be purified from star anise oil. Main uses are alcoholic beverages, food flavouring and oral care products (34, 39). For Oil of star anise, Chinese type (*Illicium verum* Hook. f.) an ISO standard exists: ISO 11016:1999.

JASMINUM GRANDIFLORUM FLOWER EXTRACT

CAS 84776-64-7; EC 283-993-5
(*Jasmine, Jasminum grandiflorum*,

<i>Jasmine abs.</i>	<i>ext. = INCI)</i>
JASMINUM OFFICINALE FLOWER OIL	CAS 90045-94-6; EC 289-960-1 (<i>Jasmine, Jasminum officinale</i> , <i>ext. = INCI)</i>
JASMINUM OFFICINALE OIL	CAS 8022-96-6; EC / (Oils, <i>jasmine</i>) INCI: JASMINUM OFFICINALE OIL

Current regulation: /

Clinical data:

In the Frosch 2002 b study, a total of 1.2% of 1606 consecutive patients had a positive PT to “jasmine absolute”, tested 5% in pet. (17). The deGroot 2000 study yielded 13 positive reactions to “jasmine, synthetic” in 1825 consecutively tested patients (12). In the early Larsen 1977 study, 18 of 20 “perfume sensitive patients” reacted to “Jasmin synthetic” 10% pet. (18), while 7 reacted to “Jasmin absolute” (10% pet.) – all of these also positive to the synthetic fragrance. The Sugiura 2000 study set in Nagoya, Japan, yielded 1% positive PT reactions in 1483 patients PTed for suspected cosmetic dermatitis, using 5% pet. as test concentration (14). The Larsen 2001 study in 178 patients with known contact allergy to fragrance ingredients found 16.9% positive reactions to jasmine absolute (10% pet.) (19). In the An 2005 study, 5 of 422 consecutive patients, i.e., 1.2%, had a positive reaction to Jasmine officinale oil (Jasmine absolute, Egyptian), tested at 2% (13). In the NACDG 2009 study, 1.1% of 4447 patients tested with “Jasmine absolute 2% pet.” were found PT-positive (21). The Belsito 2006 study (20) yielded 0.4% positive reactions to “jasmine absolute”. The Goossens 1997 study found 5 of 111 patients positive to “jasmine absolute” (10% pet.)– all sensitised to other fragrance allergens (23). In 63 patients positive to the FM I, 13 had positive PT reactions to “jasmine absolute”, 2% pet., and 12 to “jasmine synthetic”, 2% pet. in the Santucci 1987 study – the amount of concomitant reactivity was not examined (28). Nakayama et al. found 1974 (after (29)) 19 “strong positive” and 25 “weak positive” reactions to “jasmin oil” (unknown test concentration) in 183 patients. The IVDK 2010 c study identified 1.5% positive reactions in 3668 consecutively tested patients and 1.2% positive reactions in 982 patients tested in the context of a special series (30). In a study from Alicante, Spain, 86 selected patients were tested with jasmine absolute, yielding 3 positive reactions, and with “Jasmine synthetic”, also resulting in 3 positive reactions (48).

Additional information:

Jasminum Grandiflorum Flower Extract is an extract obtained from the flowers of the Spanish Jasmine, *Jasminum grandiflorum* L., Oleaceae

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=39752>, last accessed 2009-11-12).

Jasminum Officinale Flower Oil is an essential oil obtained by molecular distillation of the flowers from the Jasmine, *Jasminum officinale* L., Oleaceae

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=39754>, last accessed 2009-11-25).

Jasminum Officinale Oil is the volatile oil obtained from the flowers of the Jasmine, *Jasminum officinale* L., Oleaceae

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=34776>, last accessed 2010-01-05); this latter extract is used by Almirall/Hermal/Trolab for the preparation of a PT allergen.

Jasmine absolute is obtained by solvent extraction, via concrete, from the flowers of *J. grandiflorum* (L.) Aiton from China and India. The main volatile compound is benzyl acetate, however, minor compounds such as indole [120-72-9], cis-jasmone [488-10-8] and

methyl jasmonate [1211-29-6] contribute to the typical jasmine fragrance (34). Reported compounds include the following (maximum observed concentration given in parentheses): benzyl acetate (28); benzyl benzoate (24.0); phytol acetate (9); isophytol (8.5); phytol (7.4); linalool (7.0); eugenol (4.0); squalene (4); indole (3.5); benzyl alcohol (2.5); cis-jasmone (2.5); methyl linolenate (2.0); methyl palmitate (1.4); p-cresol (1.0); cis-3-hexenyl benzoate (1.0); benzyl salicylate (0.4); jasmin lactone (0.9); methyl jasmonate (0.7); isoeugenol (0.4) ((30), also according to (17))

JUNIPERUS VIRGINIANA OIL

CAS 8000-27-9; EC / (Oils, cedarwood) [this also refers to *Cedrus atlantica* ...] / 85085-41-2; EC 285-370-3 (*Juniper*, *Juniperus virginiana*, ext. = INCI)
CAS 85085-41-2; EC 285-370-3

JUNIPERUS VIRGINIANA WOOD OIL
Cedar Wood Oil (Virginian)

Current regulation: /

Clinical data:

In the Frosch 2002 b study, a total of 0.6% of 1606 consecutive patients had a positive PT to “cedarwood oil (Moroccan and Chinese 1:1)”, tested 10% in pet. (17). After application of Penaten-baby™ oil as immersion oil for dermatoscopy a patient developed multiple patches of eczema at the application sites. Investigation revealed that the oil was kept in a bottle previously used for *Juniperus virginiana* oil, to which contact sensitisation was verified by patch testing (233).

Additional information:

ISO 4720:2009 nomenclature: *Juniperus virginiana* L.. *Juniperus Virginiana* Oil is the volatile oil obtained from the fruits and leaves of the Red Cedar, *Juniperus virginiana* L., Cupressaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=78070>, last accessed 2010-01-05)

Juniperus Virginiana Wood Oil is an essential oil obtained from the wood and twigs of the Red Cedar, *Juniperus virginiana* L., Cupressaceae. It contains chiefly (alpha and beta) cedrene and cedral (cedar camphor), cuparene, thujopsene, widdrol (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=39767>, last accessed 2009-11-12)(233). According to Surburg/Panten by GC: alpha-cedrene 22-35%, thujopsene 10-25%, cedrol 16-25% (34).

See also *Cedrus atlantica*. According to (30) the maximum observed concentration in cedar wood oil are (in %): α-cedrene (32); thujopsene (25); cedrol (25); β-cedrene (6); widdrol (5) and cuparene (traces) (30).

For Oil of cedarwood, Virginian (*Juniperus virginiana* L.) an ISO standard is available: ISO 4724:2004. For Oil of cedarwood, Texas (*Juniperus mexicana* Schiede) an ISO standard exists: ISO 4725:2004.

LAURUS NOBILIS OIL

CAS 8002-41-3; EC / (Oils, laurel)
INCI: *LAURUS NOBILIS OIL* / 8007-48-5; EC / (Oils, sweet bay)/ 84603-73-6; EC 283-272-5 (*Laurus nobilis*, ext.) INCI: *LAURUS NOBILIS EXTRACT*

Laurel oil

Current regulation: Annex II, n° 359 (seed oil)

Clinical data:

In the Wöhrle 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded n=4 (0.6%) positive reactions to “laurel oil” 2% pet. (22).

After sensitisation by a one-time occlusive application a 36 year old Turkish patient developed widespread allergic contact dermatitis 3 days after massage with olive oil containing *Laurus nobilis* oil; sensitisation was proven by a strong positive reaction to the commercial test preparation and the massage oil previously used (234). Topical application of laurel oil for knee arthropathy led to an erythema exudativum multiforme-like rash on the legs of a 63 year old patient; interestingly, laurel oil yielded a “target like” strongly positive PT reaction in this case (235). In an earlier Turkish case with a similar history, the EEM-like appearance was lacking; however, a very intense, edematous reaction was noted (236). In a series of 40 of 744 consecutive patients PTed with an extended fragrance series (Sheffield 1999), 2 positive reactions to “laurel oil” were observed (3). The IVDK 2010 c study identified 1.0% positive reactions in 6297 patients tested in the context of a special series (30).

Additional information:

ISO 4720:2009 nomenclature: *Laurus nobilis* L. Laurel leaf oil is obtained by steam distillation of leaves from *Laurus nobilis* L. (Lauraceae), an evergreen cultivated primarily in the Mediterranean countries. The main components are 1,8-cineole (30-70%), linalool (about 10%) and eugenol (34). According to (30) the maximum observed concentration in laurel oil are (in %): 1,8-cineole (70); β -caryophyllene (11); linalool (11); limonene (5.0); eugenol (2.0); geraniol (0.3) (30).

LAVANDULA HYBRIDA HERB OIL

CAS 91722-69-9; EC 294-470-6
(Lavender, *Lavandula hybrida*, ext.
= INCI)

Lavandin Oil

Current regulation: /

Clinical data:

The Rudzki 1976 study found 1 positive reaction in 200 patients to “lavandin” essential oil, 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=4 (4.6%) positive reactions to “lavandin” essential oil 2% pet. (27). In the Frosch 1995 dose-finding pilot study, no positive reaction to 1% and 5% lavandin oil in pet., tested in 205 consecutive patients in Dortmund and Göttingen, and just 1 irritant reaction to the higher concentration, were observed (15).

Additional information:

ISO 4720:2009 nomenclature: *Lavandula angustifolia* Mill. x *Lavandula latifolia* Medik.

Lavandula Hybrida Herb Oil is an essential oil distilled from the flowering herbs of the Lavandin, *Lavandula hybrida*,

Labiatae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=39789>), last accessed 2010-01-29. Nomenclature according to Surburg/Panten:

Lavandula x *intermedia* Lois, which is a hybrid of lavender and spike (see below) (34). The oils from the most important variants, abrial and grosso, contain linalool (24-38%), linalyl acetate (20-38%) as well as 1,8-cineole (4-11%), and camphor (6-11%) (34). A third variant is called super because of its high concentration of linalyl acetate (35-47%), more closely resembling lavender oil (34). For Oil of lavandin Grosso (*Lavandula angustifolia* Mill. x *Lavandula latifolia* Medik.), French type an ISO standard exists: ISO 8902:2009, for Oil of

lavandin Abrial (*Lavandula angustifolia* Miller x *Lavandula latifolia* Medikus), French type a different ISO standard: ISO 3054:2001.

It is a “top 100” substance (IFRA, pers. comm.2010)

Considering the content of well-known allergenic compounds, this essential oil is regarded as established contact allergen in humans.

LAVANDULA OFFICINALIS FLOWER OIL

CAS 84776-65-8, 8000-28-0; EC 283-994-0 (*Lavender, Lavandula angustifolia angustifolia*, ext. = INCI)

Lavender oil

Current regulation: /

Clinical data:

In a large series from Nagoya, Japan, 1483 patients were tested with lavender oil 20% in pet., with overall 3.7% positive reactions from 1990 to 1998. However, within this period, a sharp increase was noted in 1997 and 1998, which as attributed to changed exposure by M. Sugiura et al. (14). On the individual level, relevance of positive reactions remained unclear in about half of the cases. The Coimbra 2000 study found in 67 patients with positive reaction to the FM I who were tested with "lavender absolute" (2% pet.) 6.6% positive reactions (9). In the An 2005 study, 5 of 422 consecutive patients, i.e., 1.2%, had positive reactions to “*Lavandula angustifolia* oil” (Lavender absolute) 2% (13). The Goossens 1997 study found 4 of 111 patients positive to “lavender oil 20% pet.”– all of them sensitised to other fragrance allergens (23). The Rudzki 1976 study found no positive reaction in 200 patients to “lavender” essential oil, 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=3 (3.5%) positive reactions to “lavender” essential oil 2% pet. (27). Nakayama et al. found 1974 (after (29)) 6 “strong positive” reactions to “Lavender oil” (unknown test concentration) in 183 patients. In a study from Alicante, Spain, 86 selected patients were tested with “lavender absolute”, yielding 2 positive reactions (48). R. Goiriz et al. report on a case of photo contact allergy (10 controls negative) in a 45 year old woman developing after application of a ketoprofen-containing topical gel (“Fastum”)(237). A physiotherapist developed acute, recurrent dermatitis after use of “Diffiam® gel”, scented with lavender oil. Both the gel and lavender oil (2% pet.) tested positive; avoidance resulted in clearing (238). In a study on 218 patients with known contact allergy to fragrance ingredients, Larsen (2002 c) found positive reactions to 10% lavender oil (pet.) in 2.8% of these (1). A case of vulvovaginitis with spread and affecting the dominant hand applying various tea tree and lavender oil creams was reported by S. Varma; the PT with 10% lavender oil abs. in pet. (50 controls negative) was positive (239). In two cases, facial “pillow dermatitis” due to lavender oil, applied to the pillows, developed, confirmed by positive PT to lavender abs. (2% pet.) (240).

Additional information:

ISO 4720:2009 nomenclature: *Lavandula angustifolia* Mill. *Lavandula officinalis* Flower Oil is an essential oil obtained from the fresh flowering tops of the Lavender, *Lavandula officinalis* (syn: *L. vera*), *Labiatae*. It contains 30-40% esters calculated as linalyl acetate, linalool, pinene, limonene, geraniol, some eucalyptol (cineol) (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=40370>, last accessed 2009-11-09). According to Surburg/Panten, lavender oil is obtained by steam distillation of freshly cut flowering tops of *Lavandula angustifolia* Mill. (Lamiaceae). Main constituents according to GC are linalyl acetate (25-45%), cis-ocimene (4-10%), trans-ocimene (1.5-6%), 1,8-cineole (≤ 1%) camphor (≤ 0.5%), linalool (25-38%), 1-terpinen-4-ol

(2-6%) and lavandulyl acetate [25905-14-0] ($\geq 2\%$) (34).

In addition to distillation, both *Lavandula officinalis* and *Lavandin* are also solvent extracted, yielding concretes and, after ethanol extraction, absolutes, which are said to have a longer-lasting odour (34).

For Oil of lavender (*Lavandula angustifolia* Mill.) an ISO standard exists: ISO 3515:2002.

LAVANDULA SPICA HERB OIL

CAS 97722-12-8; EC 307-762-6
(Lavender, *Lavandula spica*, ext. =
INCI

"Spike Oil"

Current regulation: ...

Clinical data:

The Rudzki 1976 study found 1 positive reaction in 200 patients to "spike" essential oil, 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=8 (9.3%) positive reactions to "spike" essential oil 2% pet. (27).

Additional information:

ISO 4720:2009 nomenclature: *Lavandula latifolia* Medik. *Lavandula Spica Herb Oil* is an essential oil distilled from the flowering herbs of the Spikenard, *Lavandula spica* (syn: *Lavandula latifolia*), *Labiatae*. It contains eucalyptol (35%), camphor, linalool, borneol, terpineol, D-camphene and sesquiterpenes (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=40372>, last accessed 2010-01-29). According to Surburg/Panten, Spanish spike lavender oil is steam distilled from the flowering tops of *Lavandula latifolia* Medik.. The main components are linalool (34-50%), 1,8-cineole (16-39%) and camphor (8-16%) (34). For Oil of spike lavender (*Lavandula latifolia* (L.f.) Medikus), Spanish type an ISO standard exists: ISO 4719:1999

Considering the content of well-known allergenic compounds, this essential oil is regarded as established contact allergen in humans.

LITSEA CUBEBA FRUIT EXTRACT

CAS 90063-59-5, 68855-99-2; EC
290-018-7 (*Litsea cubeba*, ext.) INCI:
LITSEA CUBEBA OIL

Current regulation: ...

Clinical data:

The Rudzki 1976 study found 3 positive reaction in 200 patients to "Litsea cubeba" essential oil 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=7 (8.1%) positive reactions to this essential oil 2% pet. (27).

Additional information:

ISO 4720:2009 nomenclature: *Litsea cubeba* (Lour) Pers. *Litsea Cubeba Fruit Extract* is an extract obtained from the fruits of the plant, *Litsea cubeba*, *Lauraceae* (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=40036>, last accessed 2009-11-24). The content by GC is: neral (25-33%), geranial (38-45%) – i.e. about $\frac{3}{4}$ citral, for which the extract had previously served as a raw material (34); direct use for perfuming is limited to household products (39). For Oil of *Litsea cubeba* (*Litsea cubeba* Pers.) an ISO standard exists: ISO 3214:2000.

In a LLNA study by RIFM, the “Litsea cubeba oil” as used was reported to contain 85.7% citral, 2.9% limonene, 1.7% linalool, 1.4% citronellal and < 1% caryophyllene and methyl heptanone, according to analyses of the supplier. The EC3 value was calculated as 8.4 % (225).

Considering the content of well-known allergenic compounds, this essential oil is regarded as established contact allergen in humans.

MENTHA ARVENSIS LEAF OIL
Cornmint oil

CAS 68917-18-0 ; EC /
 INCI: MENTHA ARVENSIS OIL

Current regulation: /

Clinical data: /

Additional information:

Mentha Arvensis Leaf Oil is the oil derived from the leaves of the Horse Mint, Mentha arvensis L., Labiatae

http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details_v2&id=57860

It is a “top 200” substance and classified as R43 (IFRA, pers. comm.2010)

MENTHA PIPERITA OIL

CAS 8006-90-4; EC / (Oils,
 peppermint) INCI: MENTHA
 PIPERITA OIL / 84082-70-2; EC
 282-015-4 (Peppermint, ext.) INCI
 names: MENTHA PIPERITA ...

Peppermint oil

Current regulation: /

Clinical data:

In the Frosch 2002 b study, 0.6% of 1606 consecutive patients reacted positively to “peppermint oil (American)”, tested 2% in pet. (17). In a series of 40 of 744 consecutive patients PTed with an extended fragrance series (Sheffield 1999), 2 positive reactions to "peppermint oil" were observed (3). In the Wöhrle 2001 study, PTing 747 patients with suspected contact allergy to fragrance ingredients yielded n=1 (0.1%) positive reactions to peppermint oil 2% pet. (22). Among 512 patients referred from a dental department for diagnostic work-up of various intraoral symptoms and complaints within 4 years, 6 patients had positive (+ to +++) PT reactions to “peppermint oil” 1% pet. at D4, mostly combined with positive reactions to menthol (see above) and reporting dramatic improvement after cessation of use of peppermint-containing oral products (154). The Rudzki 1976 study found 1 positive reaction in 200 patients to “Peppermint” essential oil, 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=6 (6.9%) positive reactions to “peppermint” essential oil 2% pet. (27). In 63 patients positive to the FM I, 3 had positive PT reactions to peppermint oil, 2% pet., in the Santucci 1987 study (28). The IVDK 2010 c study identified 0.6% positive reactions in 6546 patients tested in the context of a special series (30).

An unusual case of “baboon-like” allergic contact dermatitis of the vulva after drinking excessive amounts of a herbal tea containing, among other ingredients, peppermint. While the PT reaction to peppermint oil was only weak to doubtful, dramatic improvement after cessation and prompt relapse after repeat ingestion proved the diagnosis (241). Recurrent foot and lower leg dermatitis after the application of a “foot spray” (containing peppermint

oil) was diagnosed as allergic contact dermatitis due to this ingredient in a 59 year old golf player (242). In another case, ACD after application of a transdermal system for the treatment of lumbar pain was attributed to CA to peppermint oil (2% pet.) and its main ingredient menthol (1% pet.) (155). In a patient with toothpaste-induced cheilitis, not only *M. piperita*, but also *M. arvensis*, but not *M. spicata* or *cardica* extracts (all tested 1% pet.), as well as natural and synthetic menthol caused positive PT reactions (243).

Additional information:

ISO 4720:2009 nomenclature: *Mentha x piperita* L. A standard by ISO exists for Oil of peppermint (*Mentha x piperita* L.): ISO 856:2006. A review by the Cosmetic Ingredient Review Expert Panel, Washington, DC on the “Final report on the safety assessment of *Mentha Piperita* (Peppermint) Oil, *Mentha Piperita* (Peppermint) Leaf Extract, *Mentha Piperita* (Peppermint) Leaf, and *Mentha Piperita* (Peppermint) Leaf Water” is available (163), stating that “Peppermint Oil is used at a concentration of < or = 3% in rinse-off formulations and < or = 0.2% in leave-on formulations. Peppermint Oil is composed primarily of menthol and menthone. Other possible constituents include pulegone, menthofuran, and limone. According to Surburg/Panten: (-)-menthol (34-46%), (-)-menthone (15-27%), (-)-menthyl acetate (2.5-7%) and menthofuran [17957-94-7] (0.5-6%) (34). According to (30) the maximum observed concentration in peppermint oil are (in %): (-)-menthol (49); (-)-menthone (28); (-)-menthyl acetate (8); mentofuran (8); isomenthone (8); neo menthol (6); pulegone (3.5); limonene (3.0); linalool (0.4) (30). Most of the safety test data concern Peppermint Oil. The oil is considered to present the “worst case scenario” because of its many constituents, so data on the oil were considered relevant to the entire group of ingredients. ... Repeated intradermal dosing with Peppermint Oil produced moderate and severe reactions in rabbits” concluding that “with the limitation that the concentration of pulegone in these ingredients should not exceed 1%, it was concluded that *Mentha Piperita* (Peppermint) Oil, *Mentha Piperita* (Peppermint) Extract, *Mentha Piperita* (Peppermint) Leaves, *Mentha Piperita* (Peppermint) Water are safe as used in cosmetic formulations”.

MENTHA SPICATA HERB OIL

Spearmint oil

CAS 84696-51-5, 8008-79-5; EC
283-656-2 (Spearmint, ext.)
INCI: *MENTHA VIRIDIS*
EXTRACT

Current regulation: /

Clinical data:

In the Frosch 2002 b study, 0.8% of 1606 consecutive patients reacted positively to “spearmint oil (American)”, tested 2% in pet. (17). The CAS # quoted (8008-79-5) refers, according to CosIng, to *MENTHA VIRIDIS LEAF OIL*, the volatile oil obtained from the dried tops and leaves of the Garden Mint, *Mentha viridis* L., Labiatae. The Larsen 2001 study diagnosed 5.0% positive reactions in 178 patients with known contact allergy to fragrance ingredients, using this oil at 5% pet. test concentration (19). In the An 2005 study, 6 of 422 consecutive patients, i.e., 1.4%, had positive reactions to “*Mentha viridis* oil” 5% (13). PT results with toothpaste ingredients were positive in 7 patients, of whom 4 had strong positive reactions to spearmint (244).

Additional information:

ISO 4720:2009 nomenclature: *Mentha spicata* L. *Mentha Spicata* Oil is an essential oil obtained from the herbs of the Spearmint, *Mentha spicata* L., Labiatae (syn: *Mentha viridis* L., Labiatae). It contains carvone (more than 50%), limonene, pinene

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=4>)

[0394](#), last accessed 2009-11-11). According to Surburg/Panten, the content is limonene (9-16.5%), (-)-carvone (60-70%), menthone (0-0.2%) and viridiflorol (0-0.5%) (34). Exposure by toothpastes, and subsequent contact allergic reaction of the lips or the oral mucosa, have been reported (e.g., (245, 246)). L-Carvone is a component of the oil from *Mentha spicata* (spearmint) (53) and had been tested with positive results in “toothpaste cases”, even at a concentration as low as 0.067% (68).

For Oil of spearmint -- Part 1: Native type (*Mentha spicata* L.) an ISO standard exists: ISO 3033-1:2005, for Oil of spearmint -- Part 2: Chinese type (80 % and 60 %) (*Mentha viridis* L. var. *crispa* Benth.), redistilled oil: ISO 3033-2:2005, for Oil of spearmint -- Part 3: Indian type (*Mentha spicata* L.), redistilled oil: ISO 3033-3:2005 and for Oil of spearmint -- Part 4: Scotch variety (*Mentha x gracilis* Sole): ISO 3033-4:2005.

MYROXYLON PEREIRAE RESIN

CAS 8007-00-9; EC 232-352-8

(Balsams, Peru)

Balsam of Peru

INCI: MYROXYLON PEREIRAE
/ Balsams, Peru

Current regulation: Annex III, part1, n° 154

Clinical data:

This natural mixture has been employed as screening agent in Baseline series worldwide for many decades. Hence, a wealth of data is available; table 3.2 – 1 summarises results of the past 10 years.

Additional information:

ISO 4720:2009 nomenclature: *Myroxylon pereirae* (Royle) Klotzsch, syn. *Myroxylon balsamum* var. *pereirae* (Royle) Harms. *Myroxylon pereirae* resin (MPR, Balsamum peruvianum) is harvested from the balsam of Peru tree, *Myroxylon balsamicum* (L.) HARMS var. *pereirae* (ROYLE) HARMS, synonymous *Myroxylon pereirae* (ROYLE) KLOTZSCH (247) after thermal stress, almost exclusively in El Salvador. Main constituents of the pleasantly, vanilla-like smelling dark brown liquid are benzyl esters of cinnamic and benzoic acid (35 – 75%), up to 30% cinnamic acid, up to about 10% benzoic acid, approximately 5% alpha- and beta-nerolidol, benzyl alcohol and mostly less than 1% cinnamyl alcohol, benzyl ferulate and -isoferulate, cinnamic acid amyl ester, coniferyl alcohol, coniferyl benzoate, eugenol, isoeugenol, farnesol, vanillin, and several trace constituents (248-251). The composition of MPR varies with the origin and other factors; moreover, MPR is sometimes blended with other natural mixtures such as turpentine, styrax or colophonium (247).

MPR can be used to improve taste or smell in gargling solutions, cosmetic products such as soaps, shampoo or lipsticks, as well as sweets, tobacco and beverages (247, 252). According to EU legislation and IFRA guidelines MPR should not be used in products intended for skin contact; however, extracts and distillates of MPR may be used in a concentration of < 0,4% (IFRA-Guidelines, www.ifraorg.org (253)). E. Temesvári et al. report on the interesting case of severe ACD with subsequent hypopigmentation after a “temporary henna tattoo”, which was, unexpectedly, not due to p-phenylene diamine, but to the oil used to disperse the pigment, which presumably contained allergens also included in the FM I and MPR, both of which were extreme positive on a later PT (254).

In addition to delayed type hypersensitivity reactions, MPR (and some of his constituents such as benzoic acid (255)) are capable of eliciting (non-immunological) urticarial immediate reactions (256-258). In one case, the immediate reaction to MPR (and to FM I) at the test site spread systemically in terms of a generalised urticaria, while no delayed type reactions were observed to the PT (259). Generally, there is apparently no association of immediate reactions to MPR (and cinnamal or cinnamyl alcohol) and contact sensitisation to these

compounds (260). In animal experiments the sensitising potency of MPR was clearly established (248), with coniferyl benzoate identified as single compound with the most marked potency (250). However, due to the limited chemical stability of this compound is unclear whether other, more stable compounds are, in fact, more important allergens, such as cinnamic acid and (iso-) ferulic acid esters or oxidised constituents of the resin fraction (261).

Table 3.2.2 – 1: Results with contact allergy to fragrance ingredients screening agents reported since 1999 in patients patch tested for suspected allergic contact dermatitis: **Myroxylon pereiarae resin** (Balsam of Peru) 1). If not given in the publication, the confidence interval (CI) was calculated from the absolute numbers by the reviewers.

Country	Population	Years	No. tested	Crude % positive (95% CI) [§]
Tel Aviv, Israel (262) #	Consecutive patients	1999-2000	943	6.6 % (5.1 – 8.4) [§]
South Korea (13)	Consecutive patients	04/2002 – 06/2003	422	7.3% (5.1 – 10.3%) [§]
Tel Aviv, Israel (263)	Consecutive patients	1998-2004	2156	3.6 % (2.9 – 4.5) [§]
Manipal, India (264)	Dermatitis patients	1989-1998	1780	n=17
Tehran, Iran (265)	Consecutive patients	2002-2004	250	2.4 % (0.9 – 5.2) [§]
Sevilla, Spain (266)	Consecutive patients	2002-2004	863	5.8 % (4.3 – 7.6) [§]
Ankara, Turkey (267)	Consecutive patients	1992-2004	1038	2.1 % (1.3 – 3.2) [§]
Vienna, Austria (22)	Consecutive patients of one clinic	1997-2000	2660	5.4% (4.6 – 6.3%) [§]
Czech Republic (268)	Consecutive patients	1997-2001	12058	7.3% (6.8 – 7.8) [§]
Copenhagen, Denmark (269)	Consecutive patients	1985-2007	16173	3.9 % (3.6 – 4.2) [§]
Sweden (270)	Consecutive patients	2000	3790	6.5%
9 European countries (271) \$	Consecutive patients	2002-2003	9672	6.1 %
Germany, 3 Swiss + 1 Austrian Dept. (7)	Consecutive patients	2005-2008	36919	8.0% (7.7 – 8.3%)
10 depts. From 7 EU countries (272) *	Consecutive patients	1996-2000	26210	6.0 %
USA (Canada) (20)	Probably consecutive patients	2003	1603	6.6%
NACDG 2009 (21)	Consecutive patients	2005-2006	4449	11.9%

[§] Calculated by reviewers, where possible (if actual numbers were given)

Probably included in (263)

\$ > 5-fold difference between departments

* About 4-fold difference between departments

NARCISSUS SPP. EXTRACT / OIL

CAS: *diverse*

Narcissus abs.

Current regulation: /

Clinical data:

In the Frosch 2002 b study, 1.3% positive reactions to “narcissus absolute” (2% pet.) were observed in 1606 consecutive (17). The extract used by the PT allergen provider Almirall/Hermal/Trolab has the CAS number 90064-25-8. The IVDK 2010 c study identified 0.5% positive reactions in 2445 consecutively tested patients and 0.6% positive reactions in 809 patients tested in the context of a special series (30).

Additional information:

Commonly used: *Narcissus poeticus* L. According to (30) the maximum observed concentration in *Narcissus abs.* are (in %): α -terpineol (23.7); trans-Isoeugenol methyl ether (20); benzyl benzoate (20); coumarin (5.7); benzyl alcohol (4.0); Δ^3 -carene (3.4); cinnamyl alcohol (2.5); phenylethyl alcohol (2.2); ethyl palmitate (2.2); phenylpropyl acetate (1.7); 1,8-cineole (1.5); caryophyllene (1.0); benzyl acetate (0.7); isoeugenol (0.5); farnesol (0.3) (also according to (17)) (30).

OCIMUM BASILICUM HERB OIL

CAS 84775-71-3; EC 283-900-

8 (*Ocimum basilicum*, ext. = INCI)

Basil Oil (sweet)

Current regulation: /

Clinical data:

/

Additional information:

ISO 4720:2009 nomenclature: *Ocimum basilicum* L. For Oil of basil, methyl chavicol type (*Ocimum basilicum* L.) an ISO standard exists: ISO 11043:1998. *Ocimum Basilicum* Herb Oil is an essential oil obtained from the herbs of the Sweet Basil, *Ocimum basilicum* L., *Labiatae*.

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=40474>, last accessed 2009-11-24). The chemical composition varies greatly with the origin (34):

- Basil oil of the methylchavicol type (Réunion type) is extracted from flowering tops or whole plants from Réunion, Comores, Madagascar, but also other countries such as Egypt. Mainly used for seasoning food. Content by GC: methylchavicol 75-87%, linalool 0.5-3%
- Basil oil, linalool type is produced mainly in the Mediterranean area. Content by GC: Linalool 45-62%, methylchavicol trace to 30%, eugenol 2-15%
- Indian Basil oil is produced exclusively in India. Content by GC: methylchavicol trace to 70%, linalool 25%.

In a LLNA study by RIFM, the basil oil as used was reported to contain 51% linalool, 10.4% eugenol, 7.7% cineol, 3.7% bergamotene, 2.7% germacrene D, 2.7% cadinol and 1.3% cadinene, according to analyses of the supplier. The EC3 value was calculated to be < 2.5% (225).

PELARGONIUM GRAVEOLENS FLOWER OIL

CAS 90082-51-2; EC 290-140-0
(*Pelargonium graveolens*, ext. =
INCI) / 8000-46-2; EC / (Oils,
geranium) INCI: GERANIUM

Geranium Oil Bourbon

Current regulation: /

Clinical data:

The Coimbra 2000 study found in 67 patients with positive reaction to the FM I who were tested with "geranium oil Bourbon" (2% pet.) 7.4% positive reactions (9). In the Larsen 2001 study, 8.4% positive reactions were observed in 178 patients with known contact allergy to fragrance ingredients ("geranium oil Bourbon", 10% pet.) (19). The Goossens 1997 study found 3 of 111 patients positive to "geranium oil 20% pet." – all sensitised to other fragrance allergens (23). The Rudzki 1976 study found 3 positive reactions in 200 patients to "geranium" essential oil 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=2 (2.3%) positive reactions to "geranium" essential oil 2% pet. (27). Nakayama et al. found 1974 (after (29)) 3 "strong positive" reactions to "Geranium oil" (unknown test concentration) in 183 patients, Trattner/David 1 / 641 consecutive patients positive to "Geranium oil" (31). In a study from Alicante, Spain, 86 selected patients were patch tested with an extended fragrance series; n=8 reacted positively to geranium oil bourbon (48).

Additional information:

ISO 4720:2009 nomenclature: *Pelargonium x ssp.* For Oil of geranium (*Pelargonium X ssp.*) an ISO standard exists: ISO 4731:2006 *Pelargonium Graveolens Flower Oil* is the volatile oil obtained from the flowers of the Bourbon Geranium, *Pelargonium graveolens* L. Hér. Ex Aiton, *P. roseum* Willdenow (and other nondefined hybrids that have developed in different regions of the world) Geraniaceae

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=57527>, last accessed 2009-11-16)(34). The Bourbon type (Réunion, Madagascar) is more valuable than the North African and Chinese products, and differs in characteristic components: (-)-6,9-guaiadiene [36577-33-0] 5-9% in the Bourbon type, and 10-epi-gamma-eudesmol [15051-81-7] 3-6% in the African type, in addition to the main components (-)-citronellol, isomenthone, formates and tiglates. Chinese oil is similar to Bourbon oil, however, it contains more citronellol (32-43%) and lower amounts of linalool (2-4.5%) and geraniol (5-12%) (34).

In a LLNA study by RIFM, the geranium oil as used was reported to contain 41.1% citronellol, 9.8% 2,6-guiadine, 6.2% isomethone, 4.9% geraniol, 2.2% cis-rose oxide, 2.1% linalool, 1.5% geranyl formate, 1.3% phenyl ethyl tiglate, 1.0% trans-rose oxide, and geranyl tiglate and alpha-pinene at < 1%, according to analyses of the supplier. The EC3 value was calculated to be > 50% (225).

PELARGONIUM ROSEUM LEAF OIL

CAS 90082-55-6; EC 290-144-2
(*Pelargonium roseum*, ext. = INCI)

Geranium Oil; Rose Geranium Oil

Current regulation: /

Clinical data:

In the Sugiura 2000 study, among 1483 patients with suspected cosmetic dermatitis, 2.1%

positive PT reactions to "geranium oil" (tested 20% in pet.) were observed (14).

Additional information:

Pelargonium Roseum Leaf Oil is an essential oil obtained from the leaves of the plant,

Pelargonium roseum, Geraniaceae

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=40565>, last accessed 2009-11-16).

PIMENTA RACEMOSA LEAF/FRUIT OIL

CAS 85085-61-6; EC 285-385-5

Bay oil (34)

Current regulation: /

Clinical data:

/

Additional information:

ISO 4720:2009 nomenclature: *Pimenta racemosa* (Mill.) J.W. Moore. For Oil of bay [*Pimenta racemosa* (Mill.) J.W. Moore] an ISO standard exists: ISO 3045:2004 *Pimenta Racemosa* Leaf/Fruit Oil is an essential oil obtained from the fruits of the plant, *Pimenta racemosa*,

Myrtaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=41014>, last accessed 2010-02-10).

Steam distillation of the leaves of *Pimenta racemosa* (Mill.) J.W. Moore (Myrtaceae) yields bay oil, which consists of myrcene (20-30%), eugenol (42-56%) and chavicol (8-13%) (34). Considering the content of well-known allergenic compounds, this essential oil is regarded as established contact allergen in humans.

***Pinus mugo* leaf and twig oil and extract**

CAS 90082-72-7, 8000-26-8; EC 290-163-6

Dwarf pine needle oil

(German: Latschenkiefernöl)

Current regulation: Annex III, part 1, 109

Clinical data:

In the Frosch 2002 b study, 0.7% positive reactions to dwarf pine needle oil (2% pet.) were observed in 1606 consecutive (17). The Rudzki 1976 study found 4 positive reactions in 200 patients to "Pine needle" essential oil, 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=3 (3.5%) positive reactions to "pine needle" essential oil 2% pet. (27).

Additional information:

ISO 4720:2009 nomenclature: *Pinus mugo* Turra syn. *Pinus montana* Mill.) *Pinus Mugo* Twig Oil is an essential obtained from the twigs of the Pine, *Pinus mugo*,

Pinaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=41476&back=1>, last accessed 2010-03-09). *Pinus Mugo* Twig Leaf Extract is an extract obtained from the twigs leaves of the Pine, *Pinus mugo*,

Pinaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=41473&back=1>, last accessed 2010-03-09).

Dwarf pine needle oil is obtained from *Pinus mugo* Turra subsp. *mugo* and subsp. *pumilio* (Haenke) Franco (34). For Oil of dwarf pine (*Pinus mugo* Turra) an ISO standard exists: ISO 21093:2003. American pine oils contain almost no 3-carene or camphene (34).

PINUS PUMILA TWIG LEAF EXTRACT / OILCAS 97676-05-6; EC 307-681-6
(Pine, *Pinus pumila*, ext. = INCI)*Dwarf pine needle oil*

Current regulation: Annex III, part 1, 114

Clinical data: /

Additional information:

Pinus Pumila Twig Leaf Extract obtained from the twigs leaves of the Pine, *Pinus pumila*, Pinaceae

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=41483&back=1>, last accessed 2009-11-12), *Pinus Pumila* Twig Leaf Oil is the essential oil obtained from the twigs leaves of the Pine, *Pinus pumila*, Pinaceae

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=41484&back=1>, last accessed 2009-11-12). Main constituents are alpha-pinene (60-70%) and beta-pinene (20-25%). (34) Occurrence from Siberia to Japan, classified as Endangered Species

Considering the content of well-known allergenic compounds, this essential oil is regarded as established contact allergen in humans.

POGOSTEMON CABLIN OILCAS 8014-09-3; EC / (Oils,
patchouli) / 84238-39-1; EC 282-
493-4 (*Patchouli*, ext.)*Patchouli oil*INCI: POGOSTEMON CABLIN /
Patchouli, ext.

Current regulation: /

Clinical data:

In the Frosch 2002 b study, 0.8% positive reactions to patchouli oil (10% pet.) in 1606 consecutive were observed (17). Nakayama et al. found 1974 (after (29)) 3 “strong positive” and 8 “weak positive” reactions to “Patchouli oil” (unknown test concentration) in 183 patients. The IVDK 2010 c study identified 0.6% positive reactions in 2446 consecutively tested patients and 1.4% positive reactions in 828 patients tested in the context of a special series (30).

Additional information:

ISO 4720:2009 nomenclature: *Pogostemon cablin* (Blanco) Benth. syn. *Mentha cablin* Blanco. An ISO standard is available for Oil of patchouli (*Pogostemon cablin* (Blanco) Benth.): ISO 3757:2002. *Pogostemon Cablin* Leaf Oil is an essential oil obtained from the fermented leaves of the Patchouli, *Pogostemon cablin* (syn: *Pogostemon patchouli*), *Labiatae* (Lamiaceae (34)). It contains patchouli alcohol, beta-patchoulene, azulene, eugenol, sesquiterpenes

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=40927>, last accessed 2009-11-12). Although the sesquiterpene alcohol (-)-patchoulol [5986-55-0] is the main component of patchouli oil (27-35%), the compound largely contributing to the characteristic odour is norpatchoulol [41429-52-1] (0.35-1%). Other constituents include (+)-alpha-bulnesene [6391-11-0] (13-21%), (-)-alpha-gujene [3691-12-1] (11-16%), (-)-β-patchoulene [514-51-2] (1.8-3.5%) and (-)-seychellene [20085-93-2] (1-3%) (34). According to (30) the maximum observed concentration in patchouli oil are (in %): (-)-patchoulol (35); (+)-alpha-lulnesene (21); (-)-alpha-gujene (16); β-pinene (6); (-)-β-patchoulene (3.5); (-)-seychellene (3); pogostol (2.5); α-pinene (2.5); norpatchoulol (1)

(30).

It is a “top 100” substance (IFRA, pers. comm.2010).

ROSE FLOWER OIL (ROSA SPP.)	CAS 8007-01-0; EC / (Oils, rose)
ROSA ALBA FLOWER EXTRACT	CAS 93334-48-6; EC 297-122-1 (Rose, <i>Rosa alba</i> , ext. = INCI)
ROSA CANINA FLOWER OIL	CAS 84696-47-9; EC 283-652-0 (Rose, <i>Rosa canina</i> , ext.) INCI: ROSA CANINA
ROSA CENTIFOLIA FLOWER OIL	CAS 84604-12-6, EC 283-289-8 (Rose, <i>Rosa centifolia</i> , ext.) INCI: ROSA CENTIFOLIA / Rose, <i>Rosa centifolia</i> , ext.
ROSA DAMASCENA FLOWER OIL	CAS 90106-38-0; EC 290-260-3 (Rose, <i>Rosa Damascena</i> , ext. = INCI)
ROSA GALLICA FLOWER OIL	CAS 84604-13-7; EC 283-290-3 (Rose, <i>Rosa Gallica</i> , ext.) INCI: ROSA GALLICA
ROSA MOSCHATA OIL	--
ROSA RUGOSA FLOWER OIL	CAS 92347-25-6; EC 296-213-3 (Rose, <i>Rosa rugosa</i> , ext.)

Current regulation: /

Clinical data:

In the Sugiura 2000 study, 1483 patients with suspected cosmetic dermatitis were PTed with "rose oil Bulgaria" (2% pet.), yielding 0.4% positive reactions (14); Trattner/David found 2 / 641 consecutive patients positive to "Rose oil (Bulgarian)" (31). The Bulgarian rose oil usually corresponds to Rosa Damascena Flower Oil (http://en.wikipedia.org/wiki/Rose_oil, last accessed 2009-11-16). The Coimbra 2000 study found in 67 patients with positive reaction to the FM I who were tested with "rose Bulgarian oil" (2% pet.) 4.5% positive reactions (9). One case of contact allergy to "Bulgarian rose oil (2 % pet.)" – and geraniol – in a 48-year-old female with ACD after application of "Eau de Rochas" E.d.C. was diagnosed, among 326 patients with suspected contact allergy to fragrance ingredients had tested negative (273). However, other rose oils are also used (and capable of eliciting ACD) as illustrated by the case of a 27 year old woman who developed ACD after using "Rose Absolute Eau ® eau de parfum", a "non-scented" body lotion and a number of other topicals. PTing revealed a number of (previously) relevant reaction, including "Rose centifolia" (5% alc.) and "Rose oil Bulgarian" (2% pet.) essential oil preparations (274). In the An 2005 study, 5 of 422 consecutive patients, i.e., 1.2%, had positive reactions to "Rose oil Bulgarian", tested at 2% concentration (13). Nakayama et al. found 1974 (after (29)) 4 "strong positive" reactions to "Rose oil Bulgarian" (unknown test concentration) in 183 patients. In a study from Alicante, Spain, 86 selected patients were tested with rose oil absolute, yielding 6 positive reactions (48).

Additional information:

ISO 4720:2009 nomenclature: *Rosa x damascena* Mill. and *Rosa sertata* X *Rosa rugosa*. Rose Flower Oil is the volatile oil obtained from the flowers of *Rosa* spp. , rosaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=59362>, last accessed 2009-11-16). "Rose oil, meaning either rose otto (attar of rose, attar of roses) or rose absolute, is the essential oil extracted from the petals of various types of rose.

Rose ottos are extracted through steam distillation, while rose absolutes are obtained through solvent extraction or supercritical carbon dioxide extraction, with the absolute being used more commonly in perfumery" (http://en.wikipedia.org/wiki/Rose_oil, last accessed 2009-11-17). There are several more specifically named flower extracts used for masking or perfuming:

- Rosa Alba Flower Extract is an extract obtained from the flowers of the Rose, *Rosa alba* L., Rosaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=40969>, last accessed 2009-11-16).
- Rosa Canina Flower Oil is the volatile oil obtained from the flowers of the Hip Rose, *Rosa canina* L., Rosaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=59263>, last accessed 2009-11-16).
- Rosa Centifolia Flower Oil is the volatile oil obtained from the flowers of the Cabbage Rose, *Rosa centifolia* (L.), Rosaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=79757>, last accessed 2009-11-16).
- Rosa Damascena Flower Oil is the volatile oil obtained from the flowers of the Damask Rose, *Rosa damascena*, Rosaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=79760>, last accessed 2009-11-16).
- Rosa Gallica Flower Oil is the volatile oil obtained from the flowers of the French Rose, *Rosa gallica* L., Rosaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=59346>, last accessed 2009-11-16).
- Rosa Moschata Oil is the oil obtained from the Musk Rose, *Rosa moschata*, Rosaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=79761>, last accessed 2009-11-16).
- Rosa Rugosa Flower Oil is the volatile oil obtained from the flowers of the Rose, *Rosa rubiginosa* L., Rosaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=83588>, last accessed 2009-11-16).

Apparently, the *Rosa Damascena* and the *Rosa centifolia* are the species most commonly used for extraction of essential rose oils, the former mostly grown in Bulgaria, Turkey, Russia, India and China, the latter more commonly in Morocco, France and Egypt (274). Main constituents by GC are: citronellol (20-49%), geraniol (6-23%), nerol (3-12%) and phenylethyl alcohol (up to 3.5%) (34).

For Oil of rose (*Rosa x damascena* Miller) an ISO standard exists: ISO 9842:2003.

ROSMARINUS OFFICINALIS FLOWER OIL

"Rosemary Oil"

CAS 84604-14-8; EC 283-291-9
(Rosemary, ext.)
INCI: ROSMARINUM
OFFICINALIS / Rosemary, ext.

Current regulation: /

Clinical data:

The Rudzki 1976 study found no positive reaction in 200 patients to "rosemary" essential oil, 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=3 (3.5%) positive reactions to "rosemary" essential oil 2% pet. (27).

Additional information:

ISO 4720:2009 nomenclature: *Rosmarinus officinalis* L. Rosmarinus Officinalis Flower Oil is an essential oil obtained from the leaves and fresh flowering tops of the Rosemary, *Rosmarinus officinalis* L.,

Lamiaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=40978>, last accessed 2010-01-29). Major constituents are: 1,8-cineole (17-55%), alpha-pinene (9-26%), camphor (5-22%) and verbenone [18309-32-5] as traces in North African oils, but between 0.7 and 2.5% in Spanish oils (34). For Oil of rosemary (*Rosmarinus officinalis* L.) an ISO standard exists: ISO 1342:2000.

Considering the content of well-known allergenic compounds, this essential oil is regarded as established contact allergen in humans.

SALVIA spp. HERB OIL

Sage oil

SALVIA OFFICINALIS LAVANDULIFOLIA HERB OIL

CAS 97952-71-1; EC 308-365-0
(Sage, *Salvia officinalis* lavandulifolia, ext. = INCI)

SALVIA LAVANDULIFOLIA HERB OIL

CAS 90106-49-3; EC 290-272-9
(Sage, *Salvia lavandulifolia*, ext. = INCI)

SALVIA SCLAREA FLOWER OIL

CAS 84775-83-7; EC 283-911-8
(Sage, *Salvia sclarea*, ext.) INCI: SALVIA SCLAREA / Sage, *Salvia sclarea*, ext.

SALVIA HISPANICA HERB OIL

CAS 93384-40-8; EC 297-250-8
(Sage, *Salvia hispanica*, ext. = INCI)

Current regulation: /

Clinical data:

The Rudzki 1976 study found 1 positive reaction in 200 patients to “Clary sage”, 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=4 (4.6%) positive reactions to “clary sage” essential oil 2% pet. (27).

Additional information:

ISO 4720:2009 nomenclature: *Salvia officinalis* L. *Salvia Officinalis Lavandulifolia* Herb Oil is an essential oil obtained from the herbs of the Sage, *Salvia officinalis* L. spp.

lavandulifolia, Lamiaceae, Syn. Dalmatian

sage (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=41084>, last accessed 2010-01-29).

Salvia Lavandulifolia Herb Oil is an essential oil obtained from the herbs of the Sage, *Salvia lavandulifolia*,

Lamiaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=40987>, last accessed 2010-01-29).

Salvia Sclarea Flower Oil is an essential oil obtained from the flowers and foliage of the Clary Sage, *Salvia sclarea* L.,

Lamiaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=41086>, last accessed 2010-01-29).

Salvia Hispanica Herb Oil is an essential oil obtained from the herbs of the Spanish Sage, *Salvia hispanica* L.,

Lamiaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=41086>, last accessed 2010-01-29).

[tails&id=40985](#), last accessed 2010-01-29).

Clary sage oil is obtained by steam distillation of flowering tops and foliage of cultivated *Salvia sclarea* L. (Lamiaceae). Main constituents are linalyl acetate (56-78%) and linalool (6.5-24%) (34). Dalmatian sage oil is steam distilled from partially dried leaves of *S. officinalis* L. (Lamiaceae). The content by GC is: alpha-thujone (18-43%), beta-thujone (3-8.5%), 1,8-cineole (5.5-13%), camphor (3-8.5%) as main constituents (34). Spanish sage oil does not contain thujone, but mainly camphor (15-36%) and 1,8-cineole (11-30%), and is used mainly in pharmaceutical preparations and technical perfumery (34). For Oil of sage, Spanish (*Salvia lavandulifolia* Vahl) an ISO standard exists: ISO 3526:2005, for Oil of Dalmatian sage (*Salvia officinalis* L.): ISO 9909:1997.

Considering the content of well-known allergenic compounds, this essential oil is regarded as established contact allergen in humans.

SANTALUM ALBUM WOOD OIL

CAS 84787-70-2; EC 284-111-1
(Sandalwood, ext.) INCI:
SANTALUM ALBUM /
Sandalwood, ext.

Sandalwood oil ([East] India)

SANTALUM ALBUM OIL

CAS 8006-87-9; EC / (Oils,
sandalwood)

Sandalwood oil ([East] India)

Current regulation: /

Clinical data:

In the Sugiura 2000 study, 1483 patients with suspected cosmetic dermatitis were PTed with "sandalwood oil" (2% pet.), yielding 0.8% positive reactions (14). In the Frosch 2002 b study, "sandalwood oil (East India)" is mentioned with a CAS # 8015-65-4, which, however, is attributed to AMYRIS BALSAMIFERA BARK OIL, see above. Assuming that this CAS # is erroneous, study results are considered to be valid for *S. album* wood oil, tested at 2% and 10% concentration, yielding 0.4% and 0.9% positive reactions, respectively (17). Out of 6 of 15 patients with a positive reaction to the higher concentration no clinical relevance was found, compared to 2 of 7 patients positive to the lower concentration (17). The Coimbra 2000 study found in 67 patients with positive reaction to the FM I who were tested with "sandalwood oil" (2% pet.) 6.6% positive reactions (9). In the An 2005 study, 10 of 422 consecutive patients, i.e., 2.4%, had positive reactions to "Santalum album oil" 2% (13). The Goossens 1997 study found 4 of 111 patients positive to "sandalwood oil 10% pet." – all sensitised to other fragrance allergens (23). The Rudzki 1976 study found no positive reaction in 200 patients to "sandalwood", 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=2 (2.3%) positive reactions to "sandalwood" essential oil 2% pet. (27). In 63 patients positive to the FM I, 1 had a positive PT reaction to sandalwood oil, 2% pet., in the Santucci 1987 study (28). Nakayama et al. found 1974 (after (29)) 6 "strong positive" and 8 "weak positive" reactions to "Sandalwood oil" (unknown test concentration) in 183 patients. The IVDK 2010 c study identified 1.3% positive reactions in 3671 consecutively tested patients and 1.8% positive reactions in 1002 patients tested in the context of a special series (30). In a study from Alicante, Spain, 86 selected patients were tested with sandalwood oil, yielding 2 positive reactions (48).

Additional information:

ISO 4720:2009 nomenclature: *Santalum album* L. *Santalum Album* Oil is the volatile oil obtained from the heartwood of the Sandalwood, *Santalum album* L.,

Santalaceae (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.d>

[etails&id=80209](#), last accessed 2009-11-26).

Santalum Album Wood Oil is an essential oil obtained from the wood of the Sandalwood, *Santalum album* L., *Santalaceae*. It contains 75% santalol isomers (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=41092>, last accessed 2009-11-12), typically up to 55% .alpha.-santalol and up to 24% .beta.-santalol (30). East Indian sandalwood oil consists almost exclusively of closely related sesquiterpenoids; by far the main constituents are the alcohols alpha-santalol [115-71-9] (41-55%) and cis-beta-santalol [77-42-9] (16-24%), the latter being mainly responsible for the specific odour (34, 39).

An ISO standard regarding the composition of “*Santalum album* oil” is available: ISO 3518:2002. “Sandalwoods” are labelled as *Amyris balsamifera*, *Eremophila mitchelli*, *Fusanus acuminatus* (= *Santalum acuminatum*), *Santalum album*, *S. austrocaledonicum*, *S. latifolium*, *S. spicatum* and *S. yasi*. The majority of currently available trade oils, reportedly from *S. album*, contained approximately 50-70% santalols (Z-alpha and Z-beta), as analysed with gas chromatography-mass spectrometry (GC-MS) (275). A review on the toxicological properties of “*Santalum album* oil” is available (276).

AMYRIS BALSAMIFERA BARK OIL (*Sandalwood oil (Caribbean)*), CAS 8015-65-4; EC / (Oils, amyris) / 90320-49-3; EC 90320-49-3 (*Amyris balsamifera*, ext. = INCI name) is used as a cheap substitute for East Indian Sandalwood in perfumes and cosmetics. Originally cultivated primarily in Haiti where it was known as 'candle wood' and used as a torch by locals due to the tree's high oil content (<http://www.amphora-retail.com/sandalwood-amyris-essential-10ml-p-107.html>, last accessed 2009-11-12). The major components are sesquiterpenoids such as valerianol, elemol, β -eudesmol and epi-gamma-eudesmol (39). For Oil of amyris (*Amyris balsamifera* L.) an ISO standard exists: ISO 3525:2008. Amyris Balsamifera Bark Oil is the volatile oil distilled from the bark of the tree, *Amyris balsamifera*, Rutaceae

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=74455>, last accessed 2009-11-12).

SANTALUM SPICATA WOOD OIL

CAS 8024-35-9; EC 296-618-5
(*Sandalwood oil, Western Australia*)

Sandalwood oil (Australia)

Current regulation: /

Clinical data:

In clinical studies, mostly *S. album* wood oil had been used (see above); in a number of studies this is not clear.

Additional information:

ISO 4720:2009 nomenclature: *Santalum spicatum* (R.Br.) A. DC, syn. *Eucarya spicata* (R.Br.) Sprag & Summ. For Oil of Australian sandalwood (*Santalum spicatum* (R.Br.) A.DC.) an ISO standard exists: ISO 22769:2009. *Santalum Spicata* Wood Oil is an essential oil obtained from the wood of the Australian Sandalwood, *Santalum spicata*, *Santalaceae*. It contains 75% santalols and 10% farnesol (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=41093>, last accessed 2009-11-12). This oil also contains santalols as main constituents but differs somewhat in the remaining composition. Today, it makes up a considerable part of the sandalwood oil market (34).

Considering the content of well-known allergenic compounds (santalols), this essential oil is regarded as established contact allergen in humans.

TAGETES PATULA FLOWER OILCAS 91722-29-1; EC 294-431-3
(*Tagetes patula*, ext. = INCI)*"Marigold Oil; Tagetes Oil"*

Current regulation: /

Clinical data:

In an aromatherapist, an essential oil solvent-extracted from *Tagetes patula*, patch tested at 1.5% in grapeseed oil (vehicle negative, 7 controls negative to essential oils) resulted in a +++ reaction, in accordance with a work-related bilateral hand dermatitis (215).

Additional information:

Tagetes Patula Flower Oil is an essential oil obtained by hydrodistillation of the flowers of the *Tagetes*, *Tagetes patula* L., *Compositae*. It contains mainly D-limonene, ocimene, 2,6-dimethyloct-7-en-4-

one (<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=41506>, last accessed 2010-01-28). According to Surburg/Panten, tagetes oil is steam distilled from the flowering plants of *Tagetes minuta* L. (*T. glandulifera* Schrank., *Asteraceae*). Main components comprise cis-ocimene, dihydrotageton, tageton, and cis- and trans-ocimenone (34, 39).

THYMUS spp. HERB OIL**THYMUS VULGARIS HERB OIL**CAS 84929-51-1, 8007-46-3; EC 284-535-7 (*Thyme*, *Thymus vulgaris*, ext.)*"Thyme oil"*INCI: THYMUS VULGARIS /
Thyme, *Thymus vulgaris*, ext.

Current regulation: /

Clinical data:

The Rudzki 1976 study found no positive reaction in 200 patients to "thyme" essential oil, 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=4 (4.6%) positive reactions to "thyme" essential oil 2% pet. (27). In 63 patients positive to the FM I, none had a positive PT reaction to thymol, 1% pet., in the Santucci 1987 study (28).

Additional information:

ISO 4720:2009 nomenclature: *Thymus vulgaris* L. *Thymus vulgaris* Herb Oil is an essential oil obtained from the herbs of the Thyme, *Thymus vulgaris* L., *Lamiaceae*. It contains 20-40% thymol and carvacrol, cymene, pinene, linalool, bornyl acetate

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=41133>, last accessed 2010-01-29).

Other species are used for extraction, e.g., *Thymus Mastichina* (CAS 84837-14-9), *Thymus Serpillum* (CAS 84776-98-7), *Thymus Zygis* (CAS 85085-75-2), according to CosIng. The main constituent is thymol (37-56%) (34). For Oil of thyme containing thymol, Spanish type [*Thymus zygis* (Loefl.) L.] an ISO standard exists: ISO 14715:2010, for Oil of Spanish wild marjoram (*Thymus mastichina* L.): ISO 4728:2003.

TURPENTINE (oil)

CAS 8006-64-2 / 9005-90-7 / 8052-14-0; EC 232-350-7 / 232-688-5 / -

Current regulation: III/124 ; III/125 ; III/126

Clinical data:

Oil of turpentine has been patch tested in a number of baseline series, i.e., in consecutive patients, although not included in the European Baseline series.

In a series of 24 patients with occupational contact dermatitis from the pottery industry, Lear at al. found 14 to be sensitised to “Indonesian oil of turpentine” and 8 to alpha-pinene (190)

Table 3.2.2 – 2: Overview of results with **Oil of turpentine** in patients patch tested for suspected allergic contact dermatitis. If not given in the publication, the confidence interval (CI) was calculated from the absolute numbers by the SCCS.

Country	Population	Years	No. tested	Crude % positive (95% CI) [§]
Lisbon, Portugal (189); virtually no .delta.-3-carene	Consecutive patients	1979-1983	4316	2.3 % (1.9 – 2.8) [§]
Birmingham, UK (190)	Potters with occup. hand dermatitis	6 months; prior to 1996	24	14 / 24 pos. to “Indonesian turpentine”
Austria/Germany (IVDK) (277)	Consecutive patients	1992-1995	27658	0.47 % (0.39 – 0.55) [§]
Austria/Germany (IVDK) (278)	Consecutive patients	1996-2002	59478	Annual prevalences 1.6 to 4.4 %
Augsburg/Germany (279)	Population sample	1998	1141	1.2% (on population level!)
Europe (ESSCA) (271)	Consecutive patients	2002/03	3767	1.6 %
Austria/Germany/Switzerland (IVDK) (7)	Consecutive patients	2005-2008	37163	1.8 %

Additional information:

ISO 4720:2009 nomenclature: *Pinus pinaster* Aiton and *Pinus massoniana* Lamb.

Turpentine, oil: Any of the volatile predominately terpenic fractions or distillates resulting from the solvent extraction of, gum collection from, or pulping of softwoods. Turpentine is a mixture of terpene hydrocarbons obtained from various species of

Pinus http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details_v2&id=41521

The composition of oil of turpentine varies with its origin, in particular, the content of .delta.-3-carene, one of its main allergenic compounds (189, 277). Similarly, the peroxide degree may vary. The main constituents are .alpha.-pinene (50-72%), .beta.-pinene (6-15%), carenes (< 0.1-17%), camphene (up to 1%), dipentene (0.5-5%), along with a number of other substances (277).

It is a “top 200” substance and classified as R43 (IFRA, pers. comm.2010)

Verbena absolute (*Lippia citriodora* Kunth.)

CAS 8024-12-2, 84961-67-1; EC /)

Current regulation: Annex III, part 1, n° 206

Clinical data: /

Additional information:

ISO 4720:2009 nomenclature: *Aloysia citriodora* Palau syn. *Lippia citriodora* Kunth syn. *Aloysia triphylla* (L' Hér.) Kuntze. An older RIFM review is available citing several positive human maximisation studies both with "Verbena absolute" and "Verbena oil" (128).

VETIVERIA ZIZANOIDES ROOT OIL

CAS 8016-96-4; EC / (Oils, vetiver)
/ 84238-29-9; EC 282-490-8
(*Vetiveria zizanioides*, ext. = INCI)

"Vetiver oil; khas khas oil"

Current regulation: ...

Clinical data:

The Rudzki 1976 study found 1 positive reaction in 200 patients to "vetiver" essential oil, 2% pet. (26). The later Rudzki 1986 study in 86 FM I positive patients found n=9 (10.4%) positive reactions to "vetiver" essential oil 2% pet. (27).

Additional information:

ISO 4720:2009 nomenclature: *Vetiveria zizanioides* (L.) Nash. *Vetiveria Zizanioides* Root Oil is an essential oil distilled from the dried roots of the grass *Vetiveria zizanioides* (L.) Nash *Poaceae*

(<http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=41293>, last accessed 2010-01-29). Vetiver oil has a high sesquiterpene content. The ketones alpha-vetivone [15764-04-2] (6-12%) and beta-vetivone [18444-79-6] (4-10%), which usually form more than 10% of the oil, as well as khusimol [16223-63-5] (24-36%) and isovelencenol [22387-74-2] (12-24%) are the main constituents (in Bourbon oil, i.e., from Réunion) (34). For Oil of vetiver (*Vetiveria zizanioides* (L.) Nash) an ISO standard exists: ISO 4716:2002.

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