Annex I: Clinical evidence regarding sensitisation to individual fragrance chemicals and to natural extracts

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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 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.

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)

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

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

<table>
<thead>
<tr>
<th>N(pos) to FM I, ref.</th>
<th>Evertia prun.</th>
<th>Isoeug.</th>
<th>Hydroxycitron.</th>
<th>Cinnamal</th>
<th>Cinnamyl alcohol</th>
<th>Eugenol</th>
<th>Geraniol</th>
<th>Alpha-amyl cinnamal</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=160 (5)</td>
<td>13.1%</td>
<td>14.8%</td>
<td>2.5%</td>
<td>8.1%</td>
<td>20.6%</td>
<td>8.8%</td>
<td>7.5%</td>
<td>5.0%</td>
</tr>
<tr>
<td>N= 991 (8)</td>
<td>18.4%</td>
<td>11.2%</td>
<td>10.1%</td>
<td>6.1%</td>
<td>6.1%</td>
<td>6.6%</td>
<td>4.6%</td>
<td>2.4%</td>
</tr>
<tr>
<td>N=50 (2)</td>
<td>19.6%</td>
<td>14.3%</td>
<td>8.9%</td>
<td>8.9%</td>
<td>7.1%</td>
<td>5.4%</td>
<td>2.7%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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)

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

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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Study period, Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>An 2005 (13)</td>
<td>South Korea (multicentre)</td>
<td>04/2002 – 06/2003 n=422 consecutive patients</td>
</tr>
<tr>
<td>Sugiura 2000 (14)</td>
<td>Nagoya, Japan</td>
<td>1990-1998 n=1483 patients with suspected cosmetic dermatitis</td>
</tr>
<tr>
<td>Frosch 1995 (15)</td>
<td>11 European depts..</td>
<td>Prior to 1995 n=1069 consecutive patients</td>
</tr>
<tr>
<td>Frosch 2002 a (16)</td>
<td>6 European depts.</td>
<td>10/1997-10/1998 n=1855 consecutive patients</td>
</tr>
<tr>
<td>Frosch 2002 b (17)</td>
<td>6 European depts.</td>
<td>Prior to 2002 n=1606 consecutive patients</td>
</tr>
<tr>
<td>Coimbra 2000 (9)</td>
<td>Portugal</td>
<td>07/1989-06/1999 n=226 with FM I SC n=67 also with other fragrances</td>
</tr>
<tr>
<td>Larsen 1977 (18)</td>
<td>US</td>
<td>1977 n=20 &quot;perfume-sensitive patients“</td>
</tr>
<tr>
<td>Larsen 2001 (19)</td>
<td>worldwide multicentre</td>
<td>? (prior to 2001) n=178 patients with known contact allergy to fragrance ingredients</td>
</tr>
<tr>
<td>Belsito 2006 (20)</td>
<td>North American (5 US, 1 Canadian) depts.</td>
<td>2003 n=1603 patients</td>
</tr>
<tr>
<td>NACDG 2009 (21)</td>
<td>US and Canada</td>
<td>2005-2006 n= 4454 patients</td>
</tr>
<tr>
<td>Wöhrl 2001 (22)</td>
<td>“FAZ” clinic Vienna</td>
<td>1997-2000 n=747 of 2660 consecutive patients tested with special series</td>
</tr>
<tr>
<td>EECDRG 1995 (15)</td>
<td>European, multicentre</td>
<td>Different fragrances, tested in 2 concentrations, in sets of about 100 patients each in different centres</td>
</tr>
<tr>
<td>Goossens 1997 (23)</td>
<td>Leuven, Belgium</td>
<td>1978-1987 n=111 “Japanese perfume series” (highly selected patients)</td>
</tr>
<tr>
<td>Malten 1984 (24)</td>
<td>Dutch multicentre</td>
<td>N=182 patients with suspected cosmetic dermatitis tested with 22 fragrance compounds</td>
</tr>
<tr>
<td>Study</td>
<td>Location</td>
<td>N</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>----------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>DeGroot 1985 (25)</td>
<td>Dutch</td>
<td>N=179 patients with suspected cosmetic dermatitis tested with 16 fragrance compounds</td>
</tr>
<tr>
<td>Rudzki 1976 (26)</td>
<td>Warsaw, Poland</td>
<td>N=200 consecutive patients</td>
</tr>
<tr>
<td>Rudzki 1986 (27)</td>
<td>Warsaw, Poland</td>
<td>N=86 patients of 299 (of 5315) patients with positive reaction to FM I tested with essential oils series</td>
</tr>
<tr>
<td>Santucci 1987 (28)</td>
<td>Rome, Italy</td>
<td>N=1500 consecutive patients; n=63 reacting positively to FM I re-tested with extended fragrance series</td>
</tr>
<tr>
<td>Nakayama 1974 (after (29))</td>
<td>Japan</td>
<td>N=183 patients with cosmetic dermatitis</td>
</tr>
<tr>
<td>IVDK 2010c (30)</td>
<td>Switzerland</td>
<td>15682 patients tested with at least one essential oil in different test series</td>
</tr>
<tr>
<td>Trattner/David (31)</td>
<td>Tel Aviv, Israel</td>
<td>N=641 consecutive patients</td>
</tr>
</tbody>
</table>
**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-(3aβ,3aα,7β,8aδ)]-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 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-Hexamethytetraline**

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; Pentylicinnamaldehyde; α-Amyl-β-phenylacrolein; α-Amylcinnamal; α-Amylcinnamaldehyde; α-Pentylicinnamaldehyde

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

<table>
<thead>
<tr>
<th>CAS #</th>
<th>4819-67-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC #</td>
<td>225-392-2</td>
</tr>
</tbody>
</table>

**2-Pentylcyclopentanone**

- 2-Pentyl-1-cyclopentanone; 2-Pentylcyclopentanone; 2-Pentylcyclopenten-1-one; 2-n-Amylcyclopentanone; 2-n-Pentyl cyclopentanone; 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

<table>
<thead>
<tr>
<th>CAS #</th>
<th>2050-08-0</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC #</td>
<td>218-080-2</td>
</tr>
</tbody>
</table>

**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)

### trans-ANETHOLE

<table>
<thead>
<tr>
<th>CAS #</th>
<th>4180-23-8</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC #</td>
<td>224-052-0 / 203-205-5</td>
</tr>
</tbody>
</table>

- 1-Methoxy-4-(1E)-1-propen-1-yl-benzene
  - (E)-p-Propenyl-anisole (BCI); (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); E-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-(Methoxyphenyl)methanol; p-(Methoxyphenyl)methanol; p-Anisalcohol; p-Anisy 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: /
<table>
<thead>
<tr>
<th><strong>ANISYLIDENE ACETONE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAS # 943-88-4</strong></td>
</tr>
<tr>
<td><strong>EC # 213-404-9</strong></td>
</tr>
<tr>
<td><strong>4-(4-Methoxyphenyl)-3-Buten-2-one</strong></td>
</tr>
<tr>
<td>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-Methoxystyrlyl methyl ketone; 4'-Methoxybenzylideneacetone; Anisalacetone; Methyl p-methoxystyrlyl ketone; NSC 31752; NSC 7946; p-Anisalacetone; p-Methoxybenzalacetone; p-Methoxybenzylideneacetone; p-Methoxystyrlyl methyl ketone</td>
</tr>
<tr>
<td>Current regulation: Annex III, part 1, n° 443</td>
</tr>
</tbody>
</table>

**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:** /

<table>
<thead>
<tr>
<th><strong>BENZALDEHYDE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAS # 100-52-7</strong></td>
</tr>
<tr>
<td><strong>EC # 202-860-4</strong></td>
</tr>
<tr>
<td><strong>Benzaldehyde</strong></td>
</tr>
<tr>
<td>Artificial Almond Oil; Benzaldehyde FFC; Benzenecarbonal; Benzenecarboxaldehyde; Benzoic acid aldehyde; Benzoic aldehyde; NSC 7917; Phenylformaldehyde; Phenylmethanal</td>
</tr>
</tbody>
</table>
| Current regulation: /

**Clinical data:**
In the Wöhrl 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:** /

<table>
<thead>
<tr>
<th><strong>BENZYL ACETATE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAS #140-11-4</strong></td>
</tr>
<tr>
<td><strong>EC # 205-399-7 / 202-940-9</strong></td>
</tr>
<tr>
<td><strong>Benzyl acetate</strong></td>
</tr>
<tr>
<td>Benzyl ester acetic acid; Benzyl alcohol, acetate (6CI); (Acetoxyethyl)benzene; Benzyl ethanoate; NSC 4550; Phenylmethyl acetate; Methyl Phenylacetate; α-Acetoxytoluene ; Methyl alpha-Toluate</td>
</tr>
</tbody>
</table>
| 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

<table>
<thead>
<tr>
<th>CAS #</th>
<th>EC #</th>
</tr>
</thead>
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<td>2550-26-7</td>
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</table>

**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

**Clinical data:**

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

**Additional information:**

### Benzyl Alcohol

<table>
<thead>
<tr>
<th>CAS #</th>
<th>EC #</th>
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<tbody>
<tr>
<td>100-51-6</td>
<td>202-859-9</td>
</tr>
</tbody>
</table>

**Phenylmethanol**

Benzyl alcohol; (Hydroxymethyl)benzene; Benzenecarbinol; Benzylic alcohol; NSC 8044; Phenylcarbinol; Benzenemethanol; Phenylmethyl alcohol; Sunmorl BK 20; TB 13G; α-Hydroxytoluene; α-Toluenol

**Clinical data:**

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. 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 (48). 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 (49). D. W. Shaw describes a patient with allergic contact dermatitis caused by benzyl alcohol in a hearing aid impression material and in topical medications (50). Another contribution points to covert exposures to benzyl alcohol even in products labelled “fragrance free” (51) 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 (52). 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 (53)), 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
**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, no 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 (52). 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 (54). Hausen et al. review the older literature and mention a study identifying 1 sensitised patient in 73 patients treated for scabies (details not given) (52). 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, no 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 Wöhrl 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 (55).

### 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 Wöhrl 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).

**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 (56).

### 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 (57).

**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; Velvethone; Verbeniaz; 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 (58).

**p-tert.-Butylidihydrocinnamaldehyde**

**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-Butylidihydrocinnamaldehyde

Current regulation: III/155

Clinical data: /

Additional information:
It is a “top 200” substance and classified as R43 (IFRA, pers. comm.2010)  
**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)propanaldehyde (REACH, EINECS); 4-(1,1-dimethylallyl)-a-methyl-benzenepropanal;  
Hydrocinnamaldehyde, p-tert-butyl-a-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-methylpropanal; 3-(p-tert-Butylphenyl)-2-methylpropanaldehyde; 3-(p-tert-Butylphenyl)isobutylaldehyde; 4-(1,1-Dimethylethyl)-a-methylbenzenepropanal; 4-tert-Butyl-a-methylhydrocinnamic aldehyde; Lilestralis; Lilial; Lysmeral; NSC 22275; ilestral; p-tert-Butyl-a-methylhydrocinnamaldehyde; p-tert-Butyl-a-methylhydrocinnamic aldehyde; pt-bucinal; α-Methyl-p-tert-butylhydrocinnamaldehyde; β-Lilial

Current regulation: Annex III, part 1, no 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 (59).

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-Trinbornancamphor; 2-Camphane; 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 (60). 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 (61). In the US, a case of contact dermatitis due to “Vics VapoRub” has been reported (62).
Additional information: It is a “top 100” substance (IFRA, pers. comm. M.Vey 2010).

**beta-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-Caryophyllene; 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:
beta-Caryophyllene autoxidizes at air exposure. As the primary oxidation products, the hydroperoxides, are very unstable and immediately form epoxides with low sensitizing capacit, the increase in allergenic activity caused by autoxidation is comparably low (63). A multicenter study identified 0.5% positive reactions to oxidized beta-caryophyllene (3.0% pet.) in 1511 consecutive patients (64). 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: /

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 (65)).

Additional information:
Carvacrol is derived from p-cymene by sulfonation followed by alkali fusion. Carvacrol

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can also be derived from savory, thyme, marjoram, oregano, lovage root, and Spanish origanum oil (65). 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 (65).

### CARVONE

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<td>(5S)-2-Methyl-5-(1-methylethenyl)-2-cyclohexen-1-one</td>
</tr>
</tbody>
</table>

Cases of allergic contact cheilitis due to L-carvone in toothpastes have been reported (66-68). 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 (69).

"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 (70). 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.) (71). Experimental findings in guinea pigs show no cross reactivity between R- and S carvone, but both enantiomers were found to be equally strong sensitizers.

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**CINNAMAL**

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<td>EC #</td>
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3-Phenyl-2-propenal

Cinnamaldehyde; 3-Phenyl-2-propenal; 3-Phenylacrolein; 3-Phenylacrylaldehyde; 3-Phenylpropenal; Abion CA; Benzylideneacetalddehyde; 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 sensitisation in the consecutive patients analysed was observed between 1984 (5.9% pos.) and 2000 (3.6% pos.); tested at 1% pet. (73). 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).

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 (74). Following industrial use as “odour masking” agent, cinnamal caused occupational ACD in an exposed worker (75).

Additional information:

A specific RIFM review is available (76); another RIFM review addresses several cinnamic compounds (77).

**CINNAMYL ALCOHOL**

<table>
<thead>
<tr>
<th>CAS #</th>
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<tr>
<td>EC #</td>
<td>203-212-3</td>
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</tbody>
</table>

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; Styrone; Styril alcohol; Styril 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). 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, 78), 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 (79), again in line with the observations in the IVDK 2010 study (7).

A RIFM review is available (80)

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**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

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 (81). 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).

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 (82).

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.
Geranial and neral have been identified as secondary oxidation products when geraniol autoxidizes (83). They have also been identified as metabolites of geraniol (84). 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).

**CITRONELAL**

- **CAS #** 106-23-0
- **EC #** 203-376-6
- 3,7-Dimethyl-6-octenal
- (±)-Citronellal; 2,3-Dihydrocitral; 3,7-Dimethyloct-6-en-1-ol; 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)

**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 (85), D-citronellol (86) and DL-citronellol (87). Another review is available by Hostynek and Maibach (88). 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-octenonitrile(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-Beno-2-pyrene; Benzo-α-pyrene; Coumarinic anhydride; NSC 8774; Rattex; Tonka bean camphor; cis-o-Coumarinic acid lactone; o-Hydroxycinnamic acid lactone

Current regulation: Annex III, part1, nº 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 (89).  
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 (52). 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. (90).  
Coumarin is a “top 100” substance and classified as R43 (IFRA, pers. comm.2010).
**Cuminaldehyde**

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<tbody>
<tr>
<td>EC #</td>
<td>204-516-9</td>
</tr>
</tbody>
</table>

### 4-(1-Methylethyl)-benzaldehyde

- 4-Isopropylbenzaldehyde; p-Isopropylbenzaldehyde; 4-(Propan-2-yl)benzaldehyde; 4-Isopropylphenylcarboxaldehyde; Cumaldehyde; Cumic aldehyde; Cuminal; Cuminaldehyde; Cuminic aldehyde; Cuminyl aldehyde; 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: ...

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**Cyclamen Aldehyde**

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<tbody>
<tr>
<td>EC #</td>
<td>203-161-7</td>
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</tbody>
</table>

### 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).

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**Cyclohexyl Acetate**

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<tr>
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</table>

### Cyclohexyletanoat

- Acetic acid cyclohexanyl ester; Acetoxy cyclohexane; 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 (91).
**alpha-CYCLOHEXYLIDENE BENZENEACETONITRILE**

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<tr>
<td>EC #</td>
<td>423-740-1</td>
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</table>

α-Cyclohexylidenebenzeneacetonitrile

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).

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**CYCLOPENTADECANONE**

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<tr>
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</table>

Cyclopentadecanone

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 patients with known contact allergy to fragrance ingredients (19).

Additional information: ...

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**DAMASCENONE ROSE KETONE-4** (← Not officially an INCI Name but Perfuming Name; Damascenone as such is not listed in CosIng)

<table>
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<tr>
<th>CAS #</th>
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<tbody>
<tr>
<td>EC #</td>
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</table>

1-(2,6,6-Trimethyl-1,3-cyclohexadien-1-yl)-2-buten-1-one

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, part 1, n° 160 (max. conc. 0.02%)

Clinical data: /

Additional information:

RIFM reviews are available (92, 93), 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 (93).

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**alpha-DAMASCONE (TMCHB)**

<table>
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<tr>
<th>CAS #</th>
<th>43052-87-5; 23726-94-5</th>
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<tbody>
<tr>
<td>EC #</td>
<td>x; 245-845-8</td>
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</tbody>
</table>

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, part 1, 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 damascene, 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-en-1-one (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 (94).

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 (95), 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 (96), supplying, however, no data on sensitisation.

cis-beta-DAMASCONE
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 (97), citing several negative and one positive HRIPTs, and a number of – mostly positive – animal experiments.

trans-beta-DAMASCONE
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-crotonylocyclohex-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 (98), 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%).

delta-DAMASCONE
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 (99), 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.

**trans-trans-delta-DAMASCONE**

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  
[S-I](α,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 (100), citing 1 positive HRIPT (2/15 with 1%).

**gamma-DAMASCONE**

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 (101), 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**

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</tbody>
</table>

**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; Mellilotin; Mellilotin (coumarin); Mellilotol

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**

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</table>

**(-)-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 (102), 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**

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**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) (92).
**DIMETHYLBENZYL CARBINYL ACETATE (DMBCA)**

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; Benzylidemethylcarbinol acetate; Benzylidemethylcarbinyl 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).

**DIMETHYL CITRACONATE**

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; Methyllinalool
**DIMETHYTETRAHYDRO BENZALDEHYDE**

<table>
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<th>![Chemical Structure]</th>
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</table>

2,4-Dimethyl-cyclohex-3-ene-1-carboxaldehyde
3,5-Dimethyl-cyclohex-3-ene-1-carboxaldehyde

Hivertal; Vertocital

**Current regulation:** /

**Clinical data:** /

**Additional information:**

It is a “top 100” substance (IFRA, pers. comm. 2010). A RIFM review is available (103), citing 1 negative human maximisation test (n=25).

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**DIPHENYL ETHER**

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</table>

Phenyl ether

1,1’-oxybis-Benzene; Barrel Therm 330; Benzene, phenoxy-; Biphenyl oxide; Chemcryl 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).

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**ETHYL ACRYLATE**

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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:** /

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**ETHYL 2-METHYLBUTYRATE**

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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

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

### ETHYLENE DODECANEDIOATE

<table>
<thead>
<tr>
<th>CAS</th>
<th>54982-83-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC</td>
<td>259-423-6</td>
</tr>
</tbody>
</table>

**1,4-dioxacyclohexadecane-5,16-dione**
Cyclic ethylene dodecanedioate; Ethylene dodecanedioate; Musk 144; Musk C-14

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

### 6-ETHYLIDENEOCTAHYDRO-5,8-METHANO-2H-BENZO-1-PYRAN

<table>
<thead>
<tr>
<th>CAS</th>
<th>93939-86-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC</td>
<td>300-376-9</td>
</tr>
</tbody>
</table>

Current regulation: /
Clinical data:
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).
Additional information: /

### 2-ETHYL-4-(2,2,3-TRIMETHYL-3-CYCLOPENTEN-1-YL)-2-BUTEN-1-OL

<table>
<thead>
<tr>
<th>CAS</th>
<th>28219-61-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC</td>
<td>248-908-8</td>
</tr>
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Current regulation: /
Clinical data: /
Additional information: It is a “top 100” substance (IFRA, pers. comm.2010).

### ETHYL VANILLIN

<table>
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<tr>
<th>CAS</th>
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</tr>
</thead>
<tbody>
<tr>
<td>EC</td>
<td>204-464-7</td>
</tr>
</tbody>
</table>

**3-Ethoxy-4-hydroxybenzaldehyde**
2-Ethoxy-4-formylphenol; 3-Ethoxy-4-hydroxybenzaldehyde; 3-Ethylvanillin; 4-Hydroxy-3-ethoxybenzaldehyde; Arovanillon; Bourbonal; Ethavan; Ethovan; Ethyprotal; Ethylvanillin; NSC 1803; NSC 67240; Protocatechuic aldehyde ethyl ether; Quantonvanil; Rhodiarome; Vanillal; Vanirox
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. (104).
Additional information: It is a “top 100” substance (IFRA, pers. comm. 2010).

**ETHYLENE BRASYLATE**

<table>
<thead>
<tr>
<th>CAS #</th>
<th>105-95-3</th>
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<tbody>
<tr>
<td>EC #</td>
<td>203-347-8</td>
</tr>
</tbody>
</table>

**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**

<table>
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<tr>
<th>CAS #</th>
<th>470-82-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC #</td>
<td>207-431-5</td>
</tr>
</tbody>
</table>

**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**

<table>
<thead>
<tr>
<th>CAS #</th>
<th>97-53-0</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC #</td>
<td>202-589-1</td>
</tr>
</tbody>
</table>

**2-Methoxy-4-(2-propen-1-yl)-phenol**

Other names:  
4-allyl-2-methoxy-phenol; 1-Alllyl-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-Alllyl-1-hydroxy-2-methoxybenzene; 4-Alllyl-2-methoxyphenol; 4-Allylguaiacol; 4-Hydroxy-3-methoxyallylbenzene; Allylguaiacol; Bioxeda; Caryophylllic acid; Dentogum; Eugenic acid; Eugenol; NSC 209525; NSC
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% to 16% of 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 (105). In the An 2005 study, 8 of 422 consecutive patients, i.e., 1.9%, had positive reaction (13) (test concentration 2%). In the Wöhrl 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).
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 (106). A case of urticaria after dental treatment with eugenol-containing material was reported from India (107); however, occasional cases are also reported from Europe (108). 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 (109).
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 (110). 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%, i.e., 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 (111) 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 (112).

GERANIOL

<table>
<thead>
<tr>
<th>CAS #</th>
<th>106-24-1</th>
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<tbody>
<tr>
<td>EC #</td>
<td>203-377-1</td>
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<tr>
<td>(2E)-3,7-Dimethyl-2,6-octadien-1-ol</td>
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<td>(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</td>
<td></td>
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</table>

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 Wöhrl 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 breakdown testing to the FM I, had a positive PT reaction (7).
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 (113). 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) (114).
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 (52).
Geraniol forms oxidation product with increased sensitizing capacity both via spontaneous autoxidation at air exposure and via metabolic oxidation. Geranial and neral together with hydroperoxide have been identified as oxidation products when geraniol autoxidizes (83). Geranial and neral were also identified as metabolites of geraniol (84). This explains the simultaneous reactions to geraniol and citral seen by (4).
A review is available by Hostynke and Maibach (115) and by RIFM (116). It is a "top 100" substance and classified as R43 (IFRA, pers. comm.2010).

GERANYL ACETATE

<table>
<thead>
<tr>
<th>CAS #</th>
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<tbody>
<tr>
<td>EC #</td>
<td>203-341-5</td>
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<tr>
<td>(2E)-1-Acetat-3,7-dimethyl-2,6-Octadien-1-ol</td>
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</tbody>
</table>
| (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-
<table>
<thead>
<tr>
<th><strong>dimethyl-2,6-octadienyl ester; Acetic acid geraniol ester;</strong> 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</th>
</tr>
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<tbody>
<tr>
<td><strong>Current regulation:</strong> /</td>
</tr>
<tr>
<td><strong>Clinical data:</strong> /</td>
</tr>
<tr>
<td><strong>Additional information:</strong> It is a “top 100” substance (IFRA, pers. comm. 2010).</td>
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</tbody>
</table>

**HELIOTROPINE**

<table>
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<th>CAS # 120-57-0</th>
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<tr>
<td>EC # 204-409-7</td>
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<tr>
<td><strong>1,3-Benzodioxole-5-carboxaldehyde</strong></td>
</tr>
<tr>
<td>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-carboxaldehyde; Benzo[d][1,3]dioxole-5-carboxaldehyde; Geliotropin; Heliotropin; Heliotropine; NSC 26826; Piperonaldehyde; Piperonylaldehyde; Protocatechuic aldehyde methylene ether</td>
</tr>
<tr>
<td><strong>Current regulation:</strong> /</td>
</tr>
<tr>
<td><strong>Clinical data:</strong> 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).</td>
</tr>
<tr>
<td><strong>Additional information:</strong> It is a “top 100” substance (IFRA, pers. comm. 2010).</td>
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**HEXADECANOLACTONE**

<table>
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<th>CAS # 109-29-5</th>
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<tr>
<td>EC # 203-662-0</td>
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<td><strong>Oxacycloheptadecan-2-one</strong></td>
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<tr>
<td>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</td>
</tr>
<tr>
<td><strong>Current regulation:</strong> /</td>
</tr>
<tr>
<td><strong>Clinical data:</strong> 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).</td>
</tr>
<tr>
<td><strong>Additional information:</strong> /</td>
</tr>
</tbody>
</table>
**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-Oxacyclo(4.4.0)decen-3-one  
Current regulation: Annex II, n° 1135  
Clinical data: /  
Additional information:  
A RIFM review is available (92), p. S115 ff, citing a number of positive human sensitisation experiments.

**3α,4,5,6,7,7α-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  
Acetoxydihydrocyclohexadiene; Cyclacet; Dicyclopentenyl acetate; Dicylac; Tricyclo[5.2.1.02,6]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”  

**HEXAHYDRO-METHANOINDENYL PROPIONATE**

CAS # 68912-13-0  
EC # 272-805-7  
3α,4,5,6,7,7α-hexahydro-4,7-methano-1H-indenol propanoate  
3α,4,5,6,7,7α-Hexahydro-4,7-methano-1H-indenyl propionate (Mixture of Isomers); dicyclopentadiene propionate; tricyclodecenyl propionate; tricyclo[5.2.1.02,6]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-hexamethylcyclopenta[y]-2-benzopyran  
1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[y]-2-benzopyran; 1,3,4,6,7,8-
### Hexahydro-4,6,6,8,8,8-hexamethylcyclopenta-2-benzoypyr; 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(γ)-2-benzopyran (HHCB)  
0610/02 - Opinion on Hexahydro-hexamethyl-Cyclopenta (γ)-2-Benzopyran (HHCB) (no restrictions) It is a “top 100” substance (IFRA, pers. comm.2010).

### HEXYL ACETATE

<table>
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<tr>
<th>CAS #</th>
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</thead>
<tbody>
<tr>
<td>EC #</td>
<td>205-572-7</td>
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</tbody>
</table>

**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

<table>
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<tbody>
<tr>
<td>EC #</td>
<td>202-983-3</td>
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<tr>
<td>o-Hexyl-cinnamaldehyde</td>
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</tr>
<tr>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

**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"
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 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) (118). 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: /
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-carboxaldehyde (51414-25-6)

31906-04-4: 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexencarboxaldehyde; 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).

Further clinical data with a focus on quantitative dose-response (see also section 4.3), is discussed in (120).

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 (121).

Additional information:

HYDROXYCITRONELLAL

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-; Cycalia; Cyclosia; Cyclosia base; Fixol; Hydroxycitronellal; Laurine; Lilyl aldehyde; Muguet synthetic; Muguetttine 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 Wöhrl 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).

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 (52).

**HYDROXYCITRONELLOL**

<table>
<thead>
<tr>
<th>CAS # 107-74-4</th>
<th>EC # 203-517-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,7-dimethyl-7-octanediol</td>
<td></td>
</tr>
<tr>
<td>2,6-Dimethyl-2,8-octanediol; 3,7-Dimethyl-1,7-octanediol; 3,7-Dimethyloctan-1,7-diol; Citronellol, hydroxy-; Hydroxycirol; Hydroxycitronellol; NSC 406140; NSC 67886</td>
<td></td>
</tr>
</tbody>
</table>

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 (122).

**IONONE isomeric mixture**

<table>
<thead>
<tr>
<th>CAS # 8013-90-9</th>
<th>EC # 232-396-8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isonone, mixture of alpha- and beta ionone</td>
<td></td>
</tr>
</tbody>
</table>

Current regulation: /

Clinical data: / (see single isomers)

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


A RIFM review is available on “ionone” (123), quoting negative human and experimental results.

**alpha-IONONE**

<table>
<thead>
<tr>
<th>CAS # 127-41-3</th>
<th>EC # 204-841-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3E)-4-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-3-Buten-2-one</td>
<td></td>
</tr>
</tbody>
</table>

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 (124).

**beta-IONONE**

<table>
<thead>
<tr>
<th>CAS # 79-77-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC # 201-224-3</td>
</tr>
<tr>
<td>(3E)-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-Buten-2-one</td>
</tr>
<tr>
<td>(E)-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-Buten-2-one; (E)-β-Ionone; Ionone beta; trans-β-Ionone; β-Ionone</td>
</tr>
</tbody>
</table>

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 (125).

**ISOAMYL ACETATE**

<table>
<thead>
<tr>
<th>CAS # 123-92-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC # 204-662-3</td>
</tr>
<tr>
<td>3-Methylbutyl acetate</td>
</tr>
<tr>
<td>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</td>
</tr>
</tbody>
</table>

Current regulation: /

Clinical data:
Additional information: It is a “top 100” substance (IFRA, pers. comm.2010). In CosIng, it is listed as “solvent” (http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=76810, last accessed 2010-07-13)

**ISOAMYL SALICYLATE**

<table>
<thead>
<tr>
<th>CAS # 87-20-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC # 201-730-4</td>
</tr>
<tr>
<td>3-Methylbutyl-2-hydroxybenzoate</td>
</tr>
<tr>
<td>Isopentyl 2-Hydroxybenzoate; isopentyl salicylate; Salicylic acid, isopentyl ester (6Cl,8Cl); Isopentyl alcohol, salicylate; 3-Methylbutyl salicylate; Isoamyl o-hydroxybenzoate; Isoamyl salicylate; Isopentyl salicylate; NSC 7952</td>
</tr>
</tbody>
</table>

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 (126).

**ISOBERGAMATE**

CAS # 68683-20-5
EC # 272-066-0

4-(isopropyl)cyclohexadiene-1-ethyl formate

Structure is incompletely defined
4-(1-methylethyl)-1,7-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 (127).

**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-methylstyrrene; 4-Propenylguaiaicol; 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 Wöhrl 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% (128). 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 patients tested in a more aimed manner, partly as break-down testing to the FM I, had a positive PT reaction (7).

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%) (52). 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 (129). In an earlier study, 5 of 7 patients positive to isoeugenol also displayed positive reactions to isoeugenol acetate (1.2% eth.) (130) (see also section 5 and 6).

ISOLOGIFOLENEKETONE

<table>
<thead>
<tr>
<th>CAS #</th>
<th>33407-62-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC #</td>
<td>245-890-3</td>
</tr>
</tbody>
</table>

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 idenfied 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”.

alpha-ISOMETHYL IONONE

<table>
<thead>
<tr>
<th>CAS</th>
<th>127-51-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC</td>
<td>204-846-3</td>
</tr>
</tbody>
</table>

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

gamma-Methylionone

<table>
<thead>
<tr>
<th>CAS</th>
<th>7388-22-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC</td>
<td>/</td>
</tr>
</tbody>
</table>

3 Opdyke, D. L. J.; Letizia, C. Monographs on fragrance raw materials. Isolongifolanone. Food and Chemical Toxicology (1983), 21(6), 859
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 (131). Another review is available
by Hostynék and Maibach (132), both referring to “alpha-ISOMETHYL IONONE (CAS #
127-51-5)”.

(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, nº 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 (133). Moreover, limonene is used as a solvent in technical applications
and cleaning and can lead to allergic contact dermatitis (e.g., a histopathology

41
technicians (134, 135) or a painter and decorator (136)). In “water-free” hand cleansers it is reported to be used in concentrations around 10 – 20% (136). Wax polishes may contain dipentene and have caused one reported case of occupational ACD in a car mechanic (137). Another case of occupational ACD from dipentene in honing oil has been reported (138). 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.) (139).

Additional information:

Limonene is a monocyclic monoterpenic 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 (70, 71, 140, 141). 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.) (71). 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(140),
• between 0.3% and 6.5% in 4 different departments in altogether 2273 patients (71, 142).


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.asp x/56, last accessed 2009-11-11). For a more general discussion see section 5. There is no scientific rational 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**

<table>
<thead>
<tr>
<th>CAS #</th>
<th>78-70-6 (isomeric mixture)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC #</td>
<td>201-134-4; 245-083-6</td>
</tr>
</tbody>
</table>

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 (143). 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 (64). 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. (144).

A review by RIFM is available both regarding linalool (145) and linalool “and related esters” (146). Another review is available by Hostyn and Maibach (147).

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.

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**LINALYL ACETATE**

<table>
<thead>
<tr>
<th>CAS #</th>
<th>EC #</th>
<th>3,7-Dimethyl-1,6-octadien-3-yl acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>115-95-7</td>
<td>204-116-4</td>
<td>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-yi acetate; 3-Acetoxy-3,7-dimethyl-1,6-octadiene; Acetic acid linalool ester; Bergamioi; Bergamol; Bergamot mint oil; Linalyl acetate; NSC 2138; dl-Linalool acetate</td>
</tr>
</tbody>
</table>

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 (148).

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 (52).

Linalyl acetate autoxidizes spontaneously at air exposure and the major allergens, the hydroperoxides, are the primary oxidation products (149). 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) (150).

A RIFM review is available reporting 7 human sensitisation experiments yielding few or no cases of sensitisation (151).

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,3αβ,4α,8αβ)] ; (+)-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)


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. (152).

**MENTHOL**

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-methylcyclohexanol-1-ol; 2-Isopropyl-5-methylcyclohexanol; 3-Hydroxy-p-methane; 5-Methyl-2-(1-methylethyl)cyclohexanol; 5-Methyl-2-isopropylcyclohexanol; Menthol alcohol; p-Menthan-3-ol

89-78-1: (1α,2β,5α)-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; (+)-Menthol; DL-Menthol; Fisherman’s Friend Lozenges; Hexahydrothymol; Menthacamphor; Menthol; Menthomenthol; NSC 2603; Peppermint camphor; Racemmenthol; Therapeutic Mineral Ice; Thymomenthol; rac-Menthol

2216-51-5: (1R,2S,5R)-5-methyl-2-(1-methylethyl)-Cyclohexanol; (1R,(1α,2β,5a)]-5-methyl-2-(1-methylethyl)-Cyclohexanol; (1R,3R,4S)-(-)-Menthol; (-)-Menthol; (--)Menthol 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

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 (153). 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 (154). 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 (155). "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." (156).

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 (52).

L-menthol and menthol (isomer not specified) are “top 100” substances (IFRA, pers. comm.2010). RIFM reviews are available regarding “menthol” (157), D-menthol (158), L-menthol (159), DL-menthol (160) and menthol, racemic (161). A CIR expert panel review is available (162).

**METHOXYCITRONELLAL**

<table>
<thead>
<tr>
<th>CAS #</th>
<th>3613-30-7</th>
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<tbody>
<tr>
<td>EC #</td>
<td>222-784-5</td>
</tr>
</tbody>
</table>

**7-Methoxy-3,7-dimethyl-octanal**

7-Methoxy-3,7-dimethyloctanal; 7-Methoxy-6,7-dihydromenthol; 7-Methoxymenthol; Methoxymenthol; Methoxymethyldihydropinocamphenol

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**

<table>
<thead>
<tr>
<th>CAS #</th>
<th>41890-92-0</th>
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<tbody>
<tr>
<td>EC #</td>
<td>255-574-7</td>
</tr>
</tbody>
</table>

**7-Methoxy-3,7-dimethyl-2-octanol**

3,7-Dimethyl-7-methoxy-2-octanol; Dihydromethoxyelgenol; Elesant; Osyrol

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 (127) citing 1 negative maximisation test (n=27).
### METHYL p-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 antranilate; 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 (163).

**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)propionaldehyde; 3-(3,4-Methylenedioxyphenyl)-2-methylpropanal; Heliofresh; Heliofres; Heligan; Helional; Heliproanal; 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).
**METHYL BENZYL ACETATE**

<table>
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<tr>
<th>CAS #</th>
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<tr>
<td>93-92-5</td>
<td>202-288-5</td>
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</table>

**1-Phenylethyl acetate**

Benzenemethanol, \(\alpha\)-methyl-, acetate; Benzyl alcohol, \(\alpha\)-methyl-, acetate; \((\pm)\)-Styrallyl acetate; \((\pm)\)-\(\alpha\)-Methylbenzyl acetate; \((\pm)\)-\(\alpha\)-Phenethyl acetate; 1-Acetoxy-1-phenylethane; 1-Phenylethyl acetate; Gardenol II; Gardenol; Methyl phenyl carbinyl acetate; Methylphenylcarbinol acetate; NSC 2397; Styrrallyl acetate; sec-Phenethyl acetate; sec-Phenylethyl acetate; \(\alpha\)-Methylbenzenemethanol acetate; \(\alpha\)-Methylbenzyl acetate; \(\alpha\)-Methylbenzyl alcohol, acetate; \(\alpha\)-Phenethyl acetate; \(\alpha\)-Phenylethyl acetate

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

**METHYL CINNAMATE**

<table>
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<tr>
<th>CAS #</th>
<th>EC #</th>
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<tr>
<td>103-26-4</td>
<td>203-093-8</td>
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**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) (164).  
Additional information:  
A RIFM review is available (165), reviewing, e.g., a number of animal studies with conflicting results. See also under Myroxylon pereirae.

**6-METHYL COUMARIN**

<table>
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<tr>
<th>CAS #</th>
<th>EC #</th>
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<tr>
<td>92-48-8</td>
<td>202-158-8</td>
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</table>

**6-Methylichromen-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 (166). Cardoso et al. report on 2 photoallergic patch test reactions to this substance, which were apparently clinically relevant, in 83 Portuguese patients tested (167). Similar results (2 of 76 patients with positive photopatchtest) were reported from New York (168).
**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 (169), 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-pentyl cyclopentyl) acetate
Cyclopentaneacetic acid, 3-oxo-2-pentyl-, methyl ester; Kharismal; MDJ; Methyl (3-oxo-2-pentylcyclopentyl)acetate; Methyl 3-oxo-2-pentylcyclopentane ethanoate; Hedione

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 (127) 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 (170).

**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%
### METHYL 2-OCTYNOATE

**CAS #** 111-12-6  
**EC #** 203-836-6  
**Methyl oct-2-ynoate**

M2O; Methyl heptin carbonate; Folione; Methyl hept-1-yn-1-carboxylate; Methyl pentylnacetylencarboxylate; NSC 72098; Vert de violette artificial  

**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 (172).  

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 oction carbonate had been found sensitisers – probably due to their very similar chemical structure (171). 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 (173).

**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-Dimethoxyallylbenezene; 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; Methylechavibetol; 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. (174).

**Additional information:**

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


### 5-METHYL-alpha-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 (175), 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 (176). 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 (177).  
Additional information:  
A RIFM review is available (178) 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: /
**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

<table>
<thead>
<tr>
<th>Current regulation:</th>
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<tbody>
<tr>
<td>Clinical data:</td>
<td>In a clinical study in 6 European centres, including 1511 consecutive patients, 1 patient had a positive reaction to oxidized myrcene (64).</td>
</tr>
<tr>
<td>Additional information:</td>
<td>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 (179).)</td>
</tr>
</tbody>
</table>

**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

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<tbody>
<tr>
<td>Clinical data:</td>
<td>/</td>
</tr>
<tr>
<td>Additional information:</td>
<td>A RIFM review exists (180), citing 2 of 3 HRIPT studies with 1 case of sensitisation to myrtenol each.</td>
</tr>
</tbody>
</table>

**NEROL**

CAS # 106-25-2  
EC # 203-378-7

**(2Z)-3,7-dimethyloct-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; Nerol 900; Neryl alcohol; cis-3,7-Dimethyl-2,6-octadien-1-ol; cis-Geraniol; β-Nerol; cis-geraniol – i.e., isomeric to geraniol

<table>
<thead>
<tr>
<th>Current regulation:</th>
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<tbody>
<tr>
<td>Clinical data:</td>
<td>In the Larsen 2002 c study, 6.0% of the fragrance sensitive patients reacted positively to 5% in pet. (1).</td>
</tr>
<tr>
<td>Additional information:</td>
<td>A RIFM review is available (181) citing (negative) human sensitisation experiments, an older study from Japan and the Larsen 2002 c study (see above). Regarding autoxidation studies – see geraniol.</td>
</tr>
</tbody>
</table>
### 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 (182) citing the occurrence of “3 positive reactions in 2273 patients”. Another RIFM review is available on cis-nerolidol (183), 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 (127), citing a negative maximisation test (n=29).
### Penta decalactone

**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-Pentadecalione; 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 (*Tanacetum parthenium*) is possible (184).

### 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 (185), 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%.

### PHENOXYETHYL ISOBUTYRATE

**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).

### PHENYLACETALDEHYDE

**CAS #** 122-78-1  
**EC #** 204-574-5  
2-Phenylacetaldehyde  
Benzylcarboxaldehyde; Hyacinthin; NSC 406309; Phenacetaldehyde; Phenylacetaldehyde; Phenylacetic aldehyde; Phenylethananal; 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) (186).  
Additional information:  
SCCS opinion: [1153/08 - Opinion on "Dermal Sensitization Quantitative Risk Assessments" (QRA: Citral, farnesol and phenylacetaldehyde)](https://www.sccs.info/assets/SCCS/opinion/1153/1153-08.pdf)

### PHENYLISOHEXANOL

**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; Phenoxyanol

Current regulation: /  
Clinical data: /
**PHENYLPROPANOL**

CAS # 122-97-4  
EC # 204-587-6

3-Phenylpropan-1-ol  
(3-Hydroxypropyl)benzene; 1-Hydroxy-3-phenylpropane; 3-Benzene propanol; 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 µg/cm²), applied in petrolatum, as reported in a RIFM review (187).

**alpha-PINENE and beta-PINENE**

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; (±)-2-Pinene; (±)-α-Pinene; Acintene A; NSC 7727; PC 500; PC 500 (terpene); Sylvapine A; α-Pinene  
127-91-3: 2(10)-Pinene; (±)-2(10)-Pinene; (±)-6,6-Dimethyl-2-methylenebicyclo[3.1.1]heptane; (±)-β-Pinene; 6,6-Dimethyl-2-methylenebicyclo[3.1.1]heptane; NSC 21447; NSC 406265; NSC 59190; Nopinen; Nopinene; PC 600; PC 600 (pesticide); Pseudopinen; 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 (188). 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 (189).

A case report from Zacher and Ippen on 2 patients with allergic contact dermatitis due to bergamot oil (190) describes positive patch test reactions to alpha-pinene and beta-pinene in one, a worker in a perfume factory.

Additional information: /

**PROPYLIDENE PHTHALIDE**

<table>
<thead>
<tr>
<th>CAS #</th>
<th>17369-59-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC #</td>
<td>241-402-8</td>
</tr>
</tbody>
</table>

3-Propylidene-2-benzofuran-1-one

3-Propylidene-1(3H)-isobenzofuranone; 3-Propylideneephthalide; Celerixa; Propylideneephthalide

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: /

**RHODINOL**

<table>
<thead>
<tr>
<th>CAS #</th>
<th>6812-78-8</th>
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</thead>
<tbody>
<tr>
<td>EC #</td>
<td>229-887-4</td>
</tr>
</tbody>
</table>

(3S)-3,7-Dimethyloct-7-en-1-ol

Rhodinol; (-)-Rhodinol; α-citronellol; (-)-α-Citronellol; (S)-α-Citronellol

Current regulation: / (see below)

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 (191). In a previous RIFM review (127), 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., 1988)”

**trans-ROSE KETONE-5**

<table>
<thead>
<tr>
<th>CAS #</th>
<th>39872-57-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC #</td>
<td>254-663-8</td>
</tr>
</tbody>
</table>

(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-buten-1-one

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Current regulation: Annex III, part 1, n° 159 (max. conc. 0.02%)
Clinical data: / 
Additional information: 
A RIFM review is available (192) 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; Salicyl; Salicylic aldehyde; α-Formylphenol; α-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 Wöhrl 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 (193). Among 24 patients sensitised to resorcinol by application of a wart remover, 2 positive reactions to salicylaldehyde were observed (194). 
Additional information: Along with other derivates 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 (195).

**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.
**beta-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-[1a,2a(Z),4a] ]-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 (196) and on “santalol” (CAS # 11031-45-1 (197). 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 (MJDCRG) 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.” (isofrom not specified) – all sensitised to other fragrance allergens as well (23). In the Larsen 2001 study, patch testing with “2-methyl-5-(2,3-dimethyl tricyclo[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 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 isofroms – often not differentiated in

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reports – are considered as one and considered as established contact allergen in humans

<table>
<thead>
<tr>
<th>SCLAREOL</th>
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<tbody>
<tr>
<td>CAS # 515-03-7</td>
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<tr>
<td>EC # 208-194-0</td>
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<tr>
<td><strong>(1R,2R,8αS)-1-[(3R)-3-hydroxy-3-methylpent-4-enyl]-2,5,5,8a-tetramethyl-3,4,4α,6,7,8-hexahydro-1H-naphthalen-2-ol</strong></td>
</tr>
<tr>
<td>((αR,1R,2R,4αS,8αS)-α-Ethenyldecahydro-2-hydroxy-α,2,5,5,8a-pentamethyl-1-naphthalenepropanol; [1R-([1α(R^<em>)],2β,4αβ,8αα]) - α-ethenyldecahydro-2-hydroxy-α,2,5,5,8a-pentamethyl-1 Naphthalenepropanol; (13R)-Labd-14-ene-8,13-diol; Sclareol; (-)-Sclareol; [1R-([1.α.(R^</em>),2.β.,4.α.β.,8.α.α.])]-2-hydroxy-α,2,5,5,8a-pentamethyl-α- vinyldecahydronaphthalene-1-propan-1-ol**</td>
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<tr>
<td>Current regulation: /</td>
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<td>Clinical data: /</td>
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<tr>
<td>Additional information: An older RIFM review exists (127), reporting several human maximisation tests with different samples of sclareol, yielding partly positive, partly negative results. A more recent RIFM review is available (198), citing no clinical data, but several maximisation studies, one of which was positive in a few volunteers, which was apparently due to an impurity.</td>
</tr>
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<td><strong>0986/06 - Opinion on Sclareol (sensitisation only)</strong></td>
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<td>(<a href="http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_056.pdf">http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_056.pdf</a>)</td>
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<table>
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<tr>
<td>CAS # 8000-41-7</td>
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<tr>
<td>EC # 232-268-1</td>
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<tr>
<td><strong>Mixtures of isomers</strong></td>
</tr>
<tr>
<td>Terpineol 318, mixture of terpineol isomers αlfa, beta, gamma</td>
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<tr>
<td>Current regulation: /</td>
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<tr>
<td>Clinical data: A RIFM review is available (199), citing negative human induction studies and one clinical study &quot;Takenaka 1986&quot;, 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).</td>
</tr>
<tr>
<td>Additional information: It is a &quot;top 100&quot; substance (IFRA, pers. comm. M.Vey 2010).</td>
</tr>
</tbody>
</table>
### alpha-TERPINEOL

**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; (±)-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-methylocyclohexene; 8-Hydroxy-p-menth-1-ene; NSC 21449; NSC 403665; PC 593; Pine Oil 593; Terpineol 350; dl-α-Terpineol; a,a,4-Trimethyl-3-cyclohexene-1-methanol; α-Terpineol

**Current regulation:** /

**Clinical data:**

A RIFM review is available (200) specifically on (−)-alpha-terpineol stating that "no data is available" regarding skin sensitisation. Another RIFM review is available on alpha-terpineol (201). 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 (188)

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

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### Terpinolene

**CAS #** 586-62-9  
**EC #** 209-578-0

1-Methyl-4-propan-2-ylidenecyclohexene

- p-Mentha-1,4(8)-diene; 1-Methyl-4-(1-methylethylene)-cyclohexene; 4-Isopropylidene-1-methylocyclohexene; Isoterpinene; Nofmer TP; Terpinolene; Terpinolene; α-Terpinolene; δ-Terpinene

**Current regulation:** Annex III, part 1, n° 133 (Peroxide value less than 10 mmoles/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 δelta.-3-carene and terpinolene, tested 5% pet., gave a positive result (negative in 10 controls) (202). Eleven patients sensitised to tea tree oil showed positive reactions to alpha-terpinene, terpinolene and ascaridol (203).

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

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**alpha-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, α,α,4-trimethyl-, acetate; p-Menth-1-en-8-ol, acetate; (±)-α-Terpineol acetate; (±)-α-Terpinyl acetate; 2-(4-Methyl-3-cyclohexen-1-yl)-2-propyl acetate; Terpinyl acetate; α-Terpinyl acetate; p-Menth-1-en-8-yl acetate; 1-Methyl-1-(4-methylcyclohex-3-enyl)ethyl ethanoate; (±)-α.,α.,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. M.Vey 2010)

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**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. M.Vey 2010). A RIFM review is available (204) quoting 1 negative human maximisation test.

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**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

<table>
<thead>
<tr>
<th>CAS #</th>
<th>EC #</th>
<th>Chemical Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>54464-57-2</td>
<td>259-174-3 / 259-175-9 / 268-978-3 / 268-979-9</td>
<td>1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-ethanone (54464-57-2)</td>
</tr>
<tr>
<td>54464-59-4</td>
<td>259-175-9 / 268-978-3 / 268-979-9</td>
<td>1-(1,2,3,4,5,6,7,8-octahydro-2,3,5,5-tetramethyl-2-naphthalenyl)-ethanone (54464-59-4)</td>
</tr>
<tr>
<td>68155-66-8</td>
<td>259-174-3 / 259-175-9 / 268-978-3 / 268-979-9</td>
<td>1-(1,2,3,5,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-ethanone (68155-66-8)</td>
</tr>
<tr>
<td>68155-67-9</td>
<td>259-174-3 / 259-175-9 / 268-978-3 / 268-979-9</td>
<td>1-(1,2,3,4,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-ethanone (68155-67-9)</td>
</tr>
</tbody>
</table>

Current regulation: /  
Clinical data: In the Frosch 2002 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-naphthalenyl)ethanone; 1',2',3',4',5',6',7',8'-Octahydro-2',3',8',8'-tetramethyl-2'-acetonaphthone; 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

# TRICHLOROMETHYL PHENYL CARBINYL ACETATE

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<tbody>
<tr>
<td>90-17-5</td>
<td>201-972-0</td>
<td>2,2,2-Trichloro-1-phenylethyl acetate</td>
</tr>
</tbody>
</table>

Current regulation: /  
Clinical data: /  
Additional information: It is a “top 100” substance (IFRA, pers. comm. M.Vey 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, 3α,4,5,6,7,7α-hexahydro-, propanoate; 4,7-Methanoinden-6-ol, 3α,4,5,6,7,7α-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. M.Vey 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. (205). 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 Almimiral/Hermal/Trolab used later instead. There was no significant difference between these proportions obtained with batches of majantol from different production processes (206).  
Additional information: /
<table>
<thead>
<tr>
<th><strong>TRIMETHYLHEXYL ACETATE</strong></th>
<th><img src="image" alt="Structure" /></th>
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<td>EC # 261-245-9</td>
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</tr>
<tr>
<td><strong>3,5,5-trimethylhexyl acetate</strong></td>
<td>1-Hexanol, 3,5,5-trimethyl-, acetate; Vanoris; neononyl acetate</td>
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<td>Clinical data: /</td>
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<tr>
<td>Additional information: It is a “top 100” substance (IFRA, pers. comm. M.Vey 2010)</td>
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<table>
<thead>
<tr>
<th><strong>TRIMETHYL-PROPYLECYCLOHEXANEPROPANOL (TMCH)</strong></th>
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<tr>
<td>CAS # 70788-30-6</td>
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<tr>
<td>EC # 274-892-7</td>
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</tr>
<tr>
<td><strong>1-(2,2,6-trimethylcyclohexyl)hexan-3-ol</strong></td>
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<tr>
<td>Other names: 2,2,6-Trimethyl-alpha-propylecyhcloxanepropanol (REACH, EINECS); alpha.-Propyl-2,2,6-trimethyl-cyclohexane propanol; 6-(2,2,6-Trimethylcyclohexyl)-4-hexanol; Finotimber; Timberol</td>
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<tr>
<td>Current regulation: /</td>
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<td>Clinical data:</td>
<td></td>
</tr>
<tr>
<td>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).</td>
<td></td>
</tr>
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<td>Additional information: ...</td>
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<table>
<thead>
<tr>
<th><strong>gamma-UNDECALACTONE</strong></th>
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<tr>
<td>CAS # 104-67-6</td>
<td></td>
</tr>
<tr>
<td>EC # 203-225-4</td>
<td></td>
</tr>
<tr>
<td><strong>5-Heptyltetrahydrofuran-2-one</strong></td>
<td>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</td>
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<td>Current regulation: /</td>
<td></td>
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</tr>
<tr>
<td>Additional information: It is a “top 100” substance (IFRA, pers. comm. M.Vey 2010)</td>
<td></td>
</tr>
</tbody>
</table>
**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; Vanillin 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 Wöhrl 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 (207). In 21 patients with contact allergy to propolis, 2 also reacted to vanillin (10% pet.) (208).

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 (209). 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 (52). 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 (52). It is a “top 100” substance and classified as R43 (IFRA, pers. comm. M.Vey 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, 3α,4,5,6,7,7α-hexahydro-, acetate; 4,7-Methanoinden-5-ol, 3α,4,5,6,7,7α-hexahydro-, acetate; NSC 142428; NSC 94573

5413-60-5: 4,7-Methano-1H-inden-6-ol, 3α,4,5,6,7,7α-hexahydro-, acetate; 4,7-Methanoinden-6-ol, 3α,4,5,6,7,7α-hexahydro-, acetate; 4,7-Methano-3α,4,5,6,7,7α-hexahydroinden-6-y acetate; 8-Acetoxytricyclo[5.2.1.02,6]dec-3-ene; Greenyl acetate; Herbaflorat; Jasmacyclene; NSC 6598

Current regulation: /

Clinical data: /

Additional information:
In CosIng, both above CAS numbers are listed under “verdyl acetate”
In the CAS, there are 2 separate entries; moreover, there are 2 separate RIFM reviews:

- # 2500-83-6: Other names: Tricyclo[5.2.1.02,6]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 (210).

- # 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[5.2.1.02,6]dec-3-ene; Tricyclodecenyl acetate; Greenyl acetate; Herbaflorat; Jasmacyclene; NSC 6598; Verdyl acetate. It is a “top 100” substance (IFRA, pers. comm. M.Vey 2010). A RIFM review is available (211), 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, 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 in small oil glands, mostly highly volatile terpene hydrocarbons. However, they also contain small amounts of non-volatile compounds such as dyes, waxes and furcocoumarines. 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) concretes, an extract of fresh plant material with nonpolar solvents, containing not only volatile, 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 nonpolar solvents. The products are usually highly viscous and thus sometimes diluted, e.g. with phthalates or benzyl benzoate. Oleoresins are concentrates prepared from spices by solvent extraction (34).

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 (212, 213), aromatherapists (214-218), beauticians doing massages (219); for further details, e.g., PT results with various essential oils, see original case reports.

Catalogue of natural extracts / essential oils evaluated

<table>
<thead>
<tr>
<th>Acorus Calamus Root Oil</th>
<th>CAS 84775-39-3; EC 283-869-0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calamus Oil; &quot;Sweet Flag Oil&quot;</td>
<td>(Acorus calamus, ext. = INCI name)</td>
</tr>
</tbody>
</table>

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:
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)
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; EC / (oils, ylang-ylang) INCI name: CANANGA ODORATA OIL

Current regulation: ...

Clinical data:

**Ylang-ylang oil**

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%) (220). 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).

Cananga oil

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. (219, 221).

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**

* Cedrus atlantica, ext. = INCI) / 8000-27-9; EC / (Oils, cedwood) INCI name: CEDRUS ATLANTICA OIL

Cedarwood oil

**CEDRUS DEODARA WOOD OIL**

* Cedrus deodara, ext. / 91771-47-5 (Cedrus deodara, ext.)

Cedarwood oil

Current regulation: /

Clinical data:

In the Wöhrl 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)

See also *Juniperus virginiana*.

**CEDRUS DEODARA WOOD OIL**

* Cedrus deodara, ext. / 91771-47-5 (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 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 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 funebris (Endl.) France), which is a weeping cypress [8000-27-9] [85085-29-6] (34).

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**CINNAMOMUM CASSIA LEAF OIL**

Cassia Oil; Cassia leaf Oil; Cinnamon Oil Chinense

**CINNAMOMUM ZEYLANICUM BARK OIL**

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.) (222).

Additional information:
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 cinnamonum 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 Cinnamom, 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)

71
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.

<table>
<thead>
<tr>
<th><strong>CITRUS AURANTIUM AMARA</strong> FLOWER OIL</th>
<th>CAS 8016-38-4; EC / (Oils, neroli)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neroli oil</td>
<td>/</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>CITRUS AURANTIUM AMARA</strong> PEEL OIL</th>
<th>72968-50-4; EC 277-143-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXPRESSED</td>
<td>(Orange, sour, ext.)</td>
</tr>
<tr>
<td>&quot;Bitter Orange Oil&quot;</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>CITRUS AURANTIUM AMARA</strong> LEAF OIL</th>
<th>72968-50-4; EC 277-143-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petitgrain oil Paraguay / ... bigarade</td>
<td>(Orange, sour, ext.)</td>
</tr>
</tbody>
</table>

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:
For Oil of neroli (Citrus aurantium L. spp. aurantium, syn. Citrus aurantium L. spp.
Expressed is an essential oil expressed from the fresh epicars 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); \textit{trans}-β-ocimene (8); geranyl acetate (5); \textit{trans}-nerolidol (5); (\textit{E},\textit{E})-farnesol (4); myrcene (4); farnesol (4,0); geraniol (3,5); citral (0,3)
(30).

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**

| Bergamot Oil, Bergamot Orange Oil | CAS 89957-91-5; EC 289-612-9 (Bergamot, ext.) |

**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 (190), one a worker in a perfume factory, the other sensitised by non-occupational use of cosmetics.

Additional information:
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=se arch.details&id=41398](http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?FuseAction=se arch.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**

| Lemon oil | CAS 84929-31-7; EC 284-515-8 (Lemon, ext.) |

**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 Wöhr 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:
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 an the country of origin, see table from (34).
**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  
It is a “top 200” substance and classified as R43 (IFRA, pers. comm.2010)

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**CITRUS SINENSIS** (syn.: AURANTIUM DULCIS)  
PEEL OIL EXPRESSED  
(Orange) Orange oil  
CAS 97766-30-8, EC 307-891-8  
(Orange, sweet, Valencia, ext. = INCI) / 8028-48-6; EC 232-433-8  
(Orange, sweet, ext.)  
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 Wöhrl 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 study identified 0.2% positive reactions in 6246 patients tested in the context of a special series (30).

Additional information:

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) (223).

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).

**CORIANDRUM SATIVUM**

*Herb 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.

<table>
<thead>
<tr>
<th>CYMBOPOGON CITRATUS LEAF OIL</th>
<th>CAS 89998-14-1; EC 289-752-0 (Cymbopogon citratus, ext. = INCI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lemon Grass Oil; Indian Verbena Oil; Indian Melissa Oil</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CYMBOPOGON SCHOENANTHUS OIL</th>
<th>CAS 8007-02-1; EC 289-754-1 (oils, lemongrass) / 89998-16-3; EC 289-752-0 (Cymbopogon Schoenanthus, ext. = INCI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lemon Grass Oil</td>
<td></td>
</tr>
</tbody>
</table>

**Current regulation:** /

**Clinical data:**

The Frosch 2002 b study on 1606 consecutive patients reported 1.6% positive reactions to “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 Wöhrl 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%), geranial (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% geranial (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 (224))

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% (224).
**CYMBOPOGON MARTINI HERB EXTRACT**

Current regulation: /  
Clinical data: /  
Additional information:  
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% (224).

**CYMBOPOGON NARDUS HERB OIL**

Current regulation: /  
Clinical data: /  
Additional information:  
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% isopugonol I, 1.4% germacrene D and eugenol and linalool at < 1%, according to analyses of the supplier. The EC3 value was calculated as > 50 % (224).

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

<table>
<thead>
<tr>
<th><strong>EUCALYPTUS SPP. LEAF OIL</strong></th>
<th>CAS 92502-70-0; EC 296-357-7 (Eucalyptus, ext. = INCI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eucalyptus Oil</strong></td>
<td>CAS 8000-48-4; EC / (Oils, eucalyptus) INCI: EUCALYPTUS GLOBULUS OIL</td>
</tr>
</tbody>
</table>

**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 Wöhrl 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 (225)

Additional information:
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); o-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).

<table>
<thead>
<tr>
<th><strong>EUGENIA CARYOPHYLLUS LEAF / FLOWER OIL</strong></th>
<th>CAS 8000-34-8; EC / (Oils, clove)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clove oil</strong></td>
<td>INCI: EUGENIA CARYOPHYLLUS OIL</td>
</tr>
</tbody>
</table>

**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 Wöhrl 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 physiotherapists developed vesicular hand dermatitis after using a "balsam from ash extract" cream. P Ting 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.) (222).

Additional information:
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% (224).

**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 (52). 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) (52).

**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' (226).
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 (227). 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 (228). 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 Wöhrl 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 breakdown testing to the FM I, had a positive PT reaction (7).

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 (229). 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 (230).

Additional information:
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.
Clinical data:
In the Frosch 2002 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 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).

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 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) |
| JUNIPERUS VIRGINIANA WOOD OIL | Cedar Wood Oil (Virginian); CAS 85085-41-2; EC 285-370-3 |

Current regulation: /
Clinical data:
In the Frosch 2002 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 (232).

Additional information:
*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, thujaopsene, widdrol (http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=39767, last accessed 2009-11-12)(232). According to Surburg/Panten by GC:

alpha-cedrene 22-35%, thujaopsene 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); thujaopsene (25); cedrol (25); β-cedrene (6); widdrol (5) and cuparene (traces) (30).


<table>
<thead>
<tr>
<th><strong>Laurus Nobilis Oil</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS 8002-41-3; EC / (Oils, laurel)</td>
</tr>
<tr>
<td>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</td>
</tr>
</tbody>
</table>

Laurel oil

Current regulation: Annex II, n° 359 (seed oil)

Clinical data:
In the Wöhrl 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 (233). 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 (234). In an earlier Turkish case with a similar history, the EEM-like appearance was lacking; however, a very intense, edematous reaction was noted (235). 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:
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:**

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.

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**LAVANDULA OFFICINALIS FLOWER OIL**

**CAS 84776-65-8; 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.

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”) (236). A physiotherapist developed acute, recurrent dermatitis after use of “Difflam® gel”, scented with lavender oil. Both the gel and lavender oil (2% pet.) tested positive; avoidance resulted in clearing (237). 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 (238). In two cases, facial “pillow dermatitis” due to lavender oil, applied to the pillows, developed, confirmed by positive PT to lavender abs. (2% pet.) (239).

Additional information:
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 (≥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).


<table>
<thead>
<tr>
<th>LAVANDULA SPICA HERB OIL</th>
<th>CAS 97722-12-8; EC 307-762-6</th>
</tr>
</thead>
</table>
| "Spike Oil"              | (Lavender, Lavandula spica, ext. = INCI)

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:
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.

<table>
<thead>
<tr>
<th>LITSEA CUBEBA FRUIT EXTRACT</th>
<th>CAS 90063-59-5; EC 290-018-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Litsea cubeba, ext.) INCI: LITSEA CUBEBA OIL</td>
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</tbody>
</table>

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).
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 ¾ 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% (224). Considering the content of well-known allergenic compounds, this essential oil is regarded as established contact allergen in humans.

**MENTHA ARVENSIS LEAF 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 ...

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 Wöhrl 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 (153). 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 (240). 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 (241). 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.) (154). 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 (242).

Additional information:
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 (162), 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); menthofuran (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; 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 (243).

**Additional information:**
*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=40394, 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., (244, 245)). L-Carvone is a component of the oil from *Mentha spicata* (spearmint) (52) and had been tested with positive results in “toothpaste cases”, even at a concentration as low as 0.067% (67). 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 %)

<table>
<thead>
<tr>
<th>MYROXYLON PEREIRAE RESIN</th>
<th>CAS 8007-00-9; EC 232-352-8</th>
</tr>
</thead>
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<tr>
<td>Balsam of Peru</td>
<td>(Balsams, Peru)</td>
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<tr>
<td>INCI: MYROXYLON PEREIRAE</td>
<td>Balsams, Peru</td>
</tr>
</tbody>
</table>

Current regulation: Annex III, part 1, nº 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:
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 (246) 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 (247-250). 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 (246).

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 (246, 251). 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 (252)). 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 (253). In addition to delayed type hypersensitivity reactions, MPR (and some of his constituents such as benzoic acid (254)) are capable of eliciting (non-immunological) urticarial immediate reactions (255-257). 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 (258). Generally, there is apparently no association of immediate reactions to MPR (and cinnamal or cinnamyl alcohol) and contact sensitisation to these compounds (259). In animal experiments the sensitising potency of MPR was clearly established (247), with coniferyl benzoate identified as single compound with the most marked potency (249). However, due to the limited chemical stability of this compound is 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 (260).

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 pereirae resin (Balsam of Peru) 1. If not given in the publication, the confidence interval (CI) was calculated from the absolute numbers by the reviewers.
<table>
<thead>
<tr>
<th>Country</th>
<th>Population</th>
<th>Years</th>
<th>No. tested</th>
<th>Crude % positive (95% CI) $</th>
<th>§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tel Aviv, Israel (261) #</td>
<td>Consecutive patients</td>
<td>1999-2000</td>
<td>943</td>
<td>6.6 % (5.1 – 8.4)</td>
<td></td>
</tr>
<tr>
<td>South Korea (13)</td>
<td>Consecutive patients</td>
<td>04/2002 – 06/2003</td>
<td>422</td>
<td>7.3% (5.1 – 10.3%)</td>
<td></td>
</tr>
<tr>
<td>Tel Aviv, Israel (262)</td>
<td>Consecutive patients</td>
<td>1998-2004</td>
<td>2156</td>
<td>3.6 % (2.9 – 4.5)</td>
<td></td>
</tr>
<tr>
<td>Manipal, India (263)</td>
<td>Dermatitis patients</td>
<td>1989-1998</td>
<td>1780 n=17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tehran, Iran (264)</td>
<td>Consecutive patients</td>
<td>2002-2004</td>
<td>250</td>
<td>2.4 % (0.9 – 5.2)</td>
<td></td>
</tr>
<tr>
<td>Sevilla, Spain (265)</td>
<td>Consecutive patients</td>
<td>2002-2004</td>
<td>863</td>
<td>5.8 % (4.3 – 7.6)</td>
<td></td>
</tr>
<tr>
<td>Ankara, Turkey (266)</td>
<td>Consecutive patients</td>
<td>1992-2004</td>
<td>1038</td>
<td>2.1 % (1.3 – 3.2)</td>
<td></td>
</tr>
<tr>
<td>Vienna, Austria (22)</td>
<td>Consecutive patients of one clinic</td>
<td>1997-2000</td>
<td>2660</td>
<td>5.4% (4.6 – 6.3%)</td>
<td></td>
</tr>
<tr>
<td>Czech Republic (267)</td>
<td>Consecutive patients</td>
<td>1997-2001</td>
<td>12058</td>
<td>7.3% (6.8 – 7.8)</td>
<td></td>
</tr>
<tr>
<td>Copenhagen, Denmark (268)</td>
<td>Consecutive patients</td>
<td>1985-2007</td>
<td>16173</td>
<td>3.9 % (3.6 – 4.2)</td>
<td></td>
</tr>
<tr>
<td>Sweden (269)</td>
<td>Consecutive patients</td>
<td>2000</td>
<td>3790</td>
<td>6.5%</td>
<td></td>
</tr>
<tr>
<td>9 European countries (270) $</td>
<td>Consecutive patients</td>
<td>2002-2003</td>
<td>9672</td>
<td>6.1%</td>
<td></td>
</tr>
<tr>
<td>Germany, 3 Swiss + 1 Austrian Dept. (7)</td>
<td>Consecutive patients</td>
<td>2005-2008</td>
<td>36919</td>
<td>8.0% (7.7 – 8.3%)</td>
<td></td>
</tr>
<tr>
<td>10 depts. From 7 EU countries (271) *</td>
<td>Consecutive patients</td>
<td>1996-2000</td>
<td>26210</td>
<td>6.0 %</td>
<td></td>
</tr>
<tr>
<td>USA (Canada) (20)</td>
<td>Probably consecutive patients</td>
<td>2003</td>
<td>1603</td>
<td>6.6%</td>
<td></td>
</tr>
<tr>
<td>NACDG 2009 (21)</td>
<td>Consecutive patients</td>
<td>2005-2006</td>
<td>4449</td>
<td>11.9%</td>
<td></td>
</tr>
</tbody>
</table>

$ Calculated by reviewers, where possible (if actual numbers were given)

# Probably included in (262)

$ > 5-fold difference between departments

* About 4-fold difference between departments

**NARCISSUS SPP. EXTRACT / OIL**

**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:
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); Δ³-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  
*Ocimum basilicum, ext. = INCI* 
**Basil Oil (sweet)**  
CAS 84775-71-3; EC 283-900-8 (Ocimum basilicum, ext. = INCI)

**Current regulation:** /  
**Clinical data:** /  
**Additional information:**  
- 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% (224).

**PELARGONIUM GRAVEOLENS** FLOWER OIL  
*Pelargonium graveolens, ext. = INCI* / 8000-46-2; EC / (Oils, geranium) INCI: GERANIUM

**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).  
**Additional information:**  
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-guaiadine, 6.2% isomenthone, 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% (224).

### PELARGONIUM ROSEUM LEAF OIL

**Geranium Oil; Rose Geranium Oil**

<table>
<thead>
<tr>
<th>CAS 90082-55-6; EC 290-144-2</th>
<th>(Pelargonium roseum, ext. = INCI)</th>
</tr>
</thead>
</table>

**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

**Bay oil (34)**

<table>
<thead>
<tr>
<th>CAS 85085-61-6; EC 285-385-5</th>
</tr>
</thead>
</table>

**Current regulation:** /

**Clinical data:**

**Additional information:**
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

**Dwarf pine needle oil**

<table>
<thead>
<tr>
<th>Dwarf pine needle oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>(German: Latschenkiefernöl)</td>
</tr>
<tr>
<td>CAS 90082-72-7; EC 290-163-6</td>
</tr>
</tbody>
</table>

**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:**
Pinus Mugo Twig Oil is an essential obtained from the twigs of the Pine, Pinus mugo,

<table>
<thead>
<tr>
<th>PINUS PUMILA TWIG LEAF EXTRACT / OIL</th>
<th>CAS 97676-05-6; EC 307-681-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dwarf pine needle oil</td>
<td>(Pine, Pinus pumila, ext. = INCI)</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>POGOSTEMON CABLIN OIL</th>
<th>CAS 8014-09-3; EC / (Oils, patchouli) / 84238-39-1; EC 282-493-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patchouli oil</td>
<td>POGOSTEMON CABLIN / Patchouli, ext.</td>
</tr>
</tbody>
</table>

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:
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 norpatchoulenol [41429-52-1] (0.35-1%). Other constituents include (+)-alpha-bulnesene [6391-11-0] (13-21%), (-)-alpha-guajene [3691-12-1] (11-16%), (-)-8-patchoulen [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);
It is a “top 100” substance (IFRA, pers. comm.2010).

ROSE FLOWER OIL (ROSA SPP.)
ROSA ALBA FLOWER EXTRACT
ROSA CANINA FLOWER OIL
ROSA CENTIFOLIA FLOWER OIL
ROSA DAMASCENA FLOWER OIL
ROSA GALlica FLOWER OIL
ROSA MOSCHATA OIL
ROSA RUGOSA FLOWER OIL

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 (272). 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 (273). 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.

Additional information:
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 Canina Flower Oil is the volatile oil obtained from the flowers of the Hip Rose, Rosa canina L., Rosaceae

- Rosa Centifolia Flower Oil is the volatile oil obtained from the flowers of the Cabbage Rose, Rosa centifolia (L.), Rosaceae

- Rosa Damascena Flower Oil is the volatile oil obtained from the flowers of the Damask Rose, Rosa damascena, Rosaceae

- Rosa Gallica Flower Oil is the volatile oil obtained from the flowers of the French Rose, Rosa gallica L., Rosaceae

- Rosa Moschata Oil is the oil obtained from the Musk Rose, Rosa moschata, Rosaceae

- Rosa Rugosa Flower Oil is the volatile oil obtained from the flowers of the Rose, Rosa rubiginosa L., Rosaceae

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 (273). Main constituents by GC are: citronellol (20-49%), geraniol (6-23%), nerol (3-12%) and phenylethyl alcohol (up to 3.5%) (34).


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**ROSMARINUS OFFICINALIS FLOWER OIL**

"Rosemary Oil"

<table>
<thead>
<tr>
<th>CAS 84604-14-8; EC 283-291-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Rosemary, ext.)</td>
</tr>
<tr>
<td><strong>INCI:</strong> ROSMARINUM OFFICINALIS / Rosemary, ext.</td>
</tr>
</tbody>
</table>

**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:**
Considering the content of well-known allergenic compounds, this essential oil is regarded as established contact allergen in humans.
### SALVIA spp. HERB 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:**


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.
<table>
<thead>
<tr>
<th><strong>SANTALUM ALBUM WOOD OIL</strong></th>
<th>CAS 84787-70-2; EC 284-111-1 (Sandalwood, ext.) INCI: SANTALUM ALBUM / Sandalwood, ext.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sandalwood oil ([East] India)</strong></td>
<td>CAS 8006-87-9; EC / (Oils, sandalwood)</td>
</tr>
</tbody>
</table>

**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).  

**Additional information:**  
*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) (274). A review on the toxicological properties of "Santalum album oil" is available (275).  

*AMYRIS BALSAMIFERA BARK OIL (Sandalwood oil (Carribean)), 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...

<table>
<thead>
<tr>
<th>SANTALUM SPICATA</th>
<th>WOOD OIL</th>
<th>CAS 8024-35-9; EC 296-618-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandalwood oil (Australia)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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:
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.

<table>
<thead>
<tr>
<th>TAGETES PATULA</th>
<th>FLOWER OIL</th>
<th>CAS 91722-29-1; EC 294-431-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Marigold Oil; Tagetes Oil&quot;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 (214).

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, dihydrotagetone, tagetone, and cis- and trans-ocimenone (34, 39).

<table>
<thead>
<tr>
<th>THYMUS spp.</th>
<th>HERB OIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>THYMUS VULGARIS</td>
<td>HERB OIL</td>
</tr>
</tbody>
</table>

"Thyme oil"

<table>
<thead>
<tr>
<th>THYMUS VULGARIS</th>
<th>HERB OIL</th>
<th>CAS 84929-51-1; EC 284-535-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Thyme, Thymus vulgaris, ext.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INCI: THYMUS VULGARIS / Thyme, Thymus vulgaris, ext.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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:
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.

<table>
<thead>
<tr>
<th><strong>TURPENTINE</strong> (oil)</th>
<th>CAS 8006-64-2 / 9005-90-7 / 8052-14-0; EC 232-350-7 / 232-688-5 / -</th>
</tr>
</thead>
</table>

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 (189)

**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.

<table>
<thead>
<tr>
<th><strong>Country</strong></th>
<th><strong>Population</strong></th>
<th><strong>Years</strong></th>
<th><strong>No. tested</strong></th>
<th><strong>Crude % positive (95% CI)§</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisbon, Portugal (188); virtually no. delta.-3-carene</td>
<td>Consecutive patients</td>
<td>1979-1983</td>
<td>4316</td>
<td>2.3 % (1.9 – 2.8) §</td>
</tr>
<tr>
<td>Birmingham, UK (189)</td>
<td>Potters with occup. hand dermatitis</td>
<td>6 months; prior to 1996</td>
<td>24</td>
<td>14 / 24 pos. to “Indonesian turpentine”</td>
</tr>
<tr>
<td>Austria/Germany (IVDK) (276)</td>
<td>Consecutive patients</td>
<td>1992-1995</td>
<td>27658</td>
<td>0.47 % (0.39 – 0.55) §</td>
</tr>
<tr>
<td>Austria/Germany (IVDK) (277)</td>
<td>Consecutive patients</td>
<td>1996-2002</td>
<td>59478</td>
<td>Annual prevalences 1.6 to 4.4 %</td>
</tr>
<tr>
<td>Augsburg/Germany (278)</td>
<td>Population sample</td>
<td>1998</td>
<td>1141</td>
<td>1.2% (on population level!)</td>
</tr>
<tr>
<td>Europe (ESSCA) (270)</td>
<td>Consecutive patients</td>
<td>2002/03</td>
<td>3767</td>
<td>1.6 %</td>
</tr>
<tr>
<td>Austria/Germany/ Switzerland (IVDK) (7)</td>
<td>Consecutive patients</td>
<td>2005-2008</td>
<td>37163</td>
<td>1.8 %</td>
</tr>
</tbody>
</table>

Additional information:
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  


The composition of oil of turpentine varies with its origin, in particular, the content of \( \delta\text{-}3\text{-} \)carene, one of its main allergenic compounds (188, 276). Similarly, the peroxide degree may vary. The main constituents are \( \alpha\text{-} \)pinene (50-72%), \( \beta\text{-} \)pinene (6-15%), carenes (< 0.1-17%), camphene (up to 1%), dipentene (0.5-5%), along with a number of other substances (276).

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

<table>
<thead>
<tr>
<th><strong>Verbena absolute (Lippia citriodora Kunth.)</strong></th>
<th>CAS 8024-12-2; EC /</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current regulation: Annex III, part 1, n° 206</td>
<td></td>
</tr>
<tr>
<td>Clinical data: /</td>
<td></td>
</tr>
<tr>
<td>Additional information:</td>
<td></td>
</tr>
<tr>
<td>An older RIFM review is available citing several positive human maximisation studies both with ”Verbena absolute” and ”Verbena oil” (127).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>VETIVERIA ZIZANOIDES ROOT OIL</strong></th>
<th>CAS 8016-96-4; EC / (Oils, vetiver) / 84238-29-9; EC 282-490-8 (Vetiveria zizanioides, ext. = INCI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Vetiver oil; khas khas oil&quot;</td>
<td></td>
</tr>
</tbody>
</table>

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:
Vetiveria Zizanoides Root Oil is an essential oil distilled from the dried roots of the grass *Vetiveria zizanioides* (L.) Nash  *Poaceae*  

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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