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Review

A toxicologic and dermatologic assessment of cyclic and non-cyclic terpene alcohols when used as fragrance ingredients ☆

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1. Chemical identity, regulatory status and exposure (Table 1)

This report summarizes safety data relevant to the risk assessment of the use of some cyclic and non-cyclic terpene alcohols as fragrance ingredients.

1.1. Rationale for grouping acyclic and cyclic terpene alcohols together

The common characteristic structural element of acyclic (non-cyclic) and cyclic terpene alcohols is the typically branched isoprene unit (2-methyl-1,3-butadiene). Materials covered in this assessment contain two (monoterpenes), three (sesquiterpenes) or four (diterpenes) isoprene units.

The group consists of *11 non-cyclic primary alcohols* (citronellol, L-citronellol, (+)(−)-citronellol, 6,7-dihydrogeraniol, 3,7-dimethyl-1-octanol, 3,7-dimethyloct-7-en-1-ol, farnesol, geraniol, hydroxycitronellol, nerol and rhodinol), *6 cyclic primary alcohols* (*p*-mentha-1,8-dien-7-ol, *p*-menthan-1-ol, myrtenol, octahydro-7.7.8. 8-tetramethyl-2,3b-methano-3bH-cyclopenta[1,3] cyclopropa[1,2] benzene-4-methanol, santalol, α-santalol), *1 non-cyclic secondary alcohol* (*trans*-3,7-dimethyl-1,6-octadien-3-ol), and *21 cyclic secondary alcohols* (borneol, L-borneol, isoborneol, carveol, L-carveol, cedrenol, cedrol, dihydrocarveol, dihydrocarveol (RRR), fenchyl alcohol, geranodyle, hydroabietyl alcohol, 6-isopropyl-2-decahydronaphthalenol, isopulegol, menthol, L-menthol, D,L-menthol, D-menthol, menthol racemic, 2(10)-pinen-3-ol and vetiverol), *17 non-cyclic tertiary alcohols* (dehydrolinalool, 6,7-dihydrolinalool, (3*E*, 5*E*)-2,6-dimethylocta-3,5-dien-2-ol, 3,7-dimethyloct-6-en-3-ol, 2,6-dimethylocta-3,5-dien-2-ol, 3,7-dimethyl-4,6-octadien-3-ol, geranyl linalool, linalool, D-linalool, L-linalool, myrcenol, nerolidol, nerolidol (*cis*), ocimenol, tetrahydrolinalool, tetrahydromuguol and tetrahydromyrcenol) and *12 cyclic tertiary alcohols* (bisabolol, 4-carvomenthenol, β-caryophyllene alcohol, dihydro-α-terpineol, elemol, geranodyle, patchouli alcohol, sclareol, terpineol, L-α-terpineol, *p*-menth-8-en-1-ol, α-terpineol, and thujanol). Sufficient data are available from farnesol, linalool, menthol and α-terpineol, i.e., compounds that contain all key structural elements and potential sites of metabolism of all other members in the group, to demonstrate that the non-cyclic and cyclic terpenes share common metabolic pathways.

In most cases, metabolism yields innocuous metabolites. Some materials, however, may generate alpha, β-unsaturated compounds or be oxidized to hydroperoxides. Such compounds have the capacity to participate in a range of nucleophilic and electrophilic addition reactions with biological material. The respective parent compounds (i.e., farnesol, geraniol, nerol, santalol, 2(10)pinen-3-ol, 2,6-dimethyloct-3,5-dien-2-ol, 3,7-dimethyl-4,6-octadien-3-ol and 6,7-dihydrogeraniol) require a more in-depth toxicity assessment. Isomers would be expected to share the same common metabolic pathways.

Tables 1 and 2 indicates the non-cyclic and cyclic terpene alcohols considered in this review, including some stereo-isomers.

Terpene alcohols are used as fragrance and flavor ingredients. They may be found in fragrances used in decorative cosmetics, fine fragrances, shampoos, toilet soaps and other toiletries as well as in non-cosmetic products such as household cleaners and detergents. This report summarizes and synthesizes animal and human data, including studies by various routes of exposure, and emphasizes the safety assessment for use as fragrance ingredients. The scientific evaluation focuses on dermal exposure, which is considered the primary exposure route for fragrance materials. Where relevant, toxicity, metabolism and biological fate data from other routes of exposure have also been considered.

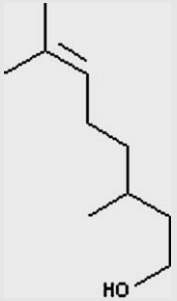
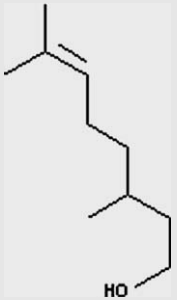
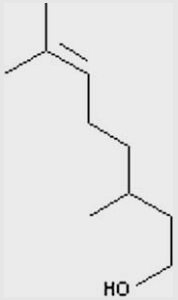
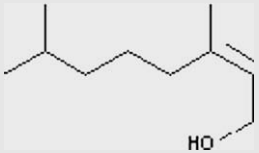
The selected data from published and unpublished reports were deemed relevant based on the nature of the protocols, quality of the data, and appropriate exposure.

Many of the terpene alcohols assessed in this report have been evaluated and approved for use as flavor ingredients in foodstuffs. In the United States, D,L-citronellol, caryophyllene alcohol, 3,7-dimethyl-1-octanol, farnesol, hydroxycitronellol, nerol, nerolidol, rhodinol, tetrahydrolinalool, and the cyclic terpene alcohols α-terpineol, *p*-menth-8-en-1-ol, borneol, carveol, 4-carvomenthenol, dihydrocarveol, fenchyl alcohol, isoborneol, isopulegol, menthol, D-neomenthol, 2(10)-pinen-3-ol and santalol (α and β) have been approved for use as flavors by the Food and Drug Administration (FDA) in accordance with (21 CFR 172.515).

The International Joint FAO/WHO Expert Committee on Food Additives (JECFA) has evaluated 28 terpene alcohols assessed in this report. An Acceptable Daily Intake (ADI) of 0–4 mg/kg body weight/day was established for menthol (JECFA, 1998a) and a group ADI of 0–0.5 mg/kg body weight/day for citral, geranyl acetate, citronellol, linalool, and linalyl acetate was maintained (JECFA, 2003). The other 22 terpene alcohols assessed by JECFA (dehydrolinalool, 3,7-dimethyl-1-octanol, rhodinol, farnesol, geraniol, hydroxycitronellol, nerol, tetrahydrolinalool, borneol, carveol, *p*-mentha-1,8-dien-7-ol, 4-carvomenthenol, dihydrocarveol, fenchyl alcohol, isoborneol, isopulegol, myrtenol, santalol, terpineol, α-terpineol, *p*-menth-8-en-1-ol and 4-thujanol) were judged by the Committee not to present a safety concern at current estimated intake levels.

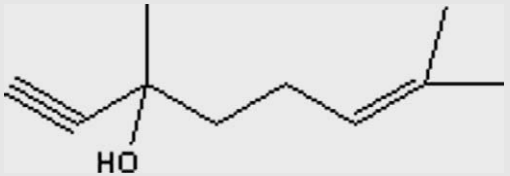
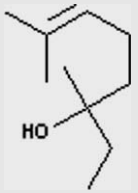
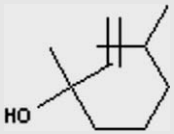
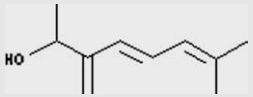
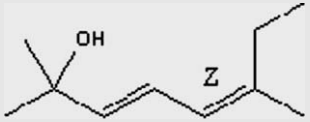
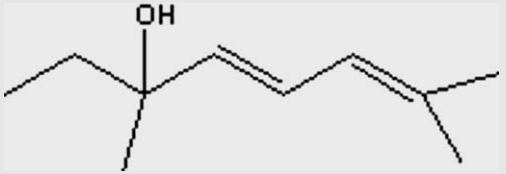
Many of the terpene alcohols assessed here are naturally present in commonly eaten foods, mainly in a wide variety of fruits, fruit peels, fruit juices, vegetables and spices, e.g. elemol (0.37 mg/kg in grapefruit juice), myrcenol (1.1 mg/kg in licorice, trace amounts in blueberry, 0.04 mg/kg in grapefruit juice, 0.04 mg/kg in grape), ocimenol (0.04 mg/kg in apricot, 0.01 mg/kg in grapefruit juice) (EFSA, 2006). Linalool and linalyl acetate are the main constituents of lavender oil (Barocelli et al., 2004),

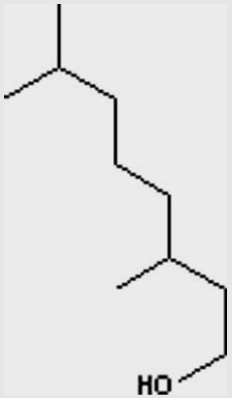
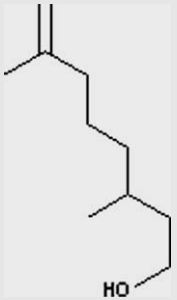
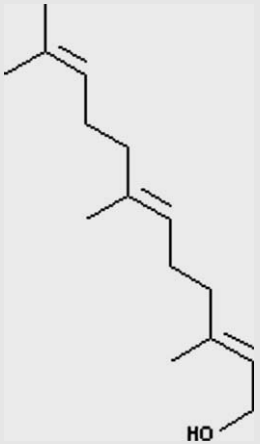
Table 1
Material identification and summary of volume of use and dermal exposure – non-cyclic terpene alcohols

Material	Synonyms	Structure	Worldwide metric tons	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level[a,b,c] (%)
D,L-*Citronellol* CAS # 106-22-9 LogK_{ow} 3.1 at 35 °C Molecular weight: 156.27	• Citronellol3,7-dimethyl-6-octen-1-ol • 6-Octen-1-ol, 3,7-dimethyl-		>1000	0.13	8.20
L-*Citronellol* CAS # 7540-51-4 LogK_{ow} 3.56 Molecular weight: 156.27	• (−)-3,7-Dimethyloct-6-en-1-ol • (*S*)-3,7-Dimethyl-6-octen-1-ol • 6-Octen-1-ol, 3,7-dimethyl-, (*S*)-		10-100	0.07	1.38
(+)-(R)-Citronellol CAS # 1117-61-9 LogK_{ow} 3.56 Molecular weight: 156.69	• (+)-β-Citronellol • (*R*)-3,7-Dimethyloct-6-en-1-ol • 6-Octen-1-ol, 3,7-dimethyl-, (*R*)-		10–100	0.0005[d]	0.02
6,7-Dihydrogeraniol CAS # 40607-48-5 LogK_{ow} 3.56 Molecular weight: 156.27	• 3,7-Dimethyl-2-octen-1-ol • 2-Octen-1-ol, 3,7-dimethyl-		Prohibited by IFRA Standard		

(*continued on next page*)

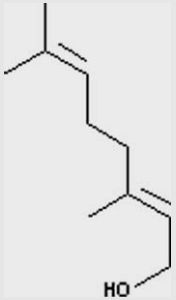
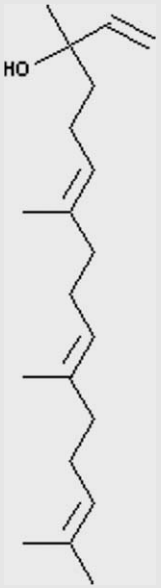
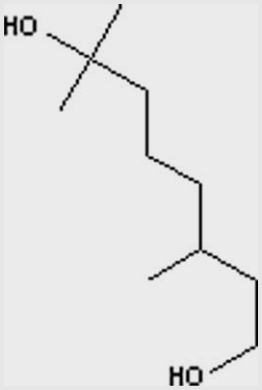
Table 1 (*continued*)

Material	Synonyms	Structure	Worldwide metric tons	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level[a,b,c] (%)
Dehydrolinalool CAS# 29171-20-8 Log K_{ow} 2.75 Molecular weight: 152.24	• Dehydro-β-linalool • 3,7-Dimethyloct-6-en-1-yn-3-ol • Linalool, dehydro-β-linalool, dehydro-6-octen-1-yn-3-ol, 3,7-dimethyl-		<0.01	0.0005[d]	0.02
3,7-Dimethyloct-6-en-3-ol CAS# 18479-51-1 Log K_{ow} 3.52 Molecular weight: 156.69	• 1,2-Dihydrolinalool • 6-Octen-3-ol, 3,7-dimethyl-		1–10	0.01	0.14
3,7-Dimethyloct-1-en-3-ol CAS# 18479-49-7 Log K_{ow} 3.47 Molecular weight: 156.69	• 6,7-Dihydrolinalool • 1-Octen-3-ol, 3,7-dimethyl-		10–100	0.0005[d]	0.02
trans-3,7-Dimethyl-1,6-octadien-3-ol CAS# 22451-63-4 Log K_{ow} 3.26 Molecular weight: 154.25	• Allo-ocimenol • (*E*)-7-Methyl-3-methyleneocta-4,6-dien-2-ol • Muguol		0.1–1	0.0892	0.49
(,5Z)-2,6-Dimethylocta-3,5-dien-2-ol CAS# 18675-16-6 Log K_{ow} 3.3 Molecular weight: 154.53	• Muguol • 3,5-Octadien-2-ol, 2,6-dimethyl-, (5*Z*)-		0.1–1	0.0005[d]	0.02
(5E)-2,6-Dimethyl-3,5-octadien-2-ol CAS# 18675-17-7 Log K_{ow} 3.3 Molecular weight: 154.53	• 3,5-Octadien-2-ol, 2,6-dimethyl-, (?,*E*)-		0.1–1	0.0005[d]	0.02
3,7-Dimethyl-4,6-octadien-3-ol CAS# 18479-54-4 Log K_{ow} 3.3 Molecular weight: 154.53	• 4,6-Octadien-3-ol, 3,7-dimethyl-		0.1–1	0.1	0.67

3,7-Dimethyl-1-octanol CAS# 106-21-8 Log K_{ow} 3.9 at 35 °C Molecular weight: 158.29	• Dihydrocitronellol • 1-Octanol, 3,7-dimethyl- • Pelargol • Tetrahydrogeraniol		100–1000	0.0005[d]	0.02
3,7-Dimethyloct-7-en-1-ol CAS# 141-25-3 Log K_{ow} 3.63 Molecular weight: 156.69	• α-Citronellol • 7-Octen-1-ol, 3,7-dimethyl- (isomer unspecified)		1–10	0.04	0.82
Farnesol CAS# 4602-84-0 Log K_{ow} 5.77 Molecular weight: 222.37	• 2,6,10-Dodecatrien-1-ol, 3,7,11-trimethyl- • Farnesyl alcohol • Trimethyl dodecatrienol • 3,7,11-Trimethyl-2,6,10-dodecatrien-1-ol		1–10	0.007	0.66

(*continued on next page*)

Table 1 (*continued*)

Material	Synonyms	Structure	Worldwide metric tons	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level[a,b,c] (%)
Geraniol CAS# 106-24-1 Log K_{ow} log P_{ow} = 2.6 (at 25 °C) Molecular weight: 154.25	• 2,6-Dimethyl-2,6-octadien-8-ol • *trans*-3,7-Dimethyl-2,6-octadien-1-ol • *trans*-3,7-Dimethyl-2,7-octadien-1-ol • Geraniol Coeur • Meranol • 2,6-Octadien-1-ol, 3,7-dimethyl-, (*e*)-		>1000	0.11	9.20
Geranyl linalool CAS# 1113-21-9 Log K_{ow} 7.97 Molecular weight: 276.47	• 1,6,10,14-Hexadecatetraen-3-ol, 3,7,11,15-tetramethyl-, (*E*,*E*)- • *E*,*E*-3,7,11,15-Tetramethyl-1,6,10,14-hexadecatetraen-3-ol		<0.1	0.0009	0.01
Hydroxycitronellol CAS# 107-74-4 Log K_{ow} 2.54 Molecular weight: 174.28	• Citronellolhydrate • 3,7-Dimethyloctane-1,7-diol • 3,7-Dimethyl-1,7-octanediol • Hydroxydihydrocitronellol • 1,7-Octanediol, 3,7-dimethyl-		10–100	0.17	2.70

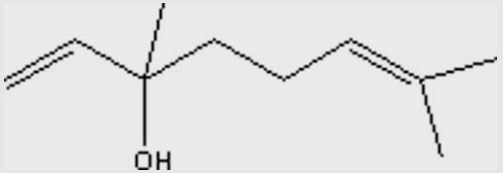
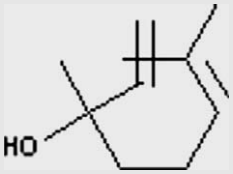
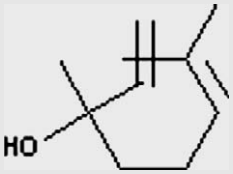
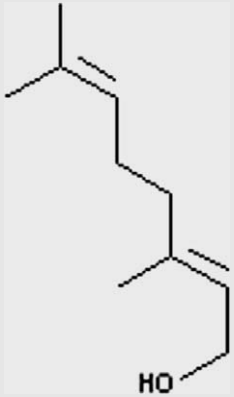
Linalool CAS# 78-70-6 Log K_{ow} 2.9 Molecular weight: 154.25	• Coriandrol • 2,6-Dimethyl-2,7-octadien-6-ol • 3,7-Dimethyl-1,6-octadien-3-ol • Licareol • Linalol • Linalyl alcohol • 1,6-Octadien-3-ol, 3,7-dimethyl- • 2,7-Octadien-6-ol, 2,6-dimethyl-		>1000	0.32	4.30
D-*Linalool* CAS# 126-90-9 Log K_{ow} 3.38 Molecular weight: 154.53	• (*S*)-3,7-Dimethyl-1,6-octadien-3-ol • 1,6-Octadien-3-ol, 3,7-dimethyl-, (*S*)-		<0.1	0.05	0.13
L-*Linalool* CAS# 126-91-0 Log K_{ow} 3.38 Molecular weight: 154.53	• (*R*)-3,7-Dimethyl-1,6-octadien-3-ol • 1,6-Octadien-3-ol, 3,7-dimethyl-, (*R*)-		10–100	0.07	0.31
Myrcenol CAS# 543-39-5 Log K_{ow} 3.46 Molecular weight: 154.25	• 7-Hydroxy-7-methyl-3-methylene-1-octene • 3-Methylene-7-methyl-1-octene-7-ol • 7-Methyl-3-methylene-1-octene-7-ol • 2-Methyl-6-methyleneoct-7-en-2-ol • 7-Octen-2-ol, 2-methyl-6-methylene-		1–10	0.0005[d]	0.02
Nerol CAS# 106-25-2 Log K_{ow} log P_{ow} = 2.7 Molecular weight: 154.25	• Allerol • *cis*-2,6-Dimethyl-2,6-octadien-8-ol • *cis*-3,7-Dimethyl-2,6-octadien-1-ol • Neraniol • Nergenol • 2,6-Octadien-8-ol, 2,6-dimethyl-, (*z*)		100–1000	0.06	1.12

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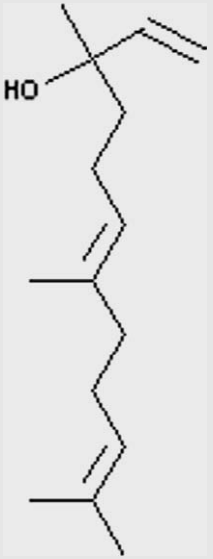
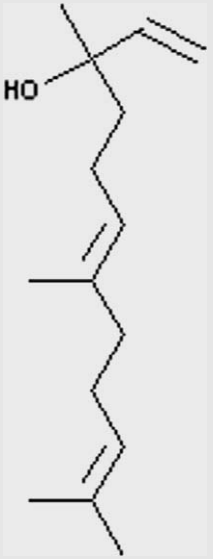
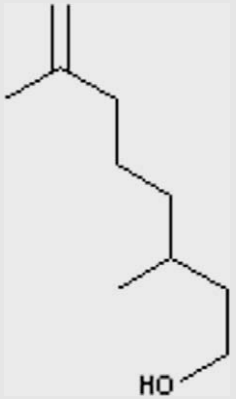
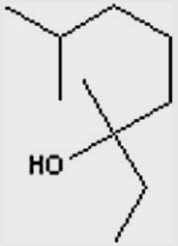
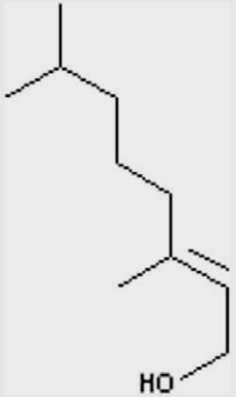
Table 1 (*continued*)

Material	Synonyms	Structure	Worldwide metric tons	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level[a,b,c] (%)
Nerolidol (*cis*) CAS# 142-50-7 Log K_{ow} 5.68 Molecular weight: 222.72	• 1,6,10-Dodecatrien-3-ol, 3,7,11-trimethyl-, [*S*-(*Z*)]- • (+)-*cis*-Nerolidol • D-Nerolidol		< 0.1	0.01	0.02
Nerolidol (isomer unspecified) CAS# 7212-44-4 Log K_{ow} 5.0 at 35 °C Molecular weight: 222.37	• 1,6,10-Dodecatrien-3-ol, 3,7,11-trimethyl- • Melaleucol • Methylvinyl homogeranyl carbinol • Peruviol • 3,7,11-Trimethyl-1,6,10-dodecatrien-3-ol • 3,7,11-Trimethyldodeca-1,6,10-trien-3-mixed isomers		10–100	0.0293	2.02

Ocimenol CAS# 5986-38-9 Log K_{ow} 3.38 Molecular weight: 154.25	• 2,6-Dimethyl-5,7-octadien-2-ol • 5,7-Octadien-2-ol, 2,6-dimethyl-		<0.1	0.0005[d]	0.02
Rhodinol CAS# 6812-78-8 Log K_{ow} 3.63 Molecular weight: 156.27	• 3,7-Dimethyl-(6- or 7-)octen-1-ol • 3,7-Dimethyl-7-octen-1-ol • 7-Octen-1-ol, 3,7-dimethyl-, (*S*)-		1–10	0.11	0.94
Tetrahydrolinalool CAS# 78-69-3 Log K_{ow} 3.6 at 45 °C Molecular weight: 158.29	• 2,6-Dimethyl-6-octanol • 3,7-Dimethyloctan-3-ol • 3-Octanol, 3,7-dimethyl-		>1000	0.0005[d]	0.02
Tetrahydromuguol CAS# 41678-36-8 Log K_{ow} 3.56 Molecular weight: 156.27	• 3,7 and 2,6-Dimethyl-2-octenol • 3,7-Dimethylocten-2-ol • Tetrahydro allo-ocimenol		1–10	0.0005[d]	0.02

(*continued on next page*)

Table 1 (*continued*)

Material	Synonyms	Structure	Worldwide metric tons	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level[a,b,c] (%)
Tetrahydromyrcenol CAS# 18479-57-7 LogK_{ow} 3.6 Molecular weight: 158.29	• 2,6-Dimethyloctan-2-ol • 2,6-Dimethyl-2-octanol • 2-Octanol, 2,6-dimethyl		100–1000	0.06	0.71

[a] 2004 Volume of use survey.
[b] Skin levels were based on the assumption that the fragrance mixture is used at 20% in a consumer product.
[c] 2002 IFRA use level survey.
[d] A default value of 0.02% was used to calculate dermal systemic exposure.

geraniol and β-citronellol of geranium Bourbon oil (Abe et al., 2003), and patchouli alcohol is the main constituent of patchouli oil (Abe et al., 2003). Farnesol is a naturally occurring phytochemical present in plant species that include rose, chamomile, lavender, and lilac. Carveol is a natural product found in the essential oils of orange peel, dill, and caraway (Crowell et al., 1992). Cherries and spearmint are dietary sources of *p*-mentha-1,8-dien-7-ol (Karp et al., 1990).

The annual worldwide production of the individual terpene alcohols varies greatly and ranges from <0.1 to 100 metric tons for most of the compounds. Linalool, geraniol, tetrahydrolinalool and terpineol are produced at >1000 metric tons per year (Table 1).

1.2. Estimated consumer exposure

Potential consumer exposure to fragrance ingredients may occur mainly through the dermal and inhalation routes of exposure.

One estimate is based on the potential percutaneous absorption over the entire body due to the use of different fragranced products. Another estimate looks at the local concentration of the materials, usually on a smaller area of skin.

As skin components may interact with fragrance materials and slow their evaporation substantially compared with relatively free evaporation from an inert surface, the quantities of fragrance ingredients available for absorption may be higher than expected based on their volatility. Results from a study by Behan et al. (1996), for example, show that after application of 75 μL of a model cologne perfume with a 10-ingredient mixture (each at 1% w/w), residual quantities on the skin after 60 minutes of free evaporation were 427 ng for linalool. No residue of linalool was however found after 60 minutes of free evaporation from a tile surface.

Potential skin exposure to the terpene alcohols was, therefore, not estimated based on their volatility but based on their concentrations in 10 types of cosmetic products (body lotion, face cream, eau de toilette, fragrance cream, anti-perspirant, shampoo, bath products, shower gel, toilet soap, and hair spray). The concentration data in the 10 product types were multiplied by the amount of product applied, the number of applications/day for each product type, and a "retention factor" (ranging from 0.01 to 1.0) to account for the length of time a product may remain on the skin and/or the likelihood of it being removed by washing. The value produced represents the maximum skin concentration associated with each product type. As a conservative measure, the total maximum skin concentration was calculated to be the sum of the maximum skin concentrations for each of the 10 product categories.

Maximum skin exposure data (the total of the 10 individual product categories) for each of the terpene alcohols assessed were also used to calculate potential systemic exposures. Systemic exposures (i.e., the dose absorbed through the skin and available to the systemic circulation) were estimated based on dermal absorption rates. Where such data were lacking, as a conservative measure, dermal absorption was considered to be 100% (i.e., the maximum skin exposure value was considered as the estimate of systemic exposure). Maximum daily exposures range from a negligible amount to 0.32 mg/kg body weight/day for the individual terpene alcohols in high-end users of cosmetic products containing these materials (see Table 1).

Secondly, maximum skin exposure to terpene alcohols used in fine fragrance products was calculated based on the use of 20% of the fragrance mixture in which they occurred and their concentration in the mixture (the maximum used) in the fine fragrance consumer product. The calculated exposures for the terpene alcohols used in cosmetic products are listed in Table 1 and range up to 9.2% for geraniol.

With regard to potential inhalation exposure, data from studies using different surrogate products (pressurized aerosol and heated oil plug-in air fresheners, a fragrance in an atomizer, and a fine fragrance aerosol) are available showing that product type and volatility of each fragrance material affect its air concentration (Isola et al., 2004a,b; RIFM, 2003b, 2004b; Rogers et al., 2005). Each surrogate product contained nine common fragrance materials at 0.06% each for the aerosol, 8.89% each for the plug-in, and 2.2% each for the fine fragrance. The fragrance materials were benzyl acetate, eugenol, hexylcinnamaldehyde, 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-benzopyran, hydroxycitronellal, β-ionone, D-limonene, linalool, and methyl dihydrojasmonate. The materials were chosen based on volatility, chemical structure, toxicity, and volume of use.

Results of the aerosol study indicated the peak air concentration of total fragrance at the adult-breathing height (5 ft.) was 2165 μg/m^3 and 1753 μg/m^3 at the child-breathing height (1.5 ft). The peaks occurred at different times. After 2 h, the concentrations ranged from 105 to 64 μg/m^3 at the adult and child heights, respectively. The Mean Aerodynamic Diameter (MAD) of the airborne particles was approximately 1.5 μm.

Plug-in study results showed that the peak total concentration was 1768 μg/m^3 at 1 h and declined to 137 μg/m^3 after 701 h.

With an atomizer, the test product (in 80% aqueous ethanol) was sprayed toward a manikin at a distance of 3.5 in. Three different anatomical areas were sprayed with three pump actuations each. The concentration of each fragrance material was measured at the adult-breathing zone (5 ft) and the child-breathing zone (1.5 ft) from the start of spray until 5 h post-spray. 0.89 g of test material was released after 9 actuations. Peak total fragrance air concentrations of 1256 μg/m^3 (adult zone) and 850 μg/m^3 (child zone) were seen at 8–18 minutes post spray.

Fine fragrance study results showed peak total concentrations of 1042 μg/m^3 at 5 minutes (adult ht.) and 2065 μg/m^3 at 5 minutes (child ht.) after spraying the test product (in 80% aqueous ethanol) with two pump actuations each at three locations (left ear, right ear, breast plate). After 5 h, at both breathing heights, the concentrations decreased to <250 μg/m^3 with some concentrations <100 μg/m^3. The MAD of the majority of particles was less than 1.0 μm.

Exposure data were not reported for nine cyclic terpenes (carveol; laevo-Carveol; β-caryophyllene alcohol; dihdyrocarveol (RRR); geranodyle; *p*-mentha-1,8-dien-7-ol; 4-thujanol; *p*-menth-8-en-1-ol; vetiverol) and 10 non-cyclic terpenes (*(+)-(R)*-Citronellol; dehydrolinalool; (,5*Z*)-2,6-dimethylocta-3,5-dien-2-ol; (5*E*)-2,6-dimethyl-3,5-octadien-2-ol; 3,7-dimethyl-1-octanol; 3,7-dimethyloct-1-en-3-ol; myrcenol; ocimenol; tetrahydrolinalool; tetrahydromuguol). A default value of 0.02% is used to calculate the maximum daily exposure on the skin which is 0.0005 mg/kg for high-end users of these products.

Exposure data were provided by the fragrance industry. Further explanation of how the data were obtained and of how exposures were determined have been previously reported by Cadby et al. (2002) and Ford et al. (2000).

2. Pharmacokinetics

2.1. Dermal route of exposure (see Tables 2-1A and 2-1B)

Data on the percutaneous absorption were available for the non-cyclic terpene alcohols citronellol, farnesol and linalool, and for the cyclic materials carveol, 4-carvomenthenol, menthol and terpineol (Bobin et al., 1997; Cal and Sznitowska, 2003; Cal, 2006; Jäger et al., 1992; Meyer and Meyer, 1959; Schäfer and Schäfer, 1982; Williams and Barry, 1991a,b). With all of these materials percutaneous penetration was shown either *in vitro* or *in vivo* (see Tables 2-1A, 2-1B).

An *in vitro* skin absorption study with linalool in three different vehicles has been conducted using human epidermal membranes from 6 tissue donors. Diffusion cells, under both occluded and unoccluded conditions, were dosed with 4% (w/v) of a ^{14}C-solution of linalool in 70/30 ethanol (EtOH)/water, DEP (diethyl phthalate) or DPG (dipropylene glycol). Permeation of linalool was then measured at 12 time-points over 24 h. The percent of applied dose absorbed at 24 h was 3.57% under unoccluded conditions and 14.1% under occluded conditions with 70/30 EtOH/water as the vehicle; 2.77% for unoccluded and 5.73% for occluded with DEP as the vehicle and 1.8% for unoccluded and 7.49% for occluded with DPG as the vehicle (RIFM, 2006c).

2.1.1. Human studies

The percutaneous penetration of citronellol, linalool, carveol, and 4-carvomenthenol was tested *in vitro* on human skin preparations (Cal and Sznitowska, 2003; Cal, 2006; Williams and Barry, 1991a,b). In addition, the influence of different vehicles on the penetration of linalool and 4-carvomenthenol was studied *in vitro* by Cal (2006). *In vivo* human data were available for linalool and menthol (Jäger et al., 1992; Atzl et al., 1972).

Cal and Sznitowska (2003) studied skin penetration and elimination of the three acyclic terpenes citronellol, linalool, and linalyl acetate. The pure terpenes were applied onto human skin *in vitro*, and after 1–4 h their content in the stratum corneum layers and in the epidermis/dermis was determined using gas chromatography. Similarly, the amounts of terpenes in the skin were analyzed during 4 h following a 1-h absorption period. Penetration into all skin layers was demonstrated after 1 h of exposure, with total amounts of linalool and citronellol of 827 and 954 μg/cm^2, respectively. During the elimination phase, a constant drop in the total amount in the skin was observed only for citronellol, while the total skin content of linalool and linalyl acetate did not change, although diffusion from the stratum corneum into the epidermis/dermis occurred. Permeability coefficients of 5.6 and 6.3 cm/h $\times$ 10^{-5} were found for carveol and 4-carvomenthenol, respectively, by Williams and Barry (1991a,b). For both linalool and 4-carvomenthenol, penetration was faster from hydrogel formulations as compared to oily solutions or emulsions (Cal, 2006).

Linalool levels in blood of a male volunteer were followed for 90 minutes after the use of 1500 mg of massage oil which contained 2% lavender oil with approximately 25% linalool and 30% linalyl acetate. Trace amounts of both linalool and linalyl acetate were detected in the blood 5 minutes after the massage. Peak plasma concentrations were reached by 19 minutes with a mean plasma concentration of 100 ng/ml for linalool and 121 ng/ml for linalyl acetate. Most of the linalool and linalyl acetate had disappeared from the blood in 90 minutes with biological half lives of approximately 14 minutes for each (Jäger et al., 1992). Atzl et al. (1972) found menthol in the urine of persons treated dermally with a menthol-containing ointment (no quantitative data available).

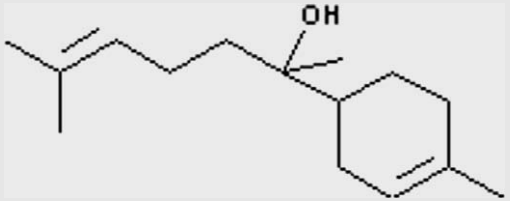
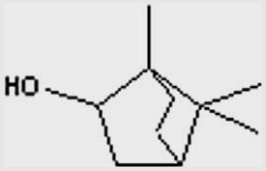
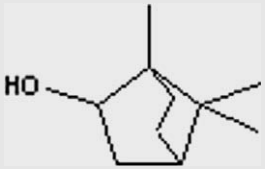
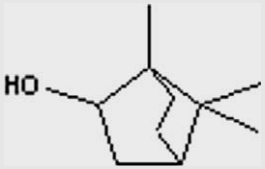
2.1.2. Animal studies

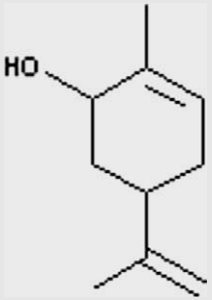
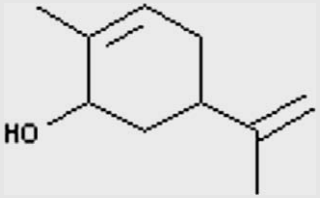
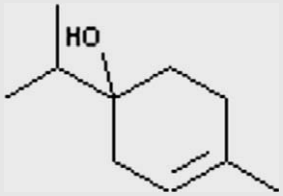
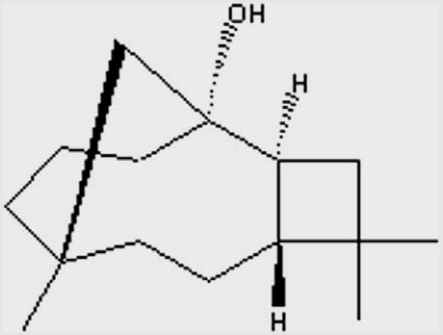
Bobin et al. (1997) reported *in vitro* studies with farnesol applied on pig skin. The authors concluded that undiluted farnesol "...seems to stay in the lipids of stratum corneum", and that farnesol at 20% and 50% in DMSO is capable of penetrating the epidermis and dermis. Only a very brief summary of this study is available, hence the reliability of these results cannot be assessed.

The percutaneous absorption of menthol (0.65% in a foam bath) was measured in mice *in vivo* using radioactive labeled material. Maximum blood levels were found 10 minutes after the onset of percutaneous absorption (Schäfer and Schäfer, 1982).

In vivo, a "relatively rapid absorption" through mouse skin was reported for terpineol by Meyer and Meyer (1959), who studied the absorption of terpineol in conjunction with eserine.

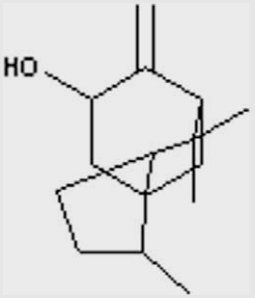
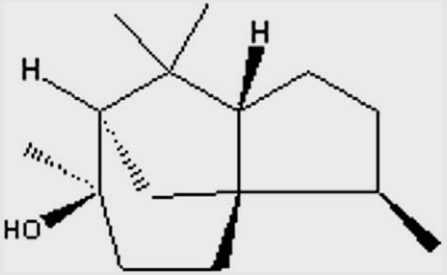
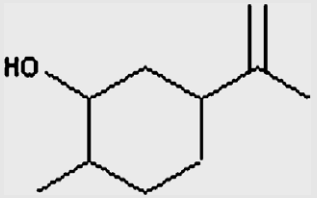
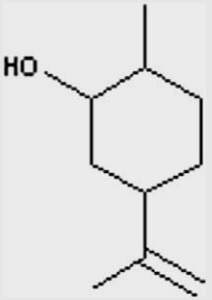
Table 2
Material identification and summary of volume of use and dermal exposure – cyclic terpene alcohols

Material	Synonyms	Structure	Worldwide metric tons	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level[a,b,c] (%)
α-*Bisabolol* CAS# 515-69-5 Log K_{ow} 5.63 Molecular weight: 222.72	• Bisabolol • 3-Cyclohexene-1-methanol,α,4-dimethyl-α-(4-methyl-3-pentenyl)-, (R*,R*)- • (*R**,*R**)-α,4-Dimethyl-α-(4-methyl-3-pentenyl)cyclohex-3-ene-1-methanol • 6-Methyl-2-(4-methyl-3-cyclohexen-1-yl)-5-hepten-2-ol		<0.1	0.0001	0.08
Borneol CAS# 507-70-0 Log K_{ow} 2.85 Molecular weight: 154.25	• Bicyclo(2.2.1)heptan-2-ol, 1,7,7-trimethyl-endo- • Bicyclo[2.2.1]heptan-2-ol, 1,7,7-trimethyl-, endo- • Borneocamphor • D,L-borneol • Bornyl alcohol • 2-Camphanol • D-Camphanol • Camphol • 2-Hydroxycamphane • 1,7,7-Trimethylbicyclo(2.2.1)heptan-2-ol		10–100	0.004	0.3
L-*Borneol* CAS# 464-45-9 Log K_{ow} 2.85 Molecular weight: 154.25	• Bicyclo[2.2.1]heptan-2-ol, 1,7,7-trimethyl-, (1*S*-endo)- • L-Bornyl alcohol • L-2-Camphanol		1–10	0.005	0.3
Isoborneol CAS# 124-76-5 Log K_{ow} 2.85 Molecular weight: 154.25	• Bicyclo[2.2.1]heptan-2-ol, 1,7,7-trimethyl-, exo- • exo-2-Bornanol • Borneol(iso) • exo-2-Camphanol • *iso*-Camphol • Isobornyl alcohol		10–100	0.01	0.3

Carveol CAS# 99-48-9 LogK_{ow} 3.29 Molecular weight: 152.24	• 2-Cyclohexen-1-ol, 2-methyl-5-(1-methylethenyl)- • *p*-Mentha-6,8-dien-2-ol • 1-Methyl-4-isopropenyL-6-cyclohexen-2-ol		0.1–1	0.0005[d]	0.02
laevo-Carveol CAS# 2102-59-2 LogK_{ow} 3.29 Molecular weight: 152.24	• 6-Cyclohexen-2-ol, 1-methyl-4-isopropenyL-, L- • L-*p*-Mentha-6,8-dien-2-ol • L-1-Methyl-4-isopropenyL-6-cyclohexen-2-ol • (1*R-cis*)-2-Methyl-5-(1-methylvinyl)cyclohex-2-en-1-ol		<0.1	0.0005[d]	0.02
4-Carvomenthenol CAS# 562-74-3 LogK_{ow} 3.33 Molecular weight: 154.25	• 3-Cyclohexen-1-ol, 4-methyl-1-(1-methylethyl)- • 1-*p*-Menthen-4-ol • 1-Methyl-4-isopropyl-1-cyclohexene-4-ol • Origanol • 4-Terpinenol		1–10	0.001	0.1
β-*Caryophyllene alcohol* CAS# 472-97-9 LogK_{ow} 4.74 Molecular weight: 222.72	• Caryolan-1-ol • Tricyclo[6.3.1.02,5]dodecan-1-ol, 4,4,8-trimethyl-, [1*R*-(1α,2Pα,5β,8β)]- • 4,4,8-Trimethyltricyclo[6.3.1.02,5]dodecan-1-ol		<0.1	0.0005[d]	0.02

(*continued on next page*)

Table 2 (*continued*)

Material	Synonyms	Structure	Worldwide metric tons	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level[a,b,c] (%)
Cedrenol CAS# 28231-03-0 LogK_{ow} 4.63 Molecular weight: 220.36	• Cedr-8(15)-en-9-ol • 1H-3a,7-Methanoazulen-5-ol, octahydro-3,8,8,-trimethyl-6-methylene- • Octahydro-3,8,8-trimethyl-6-methylene-1H-3a,7-methanoazulen-5-ol		10–100	0.1	3.2
Cedrol CAS# 77-53-2 LogK_{ow} 4.67 Molecular weight: 222.37	• Cedar camphor • Cedarwood oil alcohols • Cypress camphor • 1H-3a,7-Methanoazulene-6-ol, octahydro-3,6,8,8-tetramethyl-,[3*R*-(3α,3aβ,6α,7β,8aa]		1–10	0.03	1.5
Dihydrocarveol (R,R,R) CAS# 38049-26-2 LogK_{ow} 3.37 Molecular weight: 154.53	• Cyclohexanol, 2-methyl-5-(1-methylethenyl)-, (1α,2β,5α)- • (1α,2β,5α)-2-Methyl-5-(1-methylvinyl)cyclohexan-1-ol		<0.01	0.0005[d]	0.02
Dihydrocarveol (isomer unspecified) CAS# 619-01-2 LogK_{ow} 3.37 Molecular weight: 154.25	• Cyclohexanol, 2-methyl-5-(1-methylethenyl)- • 8-*p*-Menthen-2-ol • 6-Methyl-3-isopropenylcyclohexanol		0.1–1	0.0003	0.005

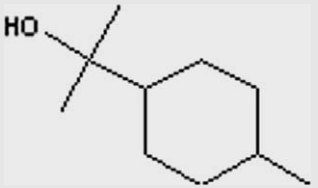
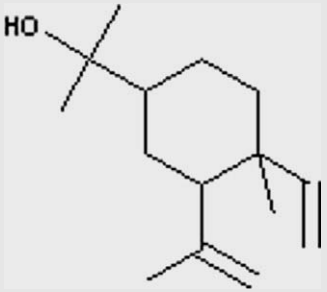
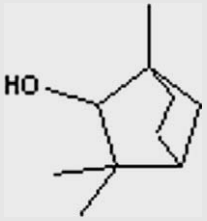
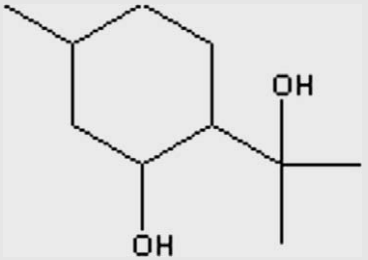
Dihydro-α-terpineol CAS# 498-81-7 LogK_{ow} 3.1–3.3 at 35 °C Molecular weight: 156.27	• Cyclohexanemethanol,α,α,4-trimethyl- • Dihydro terpineol • 1-Methyl-4-isopropylcyclohexane-8-ol		10–100	0.008	0.1
Elemol CAS# 639-99-6 LogK_{ow} 5.54 Molecular weight: 222.37	• Cyclohexanemethanol, 4-ethenyL-α,α,4-trimethyl-3-(1-methylethenyl)-,[1*R*-(1α,3α,4β • (1*S*,2*S*,4*R*)-(−)-a,a-Dimethyl-1-vinyL-o-menth-8-ene-4-methanol • α-Elemol		1–10	0.001	0.07
Fenchyl alcohol CAS# 1632-73-1 LogK_{ow} 3.17 Molecular weight: 154.25	• Bicyclo[2.2.1]heptan-2-ol, 1,3,3-trimethyl- • 2-Fenchanol • Fenchol • α-Fenchyl alcohol • 1,3,3-Trimethylbicyclo(2.2.1)heptan-2-ol • 1,3,3-Trimethyl-2-norbornanol		10–100	0.001	0.1
Geranodyle CAS# 42822-86-6 LogK_{ow} 1.8–4.0 Molecular weight: 172.27	• Cyclohexanemethanol,2-hydroxy-α,α,4-trimethyl- • 2-(2′Hydroxypropan-2′-yl)-5-methylcyclohexanol • 2-Hydroxy-α,α,4-trimethylcyclohexanemethanol • *p*-Menthane-3,8-diol		1–10	0.0005[d]	0.02

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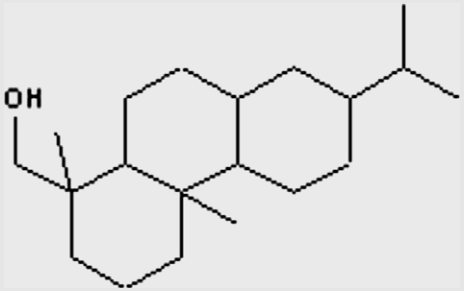
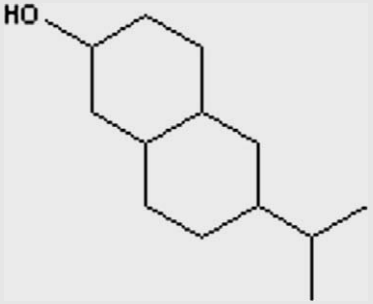
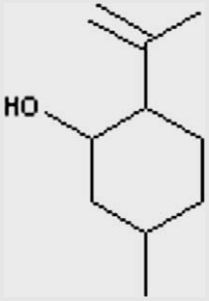
Table 2 (*continued*)

Material	Synonyms	Structure	Worldwide metric tons	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level[a,b,c] (%)
Hydroabietyl alcohol CAS# 13393-93-6 LogK_{ow} 6.4 Molecular weight: 292.51	• Abitol • Abitol (mixture of different hydroabietyl alcohols)13393-93-6		Prohibited by IFRA Standard		
6-Isopropyl-2-decahydronaphthalenol CAS# 34131-99-2 LogK_{ow} 3.98 Molecular weight: 196.33	• Decahydro-6-isopropyl-2-naphthol • Decahydro-6-(1-methylethyl)-2-naphthalenol • Decatol6-Isopropyldecalol • 2-Naphthalenol, decahydro-6-(1-methylethyl)-		Prohibited by IFRA Standard		
Isopulegol CAS# 89-79-2 LogK_{ow} 3.37 Molecular weight: 154.25	• Coolact P • Cyclohexanol, 5-methyl-2-(1-methylethenyl)- • Cyclohexanol, 5-methyl-2-(1-methyl ethenyl)-, [1*R*-(1α,2β,5α)]- • *p*-8(9)-Menthen-3-ol • *p*-Menth-8-en-3-ol • 1-Methyl-4-isopropenylcyclohexan-3-ol • 5-Methyl-2-(1-methylvinyl)cyclohexan-1-ol		1–10	0.0007	0.05

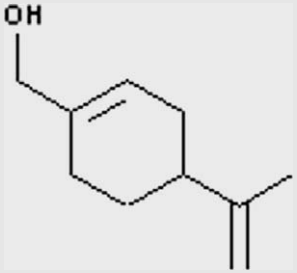
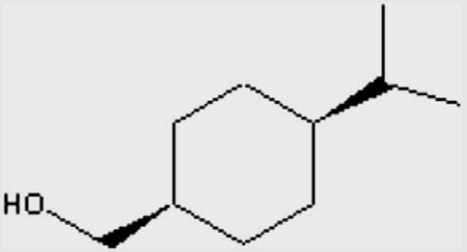
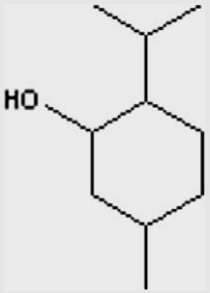
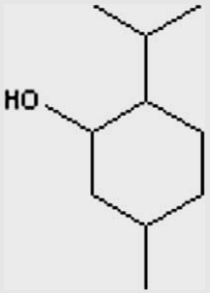
p-Mentha-1,8-dien-7-ol CAS# 536-59-4 Log K_{ow} 3.36 Molecular weight: 152.24	• *iso*-Carveol • 1-Cyclohexene-1-methanol, 4-(1-methylethenyl)- • Dihydrocuminic alcohol • Dihydrocuminyl alcohol • Hydrocumin alcohol • 1-Hydroxymethyl-4-isopropenyL-1-cyclohexene • 4-Isopropenyl-1-cyclohexenecarbinol • Perilla alcohol • Perillol		0.1–1	0.0005[d]	0.2
cis-p-Menthan-7-ol CAS# 13828-37-0 Log K_{ow} 3.45 Molecular weight: 156.27	• Cyclohexanemethanol, 4-(1-methylethyl)-, *cis* • *cis*-4-(Isopropyl)cyclohexanemethanol • Mayol • Meijiff		10–100	0.06	1.2
Menthol CAS# 89-78-1 Log K_{ow} 3.31 Molecular weight: 156.69	• Cyclohexanol, 5-methyl-2-(1-methylethyl)-, (1α,2β,5α)- • 3-Hydroxy-*p*-menthane • *p*-Methan-3-ol • 5-Methyl-2-(1-methylethyl)cyclohexanol		100–1000	0.007	0.5
D-*Menthol* CAS# 15356-60-2 Log K_{ow} 3.38 Molecular weight: 156.69	• Cyclohexanol, 5-methyl-2-(1-methylethyl)-, [1*S*-(1α,2β,5α)]- • 3-Hydroxy-*p*-menthane • (+)-Menthol • *p*-Methan-3-ol • 5-Methyl-2-(1-methylethyl)cyclohexanol		10–100	0.06	0.2

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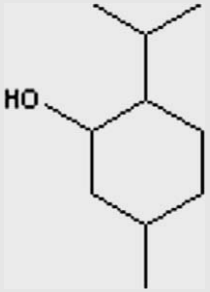
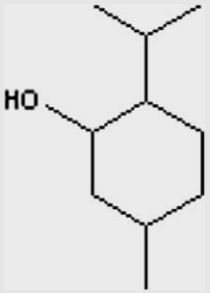
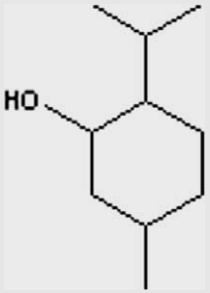
Table 2 (*continued*)

Material	Synonyms	Structure	Worldwide metric tons	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level[a,b,c] (%)
L-*Menthol* CAS# 2216-51-5 LogK_{ow} 3.38 Molecular weight: 156.27	• Cyclohexanol, 5-methyl-2-(1-methylethyl)-, [1R-(1α,2β,5α)]- • 3-Hydroxy-*p*-menthane • L-4-IsopropyL-1-methylcyclohexan-3-ol • L-3-*p*-Menthanol • Menthol Laevo Std • *p*-Methan-3-ol • 5-Methyl-2-(1-methylethyl)cyclohexanol		100–1000	0.01	0.6
D,L-*Menthol (isomer unspecified)* CAS# 1490-04-6 LogK_{ow} 3.38 Molecular weight: 156.69	• AEC Menthol Crystals BP • AEC Menthol Crystals D,L-Racemic • Cyclohexanol, 5-methyl-2-(1-methylethyl)- • Fancol Menthol • 3-Hydroxy-*p*-menthane • 2-IsopropyL-5-methylcyclohexanol • Jeen Menthol Racemic USP • *p*-Menthan-3-ol • Menthol Crystals • Menthyl alcohol • *p*-Methan-3-ol • 5-Methyl-2-(1-methylethyl)cyclohexanol • Unichem MENT		10–100	0.007	0.04
Menthol racemic CAS# 15356-70-4 LogK_{ow} 3.38 Molecular weight: 156.27	• Cyclohexanol, 5-methyl-2-(1-methylethyl)-, (1α,2β,5α)-(+/−) • 3-Hydroxy-*p*-menthane • 3-*p*-Menthanol • D,L-Menthol • *p*-Methan-3-ol • 1-Methyl-4-isopropylcyclohexan-3-ol • 5-Methyl-2-isopropylcyclohexanol • 5-Methyl-2-isopropylhexahydrophenol • 5-Methyl-2-(1-methylethyl)cyclohexanol		1–10	0.02	0.06

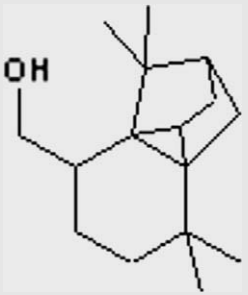
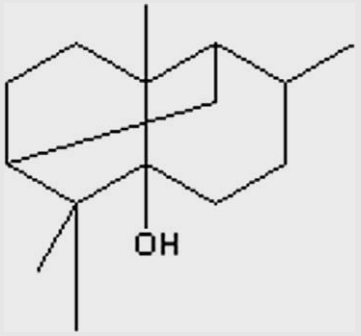
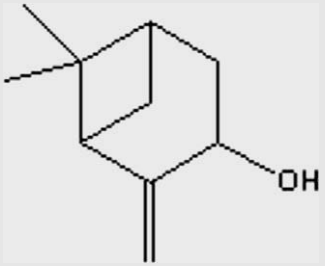
Myrtenol CAS# 515-00-4 LogK_{ow} 2.8 Molecular weight: 152.24	• Bicyclo[3.1.1]hept-2-ene-2-methanol, 6,6-dimethyl- • 6,6-Dimethylbicyclo[3.1.1]hept-2-ene-2-methanol • 6,6-Dimethyl-2-oxymethylbicyclo(1.1.3)hept-2-ene • (−)-Pin-2-ene-10-ol • 2-Pinen-10-ol		<0.1	0.003	0.01
Octahydro-7,7,8,8-tetramethyl-2,3b-methano-3bH-cyclopenta[1,3]cyclopropa[1,2]benzene-4-methanol CAS# 59056-64-3 LogK_{ow} 4.94 Molecular weight: 234.83	• 2,3b-Methano-3bH-cyclopenta[1,3]cyclopropa[1,2]benzene- 4-methanol,octahydro-7,7,8,8-tetramethyl-		1–10	0.07	0.3
Patchouli alcohol CAS# 5986-55-0 LogK_{ow} 4.67 Molecular weight: 222.37	• 1,6-Methanonaphthalene-1(2H)-ol, octahydro-4,8a,9,9-tetramethyl-, [1R-1α,4beta,4a-α,6beta[d] • (1R-(1a,4b,4aa,6b,8aa))-Octahydro-4,8a,9,9-tetramethyl-1,6-methano- (2H)-naphthol • Patchoulol		0.1-1	0.003	0.02
2(10)-Pinen-3-ol CAS# 5947-36-4 LogK_{ow} 2.81 Molecular weight: 152.24	• Bicyclo[3.1.1]heptan-3-ol, 6,6-dimethyl-2-methylene- • 6,6-Dimethyl-3-hydroxy-2-methylenebicyclo(3.1.1)heptane • 6,6-Dimethyl-2-methylenebicyclo(3.1.1)heptan–3-ol • Pinocarveol		<0.1	0.0002	0.001

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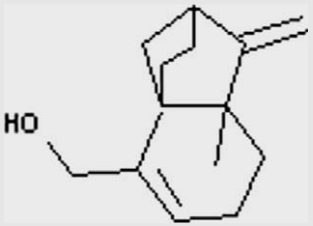
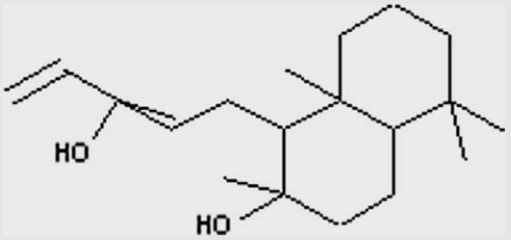
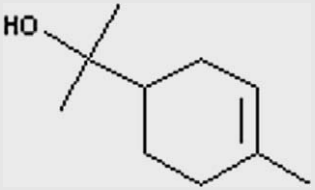
Table 2 (*continued*)

Material	Synonyms	Structure	Worldwide metric tons	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level[a,b,c] (%)
Santalol CAS# 11031-45-1 Log K_{ow} 5.18 Molecular weight: 220.56	Santalol		0.1–1	0.002	0.06
α-*Santalol* CAS# 115-71-9 Log K_{ow} 4.96 Molecular weight: 220.36	• 2-Penten-1-ol, 5-[(1*R*,3*R*,6S)2,3-dimethyltricyclo[2.2.1.02,6]hept-3-yl]-2-methyl-,(2*Z*)- • *cis*-α-Santalol		< 0.01	0.004	0.1
Sclareol CAS# 515-03-7 Log K_{ow} 6 Molecular weight: 308.51	• Labd-14-ene-8,13-diol • 1-Naphthalenepropanol,α-ethenyldecahydro-2-hydroxy-α,2,5,5,8a-pentamethyl-, [1*R*-[1α		< 0.01	0.0008	0.02
Terpineol CAS# 8000-41-7 Log K_{ow} 2.6 at 30 °C Molecular weight: 154.25	• *p*-Menthenol (mixed isomers) • Terpineol pure		>1000	0.07	1.7

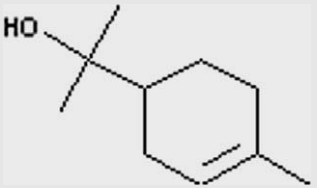
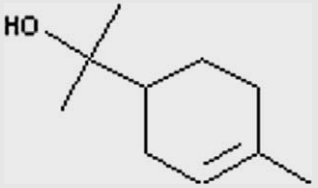
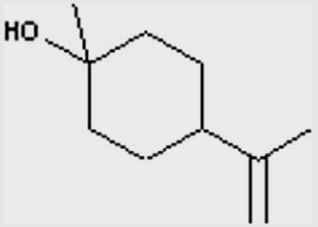
α-Terpineol CAS# 98-55-5 LogK_{ow} 3.33 Molecular weight: 154.25	• 3-Cyclohexene-1-methanol,α,α,4-trimethyl- • 1-*p*-Menthen-8-ol • *p*-Menth-1-en-8-ol (isomer unspecified) • 1-Methyl-4-isopropyl-1-cyclohexen-8-ol • α-Terpilenol • Terpineol schlechthin		100–1000	0.07	5.7
L-α *Terpineol* CAS# 10482-56-1 LogK_{ow} 3.33 Molecular weight: 154.53	• 3-Cyclohexene-1-methanol,α,α,4-trimethyl-, (*S*)- • (−)-α-Terpineol • *p*-Menth-1-en-8-ol (*S*)		1–10	0.005	0.8
p-Menth-8-en-1-ol CAS# 138-87-4 LogK_{ow} 3.41 Molecular weight: 154.25	• Cyclohexanal, 1-methyl-4-(1-methylethenyl)- • 4-Isopropenyl-1-methyl-1-cyclohexanol • 1-Methyl-4-isopropenylcyclohexan-1-ol • β-Terpinol		1–10	0.0005[d]	0.02
4-Thujanol CAS# 546-79-2 LogK_{ow} 3.19 Molecular weight: 154.25	• Bicyclo[3.1.0]hexan-2-ol, 2-methyl-5-(1-methylethyl)- • 2-Methyl-5-(1-methylethyl)bicyclo(3.1.0)hexan-2-ol • Sabinenehydrate		0.1–1	0.0005[d]	0.02

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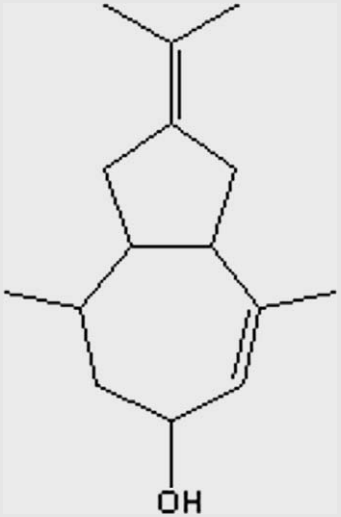
Table 2 (*continued*)

Material	Synonyms	Structure	Worldwide metric tons	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level[a,b,c] (%)
Vetiverol CAS# 68129-81-7 Log K_{ow} 4.78 Molecular weight: 220.36	• Lignolia • Vetivenol • Vetivol • Vetyvenol		< 0.01	0.0005[d]	0.02

[a] 2004 Volume of use survey.
[b] Skin levels were based on the assumption that the fragrance mixture is used at 20% in a consumer product.
[c] 2002 IFRA use level survey.
[d] A default value of 0.02% was used to calculate dermal systemic exposure.

Table 2-1A
Summary of percutaneous absorption data/non-cyclic terpene alcohols

Material	Method	Results	References
In vitro			
Citronellol	500 mg applied for 1, 2 or 4 h to the skin from the thorax region of one female cadaver	954 μg/cm^2/h	Cal and Sznitowska (2003)
Farnesol	500 mg of undiluted farnesol or 50%, 20%, 10%, 1% solutions in DMSO on pig skin, Franz diffusion cells (5/preparation), receptor fluid: methanol	1%, 10%: results not reported 20%, 50%: epidermis and dermis penetrated 100%: remained mainly in the lipids of the stratum corneum	Bobin et al. (1997)
Linalool	4% (w/v) of linalool in 70/30 EtOH/water, DEP (diethyl phthalate) or DPG (dipropylene glycol). Occluded	14.1% with 70/30 EtOH/water 5.73% with DEP 7.49% with DPG	RIFM (2006c)
	4% (w/v) of linalool in 70/30 EtOH/water, DEP, or DPG. Unoccluded	3.57% with 70/30 EtOH/water 2.77% with DEP 1.8% with DPG	RIFM (2006c)
	500 mg applied for 1, 2 or 4 h to the skin from the thorax region of one female cadaver	827 μg/cm^2/h	Cal and Sznitowska (2003)
	Influence of three different vehicles on penetration was compared (oily solution, hydrogel, o/w emulsion), human skin	Penetration from emulsion < oily solution < hydrogel	Cal (2006)
In vivo			
Linalool	1500 mg of massage oil with 2% lavender oil (containing 25% linalool and 30% linalyl acetate) were massaged for 10 minutes on the abdominal skin of a male volunteer	5 minutes after massage trace amounts in blood, peak concentrations at 19 minutes (100 ng/ml linalool and 121 ng/ml linalyl acetate); most disappeared by 90 minutes with a half-life of ca. 14 minutes	Jäger et al. (1992)

Table 2-1B
Summary of Percutaneous Absorption Data/cyclic terpene alcohols

Material	Method	Results	References
In vitro			
Carveol	Excised human skin, epidermal membrane; 150 μL, 12 h	Permeability coefficient 29.0 ± 5.59 cm/h $\times 10^{-5}$	Williams and Barry (1991a,b)
4-Carvo-menthenol	Excised human skin, epidermal membrane; 150 μL, 12 h	Permeability coefficient 25.3 ± 6.31 cm/h $\times 10^{-5}$	Williams and Barry (1991a,b)
	Influence of three different vehicles on penetration was compared (oily solution, hydrogel, o/w emulsion), human skin	Penetration from emulsion < oily solution < hydrogel	Cal (2006)
In vivo			
Menthol	Humans, treated dermally with menthol containing ointment (no quantitative data available)	Menthol was found in urine	Atzl et al. (1972)
	Mice, 0.65% radioactive labeled menthol in a foam bath	Max. blood levels at 10 minutes after start of experiment	Schäfer and Schäfer (1982)
Terpineol	Eserine uptake in mice (2.2 cm^2 of shaved abdominal skin were exposed for 2 h to a not specified amount of terpineol with 0.23% eserine)	In spite of its tertiary OH group, terpineol was absorbed "relatively rapidly" through the skin of mice	Meyer and Meyer (1959)

2.2. Oral route

In rats, 72 h after a single oral dose of 500 mg ^{14}C-labeled linalool/kg body weight, about 55% of the radioactivity was excreted in the urine as the glucuronic acid conjugate, 15% in the faeces, and 23% as $^{14}CO_2$ in the expired air. Only 3–4% residual activity was found in tissues, with 0.5% in the liver, 0.6% in the gut, 0.8% in the skin and 1.2% in the skeletal muscle (Parke et al., 1974).

Farnesol containing four isomers (11% *cis*,*cis*-farnesol; 25% *cis*,-*trans*-farnesol; 24% *trans*,*cis*-farnesol; and 39% *trans*,*trans*-farnesol) was administered to CD rats. The major isomer present in plasma was *trans*,*trans*-farnesol; although this biologically active isomer comprised approximately 39% of the bulk material, it represented approximately 80% of the total farnesol recovered in the plasma. All other isomers were present in the plasma at levels that were either similar to or below their levels in the bulk drug (Horn et al., 2005).

In humans, between 69% and 81% of orally administered borneol (2 or 3.5 g as a single dose) were excreted in the urine as glucuronide within 6–10 h (Quick, 1928).

(−)-Elemol (2000 mg/kg body weight) was given p.o. to rabbits, and urine was collected for 72 h. 80% of the administered dose was recovered from urine (Asakawa et al., 1986).

In human volunteers, 79% of a 1000 mg oral dose of menthol or 78% of a 10–20 mg dose were eliminated as the glucuronic acid conjugate within 6 h (Quick, 1928; Atzl et al., 1972). L-menthol administered for 8 days at daily doses of 750 mg was excreted as menthyl glucuronides (27%—84%) within 24 h after the last administration (Eisenberg et al., 1955). Most of L-menthol, administered orally at 500 mg/kg body weight to F344 rats, was excreted in the bile during the first 24 h after administration (Yamaguchi et al., 1994).

Two male Wistar rats were administered 100 mg/kg body weight of sclareol in DMSO-Emulphor-saline *via* intravenous or oral dose. A very rapid biphasic disappearance was observed. No metabolites of sclareol were detectable in the plasma or urine following either i.v. or oral treatments; unchanged sclareol was excreted in rat faeces to the extent of 9% of an oral dose in 48 h. Following i.v. treatment, 0.002% of the dose was recovered in bile unchanged. Four biliary metabolites (0.4% dose) were identified (Kouzi et al., 1993).

2.3. Respiratory route of exposure

After a 1 h inhalation exposure to 5 mg/L linalool, serum linalool levels in mice were 7–9 ng/ml (Jirovetz et al., 1991). In separate

experiments, groups of 4 mice were exposed to an atmosphere containing 5 mg/L linalool. After a 1 h exposure, the serum linalool level was 8 ng/ml (Buchbauer et al., 1991; Jirovetz et al., 1990). The addition of β-glucuronidase to these serum samples resulted in an increase of linalool to 12 ng/ml.

The potential for absorption of various fragrance compounds *via* inhalation was determined in groups of four female Swiss mice exposed for 1 h to an atmosphere generated from 20 to 50 mg of essential oils or the pure materials (no data on air concentrations provided); the amounts detected in the plasma at the end of the inhalation period were 0.36 and 0.38 ng/ml for isoborneol and borneol, 1.70 and 2.90 ng/ml for geraniol and citronellol, and 4.22, 4.70 and 5.70 ng/ml for linalool, α-terpineol, and nerol, respectively. Farnesol was not detected (Buchbauer et al., 1993).

In inhalation experiments on mice with sandalwood oil (1 h exposure to 3 ml, corresponding to 50–108 mg/m^3), low concentrations of α-santalol (6.1 ng/ml ± 2 ng/ml) and β-santalol (6.3 ± 2 ng/ml) could be detected in the serum. The same inhalation experiments on mice with α-terpineol (exposure for 1 h to 3 ml, corresponding to 50–108 mg/m^3), resulted in serum concentrations of α-terpineol of 6.9 ± 1 ng/ml (Jirovetz et al., 1992).

3. Metabolism

Once taken up in the body, the terpene alcohols covered in this assessment are expected to be detoxified primarily by conjugation with glucuronic acid and excretion in the urine and to a lesser extent in the feces. Alternatively, alcohols with alkyl or alkenyl substituents may be oxidized at the allylic position to yield polar diol metabolites, which may also be excreted free or in the conjugated form. If the diol contains a primary alcohol function, it may undergo further oxidation to the corresponding carboxylic acid and be further oxidized to eventually yield carbon dioxide (Madyastha and Srivatsan, 1988a; Williams, 1959; Parke et al., 1974; JECFA, 1999).

In most cases, therefore, metabolism yields innocuous metabolites. Some substances of this assessment, however, may generate α,β-unsaturated compounds or become oxidized to hydroperoxides. These oxidation products have the capacity to participate in a range of nucleophilic and electrophilic addition reactions with biological material. The respective parent compounds, identified on the basis of their structure and chemical reactivity, are farnesol, geraniol, nerol, santalol, 2(10)pinen-3-ol, 2,6-dimethyloct-3,5-dien-2-ol, 3,7-dimethyl-4,6-octadien-3-ol and 6,7-dihydrogeraniol.

Oxidation is mediated by cytochrome P-450 dependent monooxygenases, mainly in the liver (Chadha and Madyastha, 1984; Parke et al., 1974; JECFA, 1999). Rat lung and rat kidney microsomes also are capable of ω-hydroxylation of citronellol, geraniol, linalool, and nerol involving the cytochrome P-450 system. The activity of kidney cells was lower than that of the lung cells (Chadha and Madyastha, 1982). Carveol was oxidized to carvone by liver microsomes of dogs, rabbits, and guinea pigs, but not by liver microsomes of mice, rats, monkeys and humans (Shimada et al., 2002).

Chadha and Madyastha (1984) studied the *in vivo* metabolism of geraniol and linalool in rats administered a daily oral dose of 800 mg/kg body weight of geraniol or linalool for 20 days. Metabolites isolated from the urine after administration of geraniol were geranic acid, 3-hydroxy-citronellic acid, 8-hydroxy-geraniol, 8-carboxy-geraniol and Hildebrandt acid. Metabolites isolated from the urine of rats after administration of linalool were 8-hydroxy-linalool and 8-carboxy-linalool. The cytochrome P-450 activity in the liver microsomes was increased by these pre-treatments.

The metabolic pathways of geraniol are shown in Fig. 1 (taken from JECFA, 1998b).

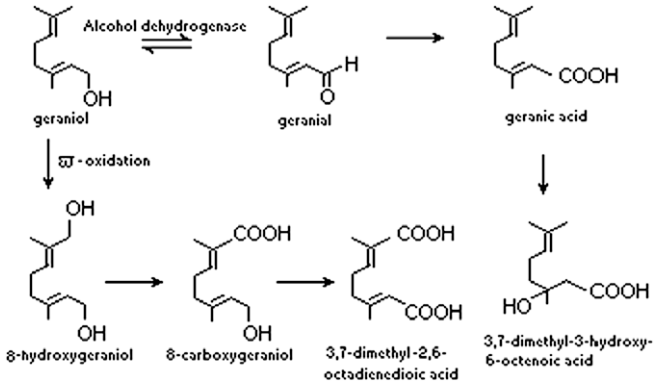


Fig. 1. Metabolic pathways of geraniol.

Glucuronic acid conjugation and excretion is the primary route of metabolism of linalool. Allylic oxidation becomes an important pathway after repeated dosing. Metabolites isolated from rat urine after daily oral administration of 800 mg/kg body weight of linalool for 20 days to male IISc strain rats were 8-hydroxylinalool and 8-carboxylinalool (see metabolites B and C in Fig. 2; figure taken from Bickers et al., 2003) (Chadha and Madyastha, 1984). This treatment induced a transient, approximately 50% increase in liver cytochrome P-450 activity. Linalool administered daily by gavage at a dose of 500 mg/kg body weight/day for 64 days to 4-week-old male Wistar rats did not induce cytochrome P-450 until the 30th day of treatment (Parke et al., 1974). It has been suggested that the biotransformation of the diol metabolites of geraniol and linalool to the corresponding aldehyde by alcohol dehydrogenase (ADH) is inhibited due to the bulky nature of the neighboring alkyl substituents and the substrate specificity of the enzyme (Eder et al., 1982a).

After a single dose of linalool to rats, reduction metabolites such as dihydro- and tetrahydrolinalool (metabolites D and E in Fig. 2) have been identified in the urine either free or in the conjugated form (Chadha and Madyastha, 1984; Parke et al., 1974a).

The non-cyclic terpene alcohols (linalool, citronellol, nerol, and geraniol) were substrates of UDPGTs (UDP-glucuronosyltransferases) and showed typical phenobarbital-inducible behavior in Wistar rats (Boutin et al., 1985).

A study by Leclerc et al. (2002) used enzymatic assays to investigate glucuronidation potency of the rat olfactory mucosa and olfactory bulb toward a series of odorant molecules in rats. (−)-Borneol was efficiently conjugated by the UDP-glucuronosyltransferases present in olfactory mucosa, whereas β-citronellol, geraniol and (−)-menthol were glucuronidated with a lower efficacy. Glucuronidation rates were much lower in the olfactory bulb.

Linalool undergoes partial ring closure to yield mainly α-terpineol and minor amounts of the terpenoid primary alcohols, geraniol and nerol (Fig. 2). In acidic (pH 1.8) artificial gastric juice and in neutral media (pH 7.5), linalool is rapidly rearranged to yield α-terpineol and small amounts of geraniol and nerol (FEMA, 1998). Both linalool and α-terpineol may then be either conjugated and excreted or oxidized to more polar excretable metabolites (see Fig. 3).

Farnesol is an endogenous by-product of the mevalonate/cholesterol biosynthetic pathway. Among other biological activities, farnesol has been demonstrated to modulate cholesterol synthesis *via* inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzymatic step in the conversion of HMG-CoA to mevalonate. Omega-oxidation of farnesol by mammalian cytochromes P-450 has been demonstrated by De Barber et al. (2004) and Staines et al. (2004). In studies with purified CYP2E1, 12-hydroxyfarnesol was obtained as the major product

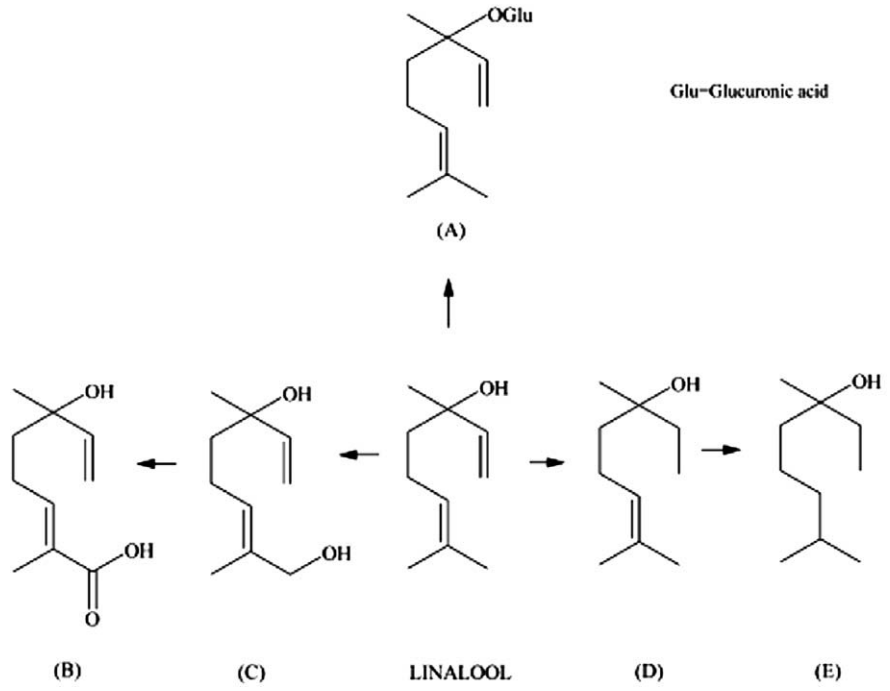


Fig. 2. Metabolism of linalool in rats.

of farnesol metabolism. Among a series of available human P-450 enzymes, only CYP2C19 also produced 12-hydroxyfarnesol. Mammalian cells expressing CYP2E1 demonstrated further farnesol metabolism to α,ω-prenyl dicarboxylic acids. Since such acids were identified in animal urine, the data suggest that CYP2E1 could be an important regulator of farnesol homeostasis *in vivo* (De Barber et al., 2004). Farnesol is also metabolized to farnesyl glucuronide, and hydroxyfarnesyl glucuronide by human tissue microsomes through specific human UGTs (uridine diphospho glucuronosyl transferases). Farnesol is a good substrate *in vitro* for glucuronidation in human liver, kidney and intestine microsomes with UGTs 1A1 (in liver) and 2B7 (in intestine microsomes) (Staines et al., 2004). Increased glutathione reductase and glutathione-*S*-transferase activities were found in rats after daily oral administration of 500 or 1000 mg/kg body weight for 28 days (Horn et al., 2005).

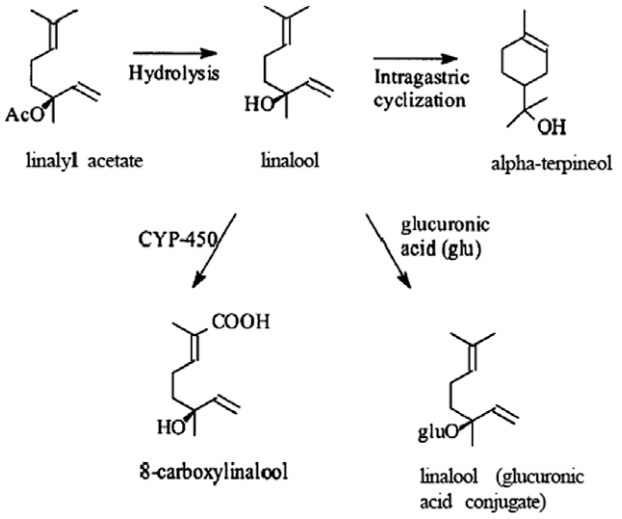


Fig. 3. Metabolic pathways of linalool.

Farnesol acts on numerous nuclear receptors such as PPAR (peroxisome proliferator-activated receptor) γ and PPAR α. In addition, farnesol is a substrate for the bile acid receptor (farnesoid X receptor), and can activate CAR (constitutive androstane receptor).

In experiments with rat C6 glial cells and an African green monkey kidney cell line (CV-1) Crick et al. (1995) showed, that farnesol can be used for isoprenoid biosynthesis and protein isoprenylation in mammalian cells. Rat liver microsomal and peroxisomal fractions are able to phosphorylate free farnesol to its diphosphate ester (Westfall et al., 1997). Farnesol can also be activated to the corresponding pyrophosphate in rat retina and subsequently be metabolized to sterols and sterol precursors (Fliesler and Keller, 1995). Westfall et al. (1997) demonstrated that farnesol can be oxidized to a prenyl aldehyde, presumably by an alcohol dehydrogenase (ADH), and that this activity resides in the mitochondrial and peroxisomal fractions.

The cyclic terpene alcohols borneol, carveol, dihydrocarveol, 4-carvomenthenol, cedrol, menthol, terpineol, isopulegol and myrtenol were substrates of UDPGTs (UDP-glucuronosyltransferases) and showed typical phenobarbital-inducible behavior in Wistar rats (Boutin et al., 1985). No induction was observed with either phenobarbital or 3-methylcholanthrene in the case of fenchyl alcohol (Boutin et al., 1985). The three terpene alcohols L-borneol, terpineol, and menthol were substrates of the hepatic UDPGT of pigs (Boutin et al., 1981). The glucuronidation of borneol occurs in rough and smooth endoplasmic reticulum, Golgi apparatus and plasma membranes of rat liver cells (Antoine et al., 1984).

The rate of glucuronidation of 0.5 mM (−)-borneol, (−)-carveol, 4-carvomenthenol, fenchyl alcohol, isoborneol, and α-terpineol by human embryonic kidney 293 cells expressing UDP-glucuronosyltransferase 1.4 protein was between 20 and 29 pmol/min/mg protein. The rates for 0.5 mM (+)-menthol, (−)-menthol and (+)-neomenthol were 43, 41 and 51 pmol/min/mg protein, respectively. Glucuronidation of 0.5 mM linalool was below the detection limit of 2 pmol/min/mg protein (Green and Tephly, 1996).

Dogs fed daily doses of 5 g of borneol for several weeks excreted about 50% as the glucuronic acid conjugate in the urine (Quick, 1927, 1928). In dogs there was a preferential conjugation of the

D-borneol compared to the L-isomer (Pryde and Williams, 1934). Wagreich et al. (1941) administered orally 2 g of borneol to each of eight human subjects. Glucuronic acid conjugation accounted for an average of 94% (79–104%) of the administered dose; when 1 g of borneol was administered orally in gelatin capsules to 26 human subjects, glucuronic acid conjugation accounted for an average of 81% (60–101%) of the dose.

In rats and dogs, *p*-mentha-1,8-dien-7-ol (perilla alcohol) is rapidly metabolized by alcohol and aldehyde dehydrogenases to the corresponding acid (perillic acid), dihydroperillic acid and perillaldehyde (Boon et al., 2000). No parent compound was detected in plasma of rats 15 minutes or 4 h after a single gavage dose of 1000 mg/kg body weight or after 10 weeks of feeding a diet containing 2% of *p*-mentha-1,8-dien-7-ol. The parent compound was not detected in plasma of dogs dosed p.o. with 250 mg/kg body weight at times ranging from 10 minutes to 48 h after administration (Haag and Gould, 1994; Phillips et al., 1995).

Allylic methyl oxidation of α-terpineol is the major route for its biotransformation in rat. In a repeated dose study, male albino rats (IISc strain) were orally administered the alicyclic tertiary alcohol α-terpineol at a daily dose of 600 mg/kg body weight for 20 days. Oxidation of the allylic methyl group yielded the corresponding carboxylic acid, which to a small extent, was reduced to yield the corresponding saturated carboxylic acid. α-Terpineol induced the liver microsomal cytochrome P-450 system to a significant extent (Madyastha and Srivatsan, 1988a).

In a minor pathway (see Fig. 4), the endocyclic alkene of α-terpineol is epoxidized and then hydrolyzed to yield a triol metabolite (1,2,8-trihydroxy-*p*-menthane) which has been reported in humans following inadvertent oral ingestion of a pine oil disinfectant containing α-terpineol (Horning et al., 1976). Similarly, 1,2,8-trihydroxy-*p*-menthane and the glucuronide of α-terpineol were found in urine samples of male Sprague–Dawley rats administered *via* a single intraperitoneal injection either pine oil or α terpineol at 100 mg (Hill et al., 1975).

In humans, rats, and rabbits, menthol is efficiently metabolized to menthol glucuronide as well as hydroxylated metabolites. Oxidation of the methyl and isopropyl groups of menthol has been reported to provide major metabolites in the rat after administration for up to 20 days (Madyastha and Srivatsan, 1988b; Quick, 1924; Yamaguchi et al., 1994).

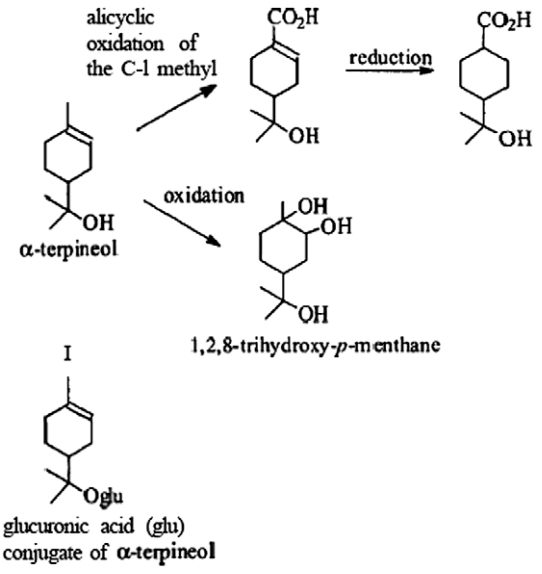


Fig. 4. Minor metabolic pathway of α-terpineol.

Rabbits fed 1 g/kg body weight of D,L-menthol and L-menthol excreted in the urine D,L-menthol glucuronides and L-menthol glucuronides in similar amounts (59% and 48% of the dose, respectively) (Williams, 1938) (see Fig. 5).

Traces of myrtenol (but not borneol) were detected in the hydrolyzed urine of sawmill workers exposed to α-pinene, β-pinene and delta-3-carene. About 1–4% of the total α-pinene intake was eliminated as *cis*- or *trans*-verbenol in human volunteers exposed for 2 h to (+)-α-pinene air concentrations of 450, 225, or 10 mg/m^3 and/or to (−)-α-pinene at 450 mg/m^3. Most of the verbenols were eliminated within 20-h after a 2-h exposure (Levin et al., 1992). The verbenols were most likely formed from α-pinene by hydroxylation and excreted conjugated to glucuronic acid (Eriksson and Levin, 1990; Eriksson et al., 1996). Myrtenol and *trans*-verbenol glucuronides were identified as metabolites of α-pinene in rabbits after gavage (Ishida et al., 1981). Myrtenol and *trans*-verbenol were identified as a metabolite of 1 mM α-pinene in reconstituted rat liver cytochrome P-450 systems (White and Agosin, 1980).

(−)-Elemol was mainly excreted conjugated with glucuronic acid or sulfate, although one oxidized metabolite, (−)-15-hydroxyelemol, was also found in lower amounts (10%) in the urine of rabbits given 2000 mg. No oxidation of the isolated terminal double bond of elemol was found (Asakawa et al., 1986).

3.1. Summary of metabolism data

Sufficient data are available from farnesol, linalool, menthol and α-terpineol, i.e., compounds that contain all key structural elements and potential sites of metabolism of all other members in the group, to demonstrate that the non-cyclic and cyclic terpenes share common metabolic pathways. The major pathways of metabolism are:

- conjugation of the alcohol with glucuronic acid,
- side-chain oxidation yielding polar metabolites, which may be conjugated and excreted,
- hydrogenation of the endocyclic double bond.

These metabolic patterns are common modes of converting tertiary, secondary and primary alcohols to polar metabolites, which are easily excreted in the urine and faeces. Unchanged parent compounds have also been detected in urine. In most cases, metabolism yields innocuous metabolites. Some materials, however, may generate α, β-unsaturated compounds or be oxidized to hydroperoxides. Such compounds have the capacity to participate in a range of nucleophilic and electrophilic addition reactions with biological material. The respective parent compounds are farnesol, geraniol, nerol, santalol, 2(10)pinen-3-ol, 2,6-dimethyloct-3,5-dien-2-ol, 3,7-dimethyl-4,6-octadien-3-ol and 6,7-dihydrogeraniol.

4. Toxicological studies

4.1. Acute toxicity (see Tables 3-1A/B, 3-2A/B, and 3-3A/B)

The acute dermal toxicity of citronellol, dihydrocitronellol (3,7-dimethyl-1-octanol), and rhodinol (α-citronellol) are low with LD_{50} values in rabbits reported to be between 2000 and 5000 mg/kg body weight. The other non-cyclic terpene alcohols included in this summary are practically non-toxic *via* the dermal route of exposure (LD_{50} values in rabbits generally greater than 5000 mg/kg body weight (Table 3-1A)).

With regard to the cyclic terpene alcohols, LD50 values have been reported for 20 materials. 4-Carveomenthenol had a dermal LD_{50} around ~2500 mg/kg body weight. The LD_{50} values for 15 of

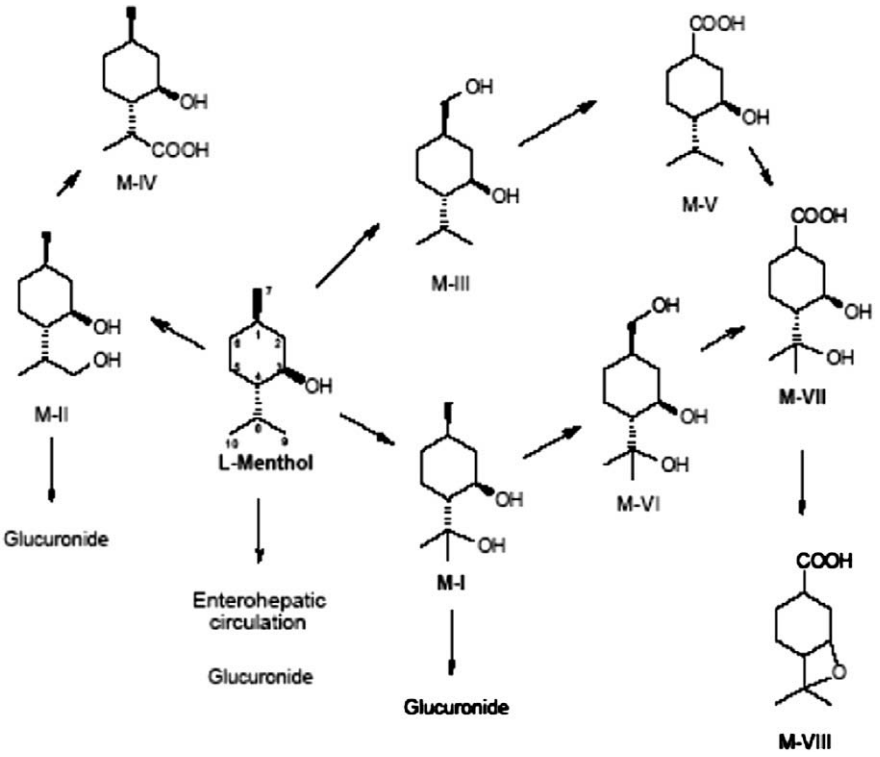


Fig. 5. Metabolic pathways of menthol.

these materials were greater than 5000 mg/kg body weight. The LD_{50} values in four other materials were greater than 2000 mg/kg body weight (which was the highest dose tested) indicating that these materials are practically not toxic *via* the dermal route (Table 3-1B).

The acute oral toxicity of the non-cyclic terpene alcohols is likewise low, with LD_{50} values in rats generally greater than 2000 mg/kg body weight, or, in the case of ocimenol, close to 2000 mg/kg body weight (Table 3-2A). LD_{50} values for the cyclic terpene alcohols ranged between 1000 and 2000 mg/kg body weight (4-carvomenthenol, isopulegol, myrtenol), 2000 and 5000 mg/kg (carveol, fenchyl alcohol, menthol, *p*-mentha-1,8-dien-7-ol, santalol, terpineol), indicating a low or very low toxicity. The other tested materials are practically non-toxic by the oral route (bisabolol, borneol, caryophyllene alcohol, cedrenol, dihydrocarveol, dihydroterpineol, hydroabietyl alcohol, isoborneol, 6-isopropyl-2-decahydro naphthalenol, *p*-menthan-7-ol, sclareol, verbenol, vetiverol) (Table 3-2B).

Table 3-1A
Acute dermal toxicity studies/non-cyclic terpene alcohols

Material	Species	No. of animals/dose group	LD_{50} (mg/kg)[a]	References
D,L-Citronellol	Rabbit	5	2650 (95% CI 1780–3520)	RIFM (1973a)
Dehydrolinalool	Rabbit	10	>5000	RIFM (1977a)
6,7-Dihydrogeraniol	Rabbit	10	>2000	RIFM (1985d)
3,7-Dimethyl-1-octanol	Rabbit	4	~2400 (95% CI 1700–3400)	RIFM (1973b)
	Rabbit	6	<5000	RIFM (1973b)
Farnesol	Rat	5	>15	RIFM (1983f)
Farnesol	Rabbit	10	>5000	RIFM (1974b)
Geranyl dihydrolinalool[b]	Rabbit	10	>5000	RIFM (1982a)
Geraniol	Rabbit	3	>5000	RIFM (1972a)
Geranyl linalool	Rabbit	10	>200	RIFM (1978f)
	Rabbit	10	>5000	RIFM (1982a)
Hydroxycitronellol	Rabbit	4	~5000	RIFM (1973h)
Linalool	Rabbit	3	5610 (95% CI 3580–8370)	RIFM (1970a)
trans-3,7-Dimethyl-1,6-octadien-3-ol	Rabbit	4	~5000 ml	RIFM (1973h)
Myrcenol	Rabbit	10	>5000	RIFM (1972a)
Nerol	Rabbit	10	>5000	RIFM (1972a)
Nerolidol	Rabbit	10	>5000	RIFM (1973f)
Ocimenol	Rabbit	10	>5000	RIFM (1974a)
Rhodinol	Rabbit	4	3600 (95% CI 2600–4900)	RIFM (1973a)
Tetrahydrolinalool	Rabbit	10	>5000	RIFM (1976b)
Tetrahydromuguol	Rabbit	10	>5000	RIFM (1974a)
Tetrahydromyrcenol	Rabbit	10	>5000	RIFM (1982b)

[a] Units have been converted to make easier comparisons; original units are in the Fragrance Material Reviews.
[b] This material is not one of the materials being reviewed as it is not used in fragrances, but it is included in this table because it is structurally related.

Table 3-1B
Acute dermal toxicity studies/cyclic terpene alcohols

Material	Species	No. of animals/dose group	LD_{50} (mg/kg)[a]	References
L-Borneol	Rabbit	10	>2000	RIFM (1972a)
iso-Borneol	Rabbit	5	>5000	RIFM (1977a)
L-Carveol	Rabbit	6	>5000	RIFM (1972b)
p-Mentha-1,8-dien-7-ol	Rabbit	10	>5000	RIFM (1977a)
4-Carvomenthenol	Rabbit	4	>2500	RIFM (1977a)
Caryophyllene alcohol[b]	Rabbit	10	>5000	RIFM (1973f)
Cedrenol	Rabbit	10	>5000	RIFM (1974a)
Cedrol	Rabbit	6	>5000	RIFM (1973a)
Dihydrocarveol	Rabbit	10	>5000	RIFM (1977a)
Dihydro-α-terpineol	Rabbit	7	>5000	RIFM (1973a)
Hydroabietyl alcohol	Rabbit	6	>5000	RIFM (1972c)
Isopulegol	Rabbit	4 (2/sex)	~3000	RIFM (1971d)
cis-*p*-Menthan-7-ol	Rabbit	6	>2000	RIFM (1979f)
Menthol, racemic	Rabbit	4	~5000 ml	RIFM (1973h)
L-Menthol	Rabbit	10	>5000	RIFM (1974a)
cis-2-Pinanol[b]	Rabbit	6 (3/sex)	>5000	RIFM (1979a)
Santalol	Rabbit	6	>5000	RIFM (1972b)
Sclareol	Rabbit	6	>5000	RIFM (1979a)
Terpineol	Rabbit	1–3 (female), 3 doses	>3000	RIFM (1971a)
Vetiverol	Rabbit	8	>5000	RIFM (1977a)
Geranodyle	Rats	10	>2000	RIFM (1987h)

[a] Units have been converted to make easier comparisons; original units are in the Fragrance Material Reviews.
[b] This material is not one of the materials being reviewed as it is not used in fragrances, but it is included in this table because it is structurally related.

Table 3-2A
Acute oral toxicity studies/non-cyclic terpene alcohols

Material	Species	No. of animals/dose group	LD_{50} (mg/kg)[a]	References
D,L-Citronellol	Rat	10	3450 (95% CI 3210–3690)	RIFM (1973a)
Dehydrolinalool	Rat	10	4200 (95% CI 3700–4800)	RIFM (1977a)
	Rat	Not reported	3100	RIFM (1978c)
	Mouse	8 (4/sex)	1500	RIFM (1992b)
	Mouse	8 (4/sex)	2200	RIFM (1992b)
6,7-Dihydrogeraniol	Rat	10	>5000	RIFM (1985a)
3,7-Dimethyl-1-octanol	Rat	10	>5000	RIFM (1973b)
3,7-Dimethyloct-7-en-1-ol	Rat	10/sex	Males: ml5050 (95% CI 4140–6160 ml) Females: 2070 (95% CI 1940–3750 ml)	RIFM (1981b)
Farnesol	Rat	10	>5000	RIFM (1974b)
	Rat	10 (5/sex)	>20,000 ml	RIFM (1976d)
	Rat	10	>5000	RIFM (1981d)
	Mouse	10	8764 ± 821	RIFM (1967b)
Geraniol	Rat	10 (5/sex)	3600 (95% CI 2840–4570)	Jenner et al. (1964) and Bär and Griepentrog (1967)
	Rat	5	4800	Yamawaki (1962)
Geranyl dihydrolinalool[b]	Rat	10	>5000	RIFM (1982a)
Geranyl linalool	Rat	10	>5000	RIFM (1982a)
	Rat	10	>5000	RIFM (1978f)
	Mouse	10	14,632 ± 849	RIFM (1967b)
Hydroxycitronellol	Rat	10 (5/sex)	>5000 ml	RIFM (1973c)
Linalool	Rat	10 (5/sex)	2790 (95% CI 2440–3180)	Jenner et al. (1964)
	Mouse	10 (male and female)	3918 (±301)	RIFM (1967a)
	Mouse	8 (4/sex)	3500	RIFM (1992b)
	Mouse	8 (4/sex)	2200	RIFM (1992b)
trans-3,7-Dimethyl-1,6-octadien-3-ol	Rat	10 (5/sex)	4180 ml (95% CI 3770–4640 ml)	RIFM (1973c)
Myrcenol	Rat	10	5300 (95% CI 4500–6100)	RIFM (1972a)
Nerol	Rat	10	4500 (95% CI 3400–5600)	RIFM (1972a)
Nerolidol	Rat	10	>5000	RIFM (1973d)
	Mouse	5 (male)	9976 (±350)	RIFM (1967a)
Ocimenol	Rat	10	1700	RIFM (1974a)
Rhodinol	Rat	10	>5000	RIFM (1973a)
Tetrahydrolinalool	Rat	10	>5000	RIFM (1976b)
	Mouse	10 (male and female)	6233 (±498)	RIFM (1967a)
Tetrahydromuguol	Rat	10	>5000	RIFM (1974a)
Tetrahydromyrcenol	Rat	10	>5000	RIFM (1982b)

[a] Units have been converted to make easier comparisons; original units are in the Fragrance Material Reviews.
[b] This material is not one of the materials being reviewed as it is not used in fragrances, but it is included in this table because it is structurally related.

Clinical signs after dermal or oral administration of non-cyclic or cyclic terpene alcohols were non-specific and included stimulation of the central nervous system (CNS) immediately after administration, followed by CNS depression at doses near the LD_{50} values.

Table 3-2B
Acute oral toxicity studies/cyclic terpene alcohols

Material	Species	No. of animals/dose group	LD_{50} (mg/kg)[a]	References
α-Bisabolol	Rat	Not reported	>5000	BASF (1980) as cited in CIR (1999)
	Rat	20 (10/sex)	14,900 and 15,600 ml in males and females ml	Habersang et al. (1979)
	Mouse	20 (10/sex)	15,100 ml	Habersang et al. (1979)
L-Borneol	Rat	10	6500 (95% CI 5800–7200)	RIFM (1972a)
iso-Borneol	Rat	10	5200 (95% CI 4300–6200)	RIFM (1977a)
L-Carveol	Rat	10	3000 (95% CI 2340–3830)	RIFM (1972b)
p-Mentha-1,8-dien-7-ol	Rat	10	2100 (95% CI 1700–2600)	RIFM (1977a)
4-Carvomenthenol	Rat	10	1300 (95% CI 840–2100)	RIFM (1977a)
Caryophyllene alcohol[b]	Rat	10	>5000	RIFM (1973f)
Cedrenol	Rat	10	>5000	RIFM (1974a)
Dihydrocarveol	Rat	10	>5000	RIFM (1977a)
Dihydro-α-terpineol	Rat	10	>5000	RIFM (1973a)
Hydroabietyl alcohol	Rat	10	>5000	RIFM (1972c)
6-Isopropyl-2-decahydronaphthalenol	Rat	10 (5/sex)	4200 ml (95% CI 3750–4700 ml)	RIFM (1973e)
Isopulegol	Rat	10 (5/sex)	1030 (±100) ml	RIFM (1971d)
cis-*p*-Menthan-7-ol	Rat	17	>10,000	RIFM (1978b)
D,L-Menthol	Rat	Several studies	>2000	OECD (2003)
	Rat	10 (5/sex)	3180 (95% CI 2790–3620)	Jenner et al. (1964)
	Mouse	Not reported	3100	Sasaki et al. (2000)
	Mouse	10	3100	Wokes (1932)
Menthol (isomer unspecified)	Rats	5	940	FDA (1975)
	Mice	6	4400	FDA (1975)
	Mice	6	2650	FDA (1975)
L-Menthol	Mouse	10	3400	Wokes (1932)
Myrtenol	Rat	5/sex	2457 (in males), 632 (in females) and 1432 (males and females combined)	RIFM (2001a)
D,L-Neomenthol[b]	Mouse	10	4000	Wokes (1932)
cis-2-Pinanol[b]	Rat	10 (5/sex)	2050 (95% CI 1639–2580)	RIFM (1979a)
Santalol	Rat	10	3800 (95% CI 3060–4710)	RIFM (1972b)
Sclareol	Rat	10 (5/sex)	>5000	RIFM (1979a)
Terpineol	Rat	10 (male)	4300 (95% CI 2900–5700)	RIFM (1971a)
α-Terpineol	Mice	10	2830 (95% CI 2290–3497)	Yamahara et al. (1985)
cis-Verbenol[b]	Rat	10 (5/sex)	>5000	RIFM (1991a)
Vetiverol	Rat	10	>5000	RIFM (1977a)
	Mouse	10 (5/sex)	>10,000 ml	RIFM (1984b)
Geranodyle	Rats	20	>2000	RIFM (1995f)

[a] Units have been converted to make easier comparisons; original units are in the Fragrance Material Reviews.
[b] This material is not one of the materials being reviewed as it is not used in fragrances, but it is included in this table because it is structurally related.

Acute toxicity data obtained from studies employing other than the oral and dermal routes of exposure are summarized in Tables 3-3A and 3-3B.

4.2. Repeated dose toxicity (see Tables 4A and 4B)

The results of repeated dose toxicity studies with non-cyclic and cyclic terpene alcohols are summarized in Tables 4A and 4B and are described below.

4.2.1. Dermal studies

Of the non-cyclic terpene alcohols only linalool was tested in repeated dose dermal toxicity studies (RIFM, 1980a). α-Bisabolol is the only cyclic terpene alcohol for which such data were available (BASF, 1996, as cited in CIR (1999)).

SD rats (20/sex/dose) were treated dermally with 0, 250, 1000 or 4000 mg/kg body weight/day of linalool for 13 weeks (RIFM, 1980a). Slight transient erythema and slightly decreased activity were the only effects noted at 250 mg/kg body weight/day. 1000 mg/kg body weight/day caused slight erythema during the first 6 study weeks and, in females, a reduction in body weight. At 4000 mg/kg body weight/day, 9 females and 2 males died, and reduced food consumption and reduced body weight were found in males. No pathological findings were reported from hematology, clinical chemistry, or urinalysis. The no observed adverse effect level (NOAEL) can be set at 250 mg/kg body weight/day; the lowest observed adverse effect level (LOAEL) was at 1000 mg/kg body weight/day (based on body weight reduction in females).

With α-bisabolol (applied as a 4%, 10% or 20% solution in olive oil, equivalent to 50, 200 and 1000 mg/kg body weight/day) a NOAEL of 200 mg/kg body weight/day was found in a 28-day study on rats (CIR, 1999). At 1000 mg/kg body weight/day, body weight gain was slightly reduced; terminal body weights were 5.4% lower in females and 3.7% lower in males as compared to controls.

4.2.2. Oral studies

Repeated dose oral toxicity studies have been conducted on citronellol, geraniol, farnesol and linalool (Bär and Griepentrog, 1967; Horn et al., 2005; RIFM, 1958a, 1990a) and the cyclic terpene alcohols α-bisabolol, 4-carvomenthenol, geranodyle, *p*-mentha-1,8-dien-7-ol, and menthol (BASF, 1996, as cited in CIR (1999); Haag and Gould, 1994; Habersang et al., 1979; Herken, 1961; NCI, 1979; RIFM, 2000d; Schilcher and Leuschner, 1997; Thorup et al., 1983). Limited data are available on the effects of various cyclic terpene alcohols on fat metabolism (Imaizumi et al., 1985). The potential of borneol, carveol, and terpineol to induce α-2u-nephropathy in rats has been investigated (Lehman-McKeeman and Caudill, 1999). The results of these studies are summarized in Tables 4A and 4B and described below.

A 50/50 mixture of linalool and citronellol was fed to male and female rats (number and strain not specified) in the diet (RIFM, 1958a). The daily intake was calculated to be 50 mg/kg body

Table 3-3A
Acute miscellaneous toxicity studies/non-cyclic terpene alcohols

Material	Route	Species	No. of animals/dose group	LD_{50} (mg/kg)[a]	References
D,L-Citronellol	Intramuscular	Mouse	8	4000	Northover and Verghese (1962)
	Subcutaneous injection	Mouse	5	880 ± 50	Nozawa (1952)
Dehydrolinalool	i.p. injection (in peanut oil)	Mouse	8 (4/sex)	1200 (725–1520)	RIFM (1992b)
	i.p. injection (as an emulsion in 0.5% carboxymethyl cellulose and 0.4% Tween 80)	Mouse	8 (4/sex)	245	RIFM (1992b)
	Inhalation, 7 h exposure to 1.0 mg/L	Rat	6 (3/sex)	1 mg/L	RIFM (1988d)
Farnesol	i.p. injection	Mouse	10 (5/sex)	327 (213–514)	RIFM (1981d)
Geraniol	Intramuscular	Mouse	10	4000	Northover and Verghese (1962)
	Subcutaneous injection	Mouse	5	1090 ± 90	Nozawa (1952)
Geranyl linalool	i.p. injection	Mouse	Not reported	>2000	RIFM (1978f)
Linalool	Subcutaneous injection	Mouse	5	1470 ± 140	Nozawa (1952)
	Intramuscular	Mouse	10	8000	Northover and Verghese (1962)
	i.p. injection	Rat	5	687 (95% CI 513–920)	RIFM (1984i)
	i.p. injection (in saline with Tween 80)	Rat (male)	Not reported	307 (233–405)	Atanassova-Shopova et al. (1973)
	i.p. injection (in saline with Tween 80)	Mouse (male)	Not reported	340 (267–510)	Atanassova-Shopova et al. (1973)
	i.p. injection (in peanut oil)	Mouse	8 (4/sex)	1500 (1070–2100)	RIFM (1992b)
	i.p. injection (as an emulsion in 0.5% carboxymethyl cellulose and 0.4% Tween 80)	Mouse	8 (4/sex)	200	RIFM (1992b)
	i.p. injection (in phosphate citrate buffer)	Rat	3 normal and 3 diabetic rats	630 ml	Afifi et al. (1998)
Nerol	Intramuscular	Mouse	10	3000	Northover and Verghese (1962)
Rhodinol	Intramuscular	Mouse	10	4000	Northover and Verghese (1962)

[a] Units have been converted to make easier comparisons; original units are in the Fragrance Material Reviews.

Table 3-3B
Acute miscellaneous toxicity studies/cyclic terpene alcohols

Material	Route	Species	No./dose group	LD_{50} (mg/kg)[a]	References
α-Bisabolol	Intraperitoneal	Mouse	Not reported	633	BASF (1980) as cited in CIR (1999)
4-Carvo menthenol	Intramuscular	Rat	Not reported	1500 ml	Janku et al. (1960)
Menthol (unspecified isomer)	Subcutaneous injection	Mouse	5	1020 ± 70 mg/kg	Nozawa (1952)
L-Menthol	Intraperitoneal, in olive oil	Mouse	10	⩾200 mg/kg excitation, ⩾425 mg/kg lethargy	LeBourhis and Soenen (1973)
2(10)-Pinen-3-ol	i.v. injection	Rats	10	140	Vegezzi and Corvi Mora (1982)
Sclareol	i.p. (in sterile 0.25% aqueous agar)	Rat	1–2	1000	Malone et al. (1991)
Terpineol	i.p. injection (in saline with Tween 80)	Mouse (male)	Not reported	260 (218–311)	Atanassova-Shopova et al. (1973)
	i.p. injection (in saline with Tween 80)	Rat (male)	Not reported	228 (184–283)	Atanassova-Shopova et al. (1973)
	Subcutaneous injection	Mouse	5	1360 ± 270	Nozawa (1952)
α-Terpineol	Intramuscular	Mouse	10	2000	Northover and Verghese (1962)
	i.p. injection (in corn oil)	Rat	5/sex/group	847 (706–1016)	Lorillard (1984)

[a] Units have been converted to make easier comparisons; original units are in the Fragrance Material Reviews.

weight of each. Hematology, clinical chemistry, and urinalysis at weeks 6 and 12 showed no significant differences between test and control groups. Histopathology revealed no dose-related lesions. A slight retardation of growth was observed in males only, but was concluded by the authors to be biologically insignificant. The NOAELs for citronellol and linalool were at 50 mg/kg body weight/day (only tested dose).

Coriander oil containing 72.9% linalool was administered by gavage to male and female rats at dose levels of 160, 400 and 1000 mg/kg body weight/day for 28 days (RIFM, 1990a). Increases in absolute and relative liver weights were observed in mid- and high-dose male and females. Degenerative lesions were noted in the renal cortex in the high-dose males, and a high incidence of slight periportal hepatocellular cytoplasmic vacuolization was observed in the high-dose females. Similar lesions were noted in the low- and mid-dose females, but at a lower incidence. Based on these effects, the NOAEL was determined to be 160 mg/kg body weight/day.

No adverse effects were reported by Bär and Griepentrog (1967) after administration of 10,000 ppm geraniol in the diet to rats for 16 days (no details reported).

A study was performed to characterize the effects of farnesol on the activity of phase 1 and phase 2 drug metabolizing enzymes (Horn et al., 2005). Rats (20/sex/group) received daily gavage

exposure to farnesol doses of 0, 500, or 1000 mg/kg body weight/day for 28 days; 10 rats/sex/group were necropsied at the termination of farnesol exposure; remaining animals were necropsied after a 28-day recovery period. No deaths occurred during the study, and farnesol had no significant effects on body weight, food consumption, clinical signs, or hematology/coagulation parameters. Modest but statistically significant alterations in several clinical chemistry parameters (see Table 4A) were observed at the termination of farnesol exposure; all clinical pathology effects were reversed during the recovery period. At the termination of dosing, the activities of CYP1A, CYP2A1-3, CYP2B1/2, CYP2C11/12, CYP2E1, CYP3A1/2, CYP4A1-3, CYP19, glutathione reductase, NADPH/quinone oxidoreductase and UDP-glucuronosyltransferase were significantly increased in the livers of farnesol-treated rats; farnesol also increased the activity of glutathione-*S*-transferase in the kidney. The effects of farnesol on hepatic and renal enzymes were reversed during the recovery period. At the end of the dosing period, increases in absolute and relative liver and kidney weights were found in farnesol-treated rats, probably secondary to induction of drug metabolizing enzymes. These organ weight increases were

Table 4A
Repeated dose toxicity studies/non-cyclic terpene alcohols

Material	Method	Dose	Species (no./dose group)	Results (mg/kg body weight/day)[a]	References
D,L-Citronellol	Oral (diet), 12 weeks	Mixture of equal parts (by weight) of citronellol and linalool at a level of 100 mg of the blend/kg body weight/day	Rat (10/sex/dose)	(NOAEL (citronellol): 50 mg/kg body weight/day)[b] No adverse effects on efficiency of food utilization or other observable physiological criteria. A depression in growth and food intake of the male rats was attributed to impalatibility of the test material at the level administered. No abnormal findings in urinalyses; no changes in kidney and liver weights	RIFM (1958a)
	Inhalation, 100 days	0, 0.03, 0.3, 2.8 mg/m^3	Rat (25/group)	(NOAEL: 0.3 mg/m^3) 2.8 mg/m^3 affected central nervous system, liver function and olfactory function	Kostrodymov (1981)
Farnesol	Oral (gavage), 28 days with and without 28 days recovery	0, 500 or 1000 mg/kg body weight/day in corn oil (farnesol composed of four isomers: *cis*,*cis*-(11.09%), *cis*,*trans*-(25.08%), *trans*,*cis*-(24.59%) and *trans*,*trans*-(38.77%).	Rat, Sprague–Dawley (20/sex/group)	(NOAEL: 1000 mg/kg body weight/day) ⩾500 mg/kg body weight/day: Abs. and rel. liver weights (f) increased, no histopathologic alterations; serum glucose Decreased (f); all effects reversible within recovery period 1000 mg/kg body weight/day: Abs. and rel. liver weights (m) increased, rel. kidney weights (m) increased, abs. and rel. kidney weights (f) increased, no histopathologic alterations Reversible increases in the activities of some hepatic and renal metabolizing systems No effects on body weight, food consumption, clinical signs and hematology parameters Reversible modest changes in some clinical chemistry parameters (triglycerides increased (f), decreased (m), urea nitrogen decreased (f), aspartate transaminase activity decreased (f), alkaline phosphatase increased (m) All effects reversible within recovery period; all effects listed above were statistically significant	Horn et al. (2005)
Farnesol	Oral (diet) 8 weeks	1.5% farnesol	F344rats (6/group)	No effect on total or HDL serum cholesterol, no other adverse effects were observed	Rao et al. (2001)
Geraniol	Oral (diet) 16 weeks	1000 mg/kg body weight/day in diet	Rat	(NOAEL: 1000 mg/kg body weight/day in diet), no adverse effects reported	Bär and Griepentrog (1967)
	Oral (capsule) 5 weeks	100 mg/kg/day	Hen	No effects observed	Hood et al. (1978)
	Oral (diet) 16 weeks	100 or 1000 mg/kg/day	Rat	No effects observed	RIFM, 1954
	Oral (diet) 27 weeks	100 mg/kd/day	Rat	No Effects observed	Hagan et al. (1967)
Linalool	Dermal, 13 weeks	0 (vehicle), 250, 1000 or 4000 mg/kg body weight/day in saline	SD rat (20/sex/dose)	(NOAEL: 250 mg/kg body weight/day) 4000 mg/kg body weight/day: 9 females and 2 males died; lethargy in females; slight erythema; food consumption in males decreased early in study, body weight (m) decreased; liver weight increased, kidney weight (f) increased, slight to moderate epithelial hyperplasia; histology, hematology, clinical chemistry and urinalysis findings normal ⩾1000 mg/kg body weight/day: slight erythema during the first 6 weeks, body weight (f) decreased ⩾250 mg/kg body weight/day: slightly decreased activity, slight erythema during the first 3 weeks	RIFM (1980a)
	Dermal, 29 days (dose-finding study for 13 wk study)	0, 125, 250, 500, 1000, 2000, 4000 mg/kg body weight/day	SD rat (2/sex/dose)	(LOAEL: 125 mg/kg body weight/day) In all dose groups (severity depending on dose): lethargy, ataxia, piloerection and discomfort. Moderate to severe erythema and slight to moderate edema, bleeding, scabbing and moderate eschar formation on the skin, very slight to slight changes in the liver and kidney at histopathology	RIFM (1979g)
	Oral (diet), 12 week study	Mixture of equal parts (by weight) of citronellol and linalool at a level of 100 mg of the blend/kg body weight/d.	Rat (10/sex/dose)	(NOAEL (linalool): 50 mg/kg body weight/day) No adverse effects on efficiency of food utilization or other observable physiological criteria. A depression in growth and food intake of the male rats was attributed to impalatibility of the test material at the level administered. No abnormal findings in urinalyses; no changes in kidney and liver weights	RIFM (1958a)

(*continued on next page*)

Table 4A (*continued*)

Material	Method	Dose	Species (no./dose group)	Results (mg/kg body weight/day)[a]	References
Linalool (72.9% in coriander oil)	Oral (gavage), 28 day study	0 (vehicle), 160, 400 or 1000 mg coriander oil/kg body weight/day in 1% methylcellulose	SD rat (10/sex/dose)	(NOAEL: 160 mg/kg body weight/day) 160 mg/kg body weight/day: no adverse effects ⩾400 mg/kg body weight/day: abs and rel kidney weight (m) increased, abs and rel liver weight increased, total protein and serum albumin (m) increased, histopathology: lesions in the non-glandular region of the stomach (f) 1000 mg/kg body weight/day: abs. and rel. kidney weight (f) increased, total protein and serum albumin (f) increased, serum calcium (m) increased, histopathology: degenerative lesions in renal cortex (m); hepatocellular vacuolization (f) (NOAEL corresponds to 117 mg/kg body weight/day of linalool)	RIFM (1990a)

NOAEL: no observed adverse effect level, LOAEL: lowest observed adverse effect level.
m: male, f: female.
[a] Units have been converted to make easier comparisons; original units are in the Fragrance Material Reviews.
[b] NOAELs/LOAELs that are not stated in the original study reports are put in brackets.

not associated with histopathologic alterations and were reversed upon discontinuation of farnesol exposure. The authors of this study concluded that non-toxic or minimally toxic doses of farnesol could alter the metabolism, efficacy, and/or toxicity of drugs with which it is co-administered. The NOAEL can be estimated to be around 1000 mg/kg body weight/day.

α-Bisabolol was studied in several gavage studies in dogs and rats (Habersang et al., 1979). In a 4-week study with beagle dogs (3/sex/dose) 2, 3 or 4 ml/kg (∼equivalent to 2000, 3000 or 4000 mg/kg) of 95% pure material were administered. At the low dose, a reduced feed intake was noted (no further detail reported). Based on this finding, a LOAEL of ca. 1960 mg/kg body

Table 4B
Repeated dose toxicity studies/cyclic terpene alcohols

Material	Method	Dose	Species (no./dose group)	Results (mg/kg body weight/day)[a]	References
α-Bisabolol	28 days, dermal toxicity study	Applied solution contained 1%, 4%, 20% in olive oil, 87.5% pure, i.e., 50, 200, 1000 mg/kg body weight/day, 6 h/day, 7 days/week	Wistar rat (5/sex/dose)	(NOAEL: 200 mg/kg body weight/day)[b] 50, 200 mg/kg body weight/day: no effects 1000 mg/kg body weight/day: body weight gain(decreased), terminal body weight −5.4% in f, −3.7% in m, feed efficiency (decreased), transient moderate skin erythema and diffuse scale formation in some females	BASF (1996) as cited in CIR (1999)
	6 weeks, gavage study	1000 mlg/kg body weight, 7 days/week, 85% pure, vehicle: aqueous tylosis mucus, controls received vehicle alone	Wistar rat (10/sex/group)	(NOAEL: ca. 850 mg/kg body weight/day; highest tested dose) No adverse reactions	Habersang et al. (1979)
	4 weeks, gavage study	2000 or 3000 mlmg/kg body weight, 7 days/week, 98% pure, vehicle: aqueous tylosis mucus, controls received 4000 mlmg/kg body weight of the vehicle	Sprague–Dawley rat (20/sex/group)	(LOAEL: ca. 1960 mg/kg body weight/day) ⩾2000 mlmg/kg: slight motor agitation, positive ketone body reaction in the urine; inflammatory changes in liver, trachea, spleen, thymus, stomach 3000 mlg/kg: 20% mortality, increased motor agitation, body weight gain decreased; SGOT increased (f), API increased (f), SGOT(increased) (m), AP(increased) (m)	Habersang et al. (1979)
	2 weeks, gavage study	1000 mlmg/kg body weight, 7 days/week, 85% pure, vehicle: aqueous tylosis mucus, controls received vehicle alone	Dog (2/group, mixed breed)	(NOAEL: ca. 850 mg/kg body weight/day; highest tested dose) No adverse reactions	Habersang et al. (1979)
	4 weeks, gavage study	2000 or 3000 (4000) mlmg/kg body weight, 7 days/week, 98% pure, vehicle: aqueous tylosis mucus; controls received 4000 mlmg/kg of vehicle; after 2 weeks, the 3000 mlmg/kg dose was increased to 4000 mlmg/kg.	Beagle dog (3/sex/group)	(LOAEL: ca. 1960 mg/kg body weight/day ⩾2000 mlmg/kg: loss of appetite, feed intake decreased, vomiting 4000 mlg/kg: body weight gain decreased, serum creatinine increased, SGPT increased, rel. liver weight increased, no histopathological changes	Habersang et al. (1979)
Borneol	Test for α-2u-nephropathy, 3 days, gavage	150 mg/kg/ body weight/day	Rat (4/sex/group)	Hyaline droplet severity score increased over control levels (8.8 ± 0.3 as compared with 4.6 ± 0.4 of the 12 control rats)	Lehman-McKeeman and Caudill (1999)
Carveol	Test for α-2u-nephropathy, 3 days, gavage	11 mg/kg body weight/day	Rat (4/sex/group)	Hyaline droplet severity score increased over control levels (6.5 ± 0.3 as compared with 4.6 ± 0.4 of the 12 control rats)	Lehman-McKeeman and Caudill (1999)
	2 weeks, dietary study	1000 mg/kg body weight/day in diet	Rat (3–4)	Food intake decreased, body weight gain decreased, liver weight increased, cholesterol increased	Imaizumi et al. (1985)
p-Mentha-1,8-dien-7-ol	2 weeks, dietary study	1000 mg/kg body weight/day in diet	Rat (3–4)	Food intake decreased, body weight gain decreased, liver weight increased, cholesterol increased	Imaizumi et al. (1985)

Table 4B (*continued*)

Material	Method	Dose	Species (no./dose group)	Results (mg/kg body weight/day)[a]	References
4-Carvo-menthenol	28-days, gavage study	0; 400 mg/kg body weight/day	Sprague–Dawley rat (male, 5/group)	(LOAEL: 400 mg/kg body weight/day) 400 mg/kg: body weight decreased (−9%), food consumption increased (9%, 35%, +16% at weeks 2, 3, 4, respectively), rel. and absolute testes weights decreased (no quantitative data reported); pale kidney in 1/5; serum urea and creatinin levels unchanged; urinalysis normal No histopathological changes in liver and kidney	Schilcher and Leuschner (1997)
Dihydrocarveol	2 weeks, dietary study	1000 mg/kg body weight/day in diet	Rat (3–4)	No effect on food intake, body and liver weight; cholesterol increased	Imaizumi et al. (1985)
Geranodyle	28 days, gavage study	0, 50, 200, and 1000 mg/kg body weight/day	SPF-Wistar rats (5/sex/group)	(NOEL) 200 mg/kg body weight/day	RIFM (2000d)
Isopulegol	2 weeks, dietary study	1000 mg/kg body weight/day in diet	Rat (3–4)	Liver weight increased, cholesterol increased, triacylglycerol increased, Apo A-1 increased	Imaizumi et al. (1985)
Menthol (unspecified isomer)	2 weeks, dietary study	1000 mg/kg body weight/day in diet	Rat (3–4)	Cholesterol increased, triacylglycerol increased, no effect on food intake and body weight gain	Imaizumi et al. (1985)
D,L-Menthol	13 weeks, dietary study	Up to 1000 mg/kg body weight/day	F344 rat (10/sex/dose)	(NOAEL: 1000 mg/kg body weight/day) Slight increase in spontaneous interstitial nephritis in male rats at highest dose	NCI (1979)
	13 weeks, dietary study	Up to 4000 mg/kg body weight/day	B6C3F1 mouse(10/sex/dose)	(NOAEL: 2000 mg/kg body weight/day) Reduced body weight gain at highest dose level	NCI (1979)
	2 years dietary study	0, 300 or 600 mg/kg body weight/day	B6C3F1 mouse(50/sex/dose)	(NOAEL: 600 mg/kg body weight/day)	NCI (1979)
	2 years dietary study	0, 188 or 375 mg/kg body weight/day	F344 rat (50/sex/dose)	(NOAEL: 375 mg/kg body weight/day)	NCI (1979)
Menthol racemic	5.5 weeks, feeding study	0, 100, 200 mg/kg body weight/day	Rat (40/sex/dose)	(NOAEL: 200 mg/kg body weight/day) No adverse effects on weight gain or excretion of glucuronide, water and electrolytes, no interference with central nervous system reactions to stimulants	Herken (1961)
L-Menthol	71–79 days, inhalation study	0.6, 1.0, 1.7 mg/m^3 (calculated)	Sherman rat (6/sex/group)	(NOAEL: 1.0 mg/m^3) 0.6, 1.0 mg/m^3: no adverse effects 1.7 mg/m^3: Histopathologic changes indicative of irritation (tracheitis, lung congestion); no other adverse effects reported	Rakieten et al. (1954)
	28 days, gavage study	0, 200, 400, 800 mg/kg body weight/day in soy bean oil	Wistar rat (10/sex/dose)	(LOAEL: 200 mg/kg body weight/day) ⩾200 mg/kg body weight/day: liver weight (m)↑, vacuolization of hepatocytes ⩾400 mg/kg body weight/day: liver weight (f)↑	Thorup et al. (1983)
	5.5 weeks, feeding study	0, 100, 200 mg/kg body weight/day	Rat (40/sex/dose)	(NOAEL: 200 mg/kg body weight/day) No adverse effects on weight gain or excretion of glucuronide, water and electrolytes, no interference with central nervous system reactions to stimulants	Herken (1961)
Menthol (unspecified isomer)	9-months, inhalation study	1% and 5%	Rabbit	1% infection of the mucosa of the nose and sinus 5% Acute effects in the nose, sinus, and lungs	Fox (1930)
Sclareol	28 days, gavage study	8.8 mg/kg/day at approximately 0.176% w/v	CRL:CD Rats(10/sex/dose)	NOAEL at 8.8 mg/kg/day No gross or microscopic alterations, increases in liver enzymes	RIFM (2006d)
α-Terpineol	2 weeks, dietary study	1000 mg/kg body weight/day in diet	Rat (3–4)	Food intake decreased, body weight decreased, cholesterol increased, triacylglycerol increased	Imaizumi et al. (1985)
L-α-Terpineol	Test for α-2u-nephropathy, 3 days, gavage	150 mg/kg	Rat (4/sex/group)	Hyaline droplet severity score decreased (3.5 ± 1.0 as compared with 4.6 ± 0.4 of the 12 control rats)	Lehman-McKeeman and Caudill (1999)

NOAEL: no observed adverse effect level, LOAEL: lowest observed adverse effect level.
m: male, f: female.
[a] Units have been converted to make easier comparisons; original units are in the Fragrance Material Reviews.
[b] NOAELs/LOAELs that are not stated in the original study reports are put in brackets.

weight/day can be deduced. 4 ml/kg body weight/day led to reduced body weight gain, an increase in serum creatinine and GPT levels, and an increase in relative liver weight without histopathological changes. In a range-finding study, 1 ml/kg body weight/day of 85% pure material, administered for 2 weeks, had induced no adverse effect (equivalent to a NOAEL of about 850 mg/kg body weight/day). No effects were seen in groups of 10 rats/sex after daily gavage of 1.0 ml/kg of a 85% pure material for 6 weeks (equivalent to a NOAEL of ca. 850 mg/kg body weight/day); 4 weeks of gavage of 2 or 3 ml/kg body weight/day of a 98% pure material induced a slight increase in activity and, histopathologically, inflammatory changes in liver, trachea, spleen, thymus and stomach after (LOAEL, based on these findings: ca. 1960 mg/kg body weight/day).

Schilcher and Leuschner (1997) studied the repeated dose toxicity of 4-carvomenthenol in a group of 5 males Sprague–Dawley rats. The animals were given a daily dose of 400 mg/kg body weight by gavage for 28 days. There were no abnormal clinical signs, but body weight was reduced by 9% as compared to the control animals. No macroscopic or histopathological changes were found in liver and kidneys; absolute and relative testes weights were reduced in 3 animals. Kidney function, urinalysis and serum urea and creatinine levels were normal. A LOAEL of 400 mg/kg body weight/day can be suggested based on reduced body and reduced relative testes weights.

In a 28-day oral toxicity study in SPF rats (RIFM, 2000d), geranodyle was dosed by gavage at doses of 0, 50, 200 or 1000 mg/kg body weight/day. At the high dose (1000 mg/kg body weight/day), mean absolute and relative liver weights were significantly increased and statistically significant increases in total protein and globulin were also observed. In females statistically significant decreases in potassium levels were observed and hematological changes suggested very slight anemia with compensatory reticulocytosis. In males treated with the high dose, statistically significant increases in gamma glutamyltransferase activity, calcium, sodium, and creatinine levels were observed. The no observed effect level (NOEL) was established to be 200 mg/kg body weight/day.

In comprehensive 13-week and 2-year dietary studies with D,L-menthol (NCI, 1979), no adverse effects on mice and rats were found up to the highest tested dose level in rats. In mice, the only effect noted was a slight decrease in body weight (NOAEL, 13-week: 1000 mg/kg body weight/day for rats, 2000 mg/kg body weight/day for mice; NOAEL, 2 years: 375 mg/kg body weight/day in rats, 600 mg/kg body weight/day in mice). Herken (1961) found no adverse effects of D,L- and L-menthol in rats administered 100 or 200 mg/kg body weight/day for 5 1/2 weeks. Thorup et al. (1983) reported increased liver weights and vacuolization of hepatocytes in male Wistar rats after daily doses of 200 mg/kg body weight for 28 days.

Very limited data are available from 2-week dietary studies with 1% of various cyclic terpene alcohols in groups of 3–4 rats (Imaizumi et al., 1985). α-Terpineol caused a decrease in food intake, reduced body weight gain, and an increase in serum cholesterol level. Dihydrocarveol and menthol increased cholesterol levels, while carveol, *p*-mentha-1,8-dien-7-ol and isopulegol also increased liver weight.

α-2u-Globulin nephropathy, a male rat-specific renal syndrome, characterized by accumulation of protein within the proximal tubular epithelium, occurred in male rats given 1 mmol/kg body weight (ca. 150 mg/kg body weight) of borneol, carveol, or α-terpineol for 3 days by gavage and evaluated histologically for evidence of hyaline (protein) droplet accumulation (Lehman-McKeeman and Caudill, 1999). Hyaline droplet severity scores increased over control levels after treatment with borneol and carveol, but not after treatment with α-terpineol.

4.2.3. Inhalation studies

Limited information is available with regard to the repeated dose toxicity after inhalation exposure. Data are available for citronellol (Kostrodymov, 1981) and menthol (Rakieten et al., 1954).

Inhalation experiments were conducted with 0, 0.03, 0.3, and 2.8 mg/m^3 of citronellol in groups of 25 rats for a period of 100 days (Kostrodymov, 1981). At 2.8 mg/m^3, central nervous system, liver and olfactory functions were affected (no further details available). No adverse effects were reported for 0.3 mg/m^3 (NOAEL).

In an old, but well-documented study, L-menthol was administered to Sherman rats (6/sex/group) at (calculated) concentrations of 0, 0.6, 1.0 and 1.7 mg/m^3 for 71–79 days (Rakieten et al., 1954). At the highest tested dose level, histopathological changes indicative of respiratory tract irritation (tracheitis, lung congestion) were found. No other adverse effects were reported. The NOAEL in this study was 1.0 mg/m^3.

4.2.4. Summary of repeated dose toxicity studies

The database on repeated dose toxicity for the non-cyclic and cyclic terpene alcohols is limited. For repeated dermal exposure to linalool the NOAEL was 250 mg/kg body weight/day and the LOAEL was 1000 mg/kg body weight/day.

For dermally applied α-bisabolol the NOAEL was 200 mg/kg body weight/day and the LOAEL was 1000 mg/kg body weight/day. No effect levels after oral exposure were 50 mg/kg body weight/day for citronellol and linalool. Administration of 1000 mg farnesol/kg body weight/day for 28 days induced reversible increases in the activities of several hepatic and renal drug metabolizing enzymes in rats. A low level of systemic toxicity was demonstrated for two materials identified to generate reactive metabolites (farnesol, geraniol). Hence, it can be assumed that efficient detoxication mechanisms are in place. Oral NOAELs for α-bisabolol were 850 mg/kg body weight/day and for D,L-menthol were 375 or 1000 mg/kg body weight/day. The LOAEL for α-bisabolol was 1960 mg/kg body weight/day. For 4-carvomenthenol a LOAEL was 400 mg/kg body weight/day.

Some members of the terpene alcohol family have the potential to induce α-2u-globulin nephropathy in male rats. This is a male rat-specific effect and has no relevance for humans.

After inhalation exposure of rats, NOAELs of 0.3 and 1.0 mg/m^3 were found for citronellol and L-menthol, respectively.

Given the repeated dose, pharmacokinetic and metabolism data on various terpene alcohols a systemic NOAEL of 50 mg/kg body weight/day can be used for quantitative human health risk assessment of the use of terpene alcohols as fragrance materials.

4.3. Mutagenicity and genotoxicity (see Tables 5-1A, B and 5-2 A, B)

Mutagenicity and genotoxicity testing with non-cyclic and cyclic terpene alcohols has been performed primarily *in vitro*. A few materials (farnesol, geraniol, hydroxycitronellol, linalool and menthol) have been tested *in vivo*. The results of these tests are summarized in Tables 5-1A, 5-1B, 5-2A, and 5-2B.

4.3.1. In vitro mutagenicity studies

The non-cyclic terpene alcohols citronellol, dehydrolinalool, 3,7-dimethyloct-6-en-3-ol, farnesol, geraniol, linalool, and tetrahydrolinalool were inactive in bacterial mutagenicity assays (Ames tests); linalool was inactive in a mammalian cell system (mouse lymphoma cells). Positive and equivocal results were observed in two rec-assays with linalool, but may have been caused by non-specific cytotoxicity and are, therefore, of limited relevance.

The cyclic terpene alcohols, α-bisabolol, borneol, carveol, geranodyle, isopulegol, menthol (D,L- and L-), *p*-menth-8-en-1-ol,

Table 5-1A
Mutagenicity and genotoxicity: *in vitro* studies/non-cyclic terpene alcohols

Substance	Test system		Concentrations	Results	References
D,L-Citronellol	Rec-assay	*Bacillus subtilis* strains H 17 (rec+) and M 45 (rec−)	17 μg/disc	Not mutagenic	Oda et al. (1979)
	Ames assay with S9 activation	*Salmonella typhimurium* TA98, TA100	100 μL	Not mutagenic	Rockwell and Raw (1979)
	Host mediated assay, with and without beta-glucuronidase	*S. typhimurium* TA98, TA100	50–300 μL of 24 h direct urine sample or aqueous fractions of ether extracts from urine of 2 rats given 0.5 ml undiluted test material p.o.	Not mutagenic	Rockwell and Raw (1979)
Dehydrolinalool	Ames assay with and without S9 activation (standard plate and preincubation assay)	*S. typhimurium* TA98, TA100, TA1535, TA1537	20–5000 μg/plate (standard plate assay) 4–2500 μg/plate (preincubation assay)	Not mutagenic	RIFM (1989d)
3,7-Dimethyloct-6-en-3-ol	Ames assay with and without S9 activation	*S. typhimurium* TA97, TA98, TA100, TA102, TA1535	10–1000 μg/plate (standard plate assay) 3.16–316 μg/plate (preincubation assay)	Not mutagenic	RIFM (1999a)
Farnesol	Ames assay with and without S9 activation	*S. typhimurium* TA98, TA100, TA1535, TA1537	Up to 5000 μg/plate	Not mutagenic	RIFM (1989f)
	Ames assay with and without S9 activation	*S. typhimurium* (strains not reported)	NA	Not mutagenic	Rupa et al. (2003)
	Chromosomal aberration test with and without S9 activation	Chinese hamster ovary cells	NAml	Not genotoxic	Rupa et al. (2003)
Geraniol	Ames assay with and without S9 activation (liquid suspension test)	*S. typhimurium* TA100	10–3000 μg per 2 ml incubation volume	Not mutagenic	Eder et al. (1980, 1982a,b); Lutz et al., 1980
	Ames assay with and without S9 activation	*S. typhimurium* TA92, TA94, TA98, TA100, TA1535, TA1537	Up to 500 μg/plate in DMSO	Not mutagenic	Ishidate et al. (1984)
	Ames assay with and without S9 activation	*S. typhimurium* (strains not reported)	NA	Not mutagenic	Rupa et al. (2003)
	Chromosome aberration test with and without S9 activation	Chinese hamster lung fibroblasts (CHL)	Up to 0.125 mg/ml in DMSO for 48 h	8.0% cells with polyploidy, structural aberrations (4%) not increased over control; judged as equivocal result with regard to polyploidy	Ishidate et al. (1984)
	Chromosomal aberration test with and without S9 activation	Chinese hamster ovary cells	78.1–156.3 μg/ml	Significant increase in number of cells with structural aberrations seen in cultures for 3–h exposure in 1 of 2 experiments. Inconclusive results	Rupa et al. (2003)
	Rec-assay	*Bacillus subtilis* H17 (rec+)	16 μg/disk	Not mutagenic	Oda, 1978
Linalool	Ames assay with and without S9 activation (liquid suspension test)	*S. typhimurium* TA100	10–3000 μg per 2 ml incubation volume	Not mutagenic	Eder et al. (1980, 1982a,b); Lutz et al., 1980
	Ames assay with and without S9 activation	*S. typhimurium* TA92, TA94, TA98, TA100, TA1535, TA1537	Up to 1000 μg/plate in DMSO	Not mutagenic	Ishidate et al. (1984)
	Ames assay with S9 activation	*S. typhimurium* TA98, TA100	100 μL (87,000 μg)	Not mutagenic	Rockwell and Raw (1979)
	Ames assay with and without S9 activation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	5–10,000 μg/plate	Not mutagenic	RIFM (1983a) and Heck et al. (1989)
	Mutation assay	*Escherichia coli* WP2*uvrA*	125–1000 μg/plate	Not mutagenic	Yoo (1986)
	Host mediated assay, with and without β-glucuronidase	*S. typhimurium* TA98, TA100	50–300 μL of 24 h direct urine sample or aqueous fractions of ether extracts from urine of 2 rats given 0.5 ml undiluted linalool p.o.	Not mutagenic	Rockwell and Raw (1979)
	Rec assay (spore plate method)	*Bacillus subtilis* strains H 17 (rec+) and M 45 (rec−)	630–10,000 μg/disc	Questionable effect	Kuroda et al. (1984)
	Rec-assay	*Bacillus subtilis* strains H 17 (rec+) and M 45 (rec−)	17 μg/disc	Not mutagenic	Oda et al. (1979)
	Rec-assay(spore plate assay)	*Bacillus subtilis* strains H 17 (rec+) and M 45 (rec−)	10,000 μg/disc	Positive	Yoo (1986)
	Mammalian cell mutation with and without S9 activation	Mouse Lymphoma L5178Y TK+/−	3.9–300 μg/ml	Not genotoxic in one experiment and weakly positive in the other	RIFM (1982d) and Heck et al. (1989)
	Mammalian cell mutation with and without S9 activation	Mouse Lymphoma L5178Y TK+/−	12.5–274 μg/ml	Not genotoxic	RIFM (1994c)
	Chromosome aberration test with and without S9 activation	Chinese hamster lung fibroblasts (CHL)	Up to 0.25 mg/ml in DMSO for 48 h	Not genotoxic	Ishidate et al. (1984)
	Chromosomal aberration test with and without S9 activation	Chinese hamster ovary cells	16.7–500 μg/ml	Not genotoxic	RIFM (1983b)
	Sister chromatid exchange	Chinese hamster ovary cells	5–150 μg/ml	Not genotoxic	Sasaki et al. (1989)
	Unscheduled DNA synthesis	Rat hepatocytes	0.5–43.6 μg/ml	Not genotoxic	RIFM (1986c) and Heck et al. (1989)
Tetrahydrolinalool	Ames assay with and without S9 activation	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	5 concentrations, up to 3.6 mg/plate	Not mutagenic	Wild et al. (1983)

Table 5-1B
Mutagenicity and genotoxicity: *in vitro* studies/cyclic terpene alcohols

Substance	Test system		Concentrations	Results	References
α-Bisabolol	Ames test with and without S9	*S. typhimurium* TA97a, TA98, TA100, TA1535	Up to 100 μg/plate in EtOH	Not mutagenic	Gomes-Carneiro et al. (2005)
	Ames test (standard plate and pre-incubation tests) with and without S9 activation (rat liver)	*S. typhimurium* TA98, TA100, TA1535, TA1537	20–5000 μg/plate in DMSOml	Not mutagenic	BASF (1996) as cited in CIR (1999)
	Chromosomal aberration test with and without S9 activation (rat liver)	Chinese hamster V79 cells	0.78–40 μg/ml	Not genotoxic	BASF (1996) as cited in CIR (1999)
Borneol	Ames assay with and without S9 activation (rat liver)	*S. typhimurium* TA98, TA100, TA1535, TA1537, TA1538	Up to 5 mg/plate in DMSO	Not mutagenic	Simmon et al. (1977)
	Ames assay with and without S9 activation (rat liver), pre-incubation assay	*S. typhimurium* TA97, TA98, TA100	Up to 1 mg/ml in DMSO	Not mutagenic	Azizan and Blevins (1995)
	Mutation assay	*E. coli* WP2 uvrA	400–3200 μg/plate	Not mutagenic	Yoo (1986)
	Rec-assay (spore plate assay)	*Bacillus subtilis* strains H17 (rec+) and M 45 (rec−)	10,000 μg/disc	Positive	Yoo (1986)
Carveol	Ames test with and without S9 activation (rat and hamster liver)	*S. typhimurium* TA98, TA100, TA1535, TA 1537	10–560 μg/plate in DMSO, i.e., including cytotoxic concentrations	Not mutagenic	Mortelmans et al. (1986)
Isopulegol	Ames test with and without S9 activation (rat liver), pre-incubation assay	*S. typhimurium* TA98, TA100, TA1535,1537, *E. coli* WP2 uvrA	Up to 5000 μg/plate in DMSO; cytotoxic at ⩾1250 μg/plate	Not mutagenic	RIFM (1999d)
Menthol (unspecified isomer)	Ames test with and without S9 activation (rat liver)	*S. typhimurium* TA98, TA100, TA1535,1537	Up to 800 μg/plate in DMSO; cytotoxic at 800 μg/plate	Not mutagenic	Andersen and Jensen (1984)
	Ames assay with and without S9 activation	*S. typhimurium* TA92, TA94, TA98, TA100, TA1535, TA1537	Up to 5000 μg/plate in DMSO	Not mutagenic	Ishidate et al. (1984)
	Ames test (plate incorporation assay)	*S. typhimurium* TA97a, TA98, TA100, TA102	100–800 μg/plate in TA97a, TA98 and TA100; 5–500 μg/plate in TA102	Non-mutagenic	Carneiro et al. (1997) and Gomes-Carneiro et al. (1998)
	Chromosome aberration test with and without S9 activation	Chinese hamster lung fibroblasts (CHL)	Up to 0.2 mg/ml in EtOH for 48 h	Not genotoxic	Ishidate et al. (1984)
	Chromosome aberration test (anaphase chromosomes)	Human embryonic lung fibroblasts	0.1–10 μg/ml	Not clastogenic	FDA (1975)
	Chromosome aberration test with and without S9 activation	Human lymphocytes	0.1–10 mM	Not clastogenic	Murthy et al. (1991)
	Sister Chromatid Exchange assay with and without S9 activation	Human lymphocytes	0.1–10 mM	No induction of SCE	Murthy et al. (1991)
	Chromosomal aberrations	Human embryonic lung cells	0.1–10 μg/ml	Negative	FDA (1975)
D,L Menthol	Ames assay with and without S9 activation (rat liver)	*S. typhimurium*TA98, TA100, TA 2637	0.005–0.5 mg/ml in DMSO	Not mutagenic, cytotoxic at ⩾0.2 mg/ml	Nohmi et al. (1985)
	Ames test with and without S9 activation (rat and hamster liver)	*S. typhimurium* TA97, TA98, TA100, TA1535	3–666 μg/plate in DMSO; cytotoxic at ⩾333 μg/plate	Not mutagenic	Zeiger et al. (1988)
	Mammalian cell mutation with and without S9 activation	Mouse Lymphoma L5178Y TK+/−	12.5–200 μg/ml	Not genotoxic, cytotoxic at 200 μg/ml	Myhr and Caspary (1991)
	Umu test	*S. typhimurium* TA1535/pSK1002	Up to 500 μg/ml	Not mutagenic	Yasunaga et al. (2004)
	Chromosome aberration test without S9 activation	Chinese hamster V79 lung cells	0.1–0.2 mg/ml in EtOH for 24 and 48 h	Questionable results in 0.1 and 0.2 mg/ml at 24 h	Sofuni et al. (1985)
Menthol racemic	Umu test	*S. typhimurium* TA1535/pSK1002	Up to 500 μg/ml	Not mutagenic	Yasunaga et al. (2004)
	Chromosome aberration test (no information about metabolic activation system reported)	Chinese hamster ovary cells (CHO)	1.5 mM for 20 h	7% structural aberrations (cell count 45% of control)	Galloway et al. (1998)
	Chromosome aberration test with and without S9 activation	Chinese hamster ovary cells (CHO) and TK6 human lymphocytes	Without S9: 128–280 μg/ml for 3 h;With S9: 200 μg/ml for 3 h	Without S9: At 1.6 mM weak increases in aberrations, with S9 at 1.2 mM not clastogenic	Hilliard et al. (1998)
	Alkaline elution assay	Rat hepatocytes	Up to 1.3 mM (cytotoxic)	⩾0.7 mM: DNA breaks, considered "false positive" by the author	Storer et al. (1996)
	Chromosome aberration test with and without S9 activation	Chinese hamster ovary cells (CHO)	Without S9: 100, 150, 200 μg/ml for 8 h:With S9: 50, 124, 250 μg/ml for 2 h	Not clastogenic, Cytotoxic at ⩾200 μg/ml	Ivett et al. (1989)
	Chromosomal aberrations with and without S9 activation	Chinese hamster ovary cells	Up to 250 μg/ml	Negative	Tennant et al. (1987)
	Sister chromatid exchange with and without S9 activation	Chinese hamster ovary cells	Up to 167 μg/ml	Negative	Tennant et al. (1987)
	Sister Chromatid Exchange assay with and without S9 activation	Chinese hamster ovary cells (CHO)	Up to 167 μg/ml	No induction of SCE	Ivett et al. (1989)
D-Menthol	Comet assay	Chinese hamster V79 lung cells and human lymphocytes	Up to 2 mM	Not genotoxic	Hartmann and Speit (1997)

Table 5-1B (*continued*)

Substance	Test system		Concentrations	Results	References
L-Menthol	Ames assay with and without S9 activation (rat liver)	*S. typhimurium* TA100, TA98, TA97a, TA102	100–800 μg/plate for TA97a, TA98, TA100 5–800 μg/plate for TA102	Not mutagenic	Gomes-Carneiro et al. (1998)
	Ames assay with and without S9 activation (rat liver)	*S. typhimurium* TA 98, TA100, TA 1537	0.02–0.5 mg/ml	Not mutagenic Cytotoxic at ⩾0.1 mg/ml	Nohmi et al. (1985)
	Mutation assay	*E. coli* WP2*uvrA*	100–800 μg/plate	Not mutagenic	Yoo (1986)
	Rec-assay	*Bacillus subtilis* strains H 17 (rec+) and M 45 (rec−)	20 μg/disc	Not mutagenic	Oda et al. (1979)
	Rec-assay (spore plate assay)	*Bacillus subtilis* strains H 17 (rec+) and M 45 (rec−)	10,000 μg/disc	Positive	Yoo (1986)
	Chromosome aberration test with and without S9 activation (mouse liver)	Chinese hamster fibroblasts	0.1–0.3 mg/ml	Not clastogenic	Matsuoka et al. (1998)
	Chromosome aberration test without S9 activation	Chinese hamster V79 lung cells	0.03–0.125 mg/ml in DMSO for 24 and 48 h	Not clastogenic	Sofuni et al. (1985)
	Chromosome aberration test with and without S9 activation	Chinese hamster V79 lung cells	0.1–0.3 mg/ml with S9 in DMSO 0.1–0.2 mg/ml without S9	Not clastogenic	Sofuni et al. (1985)
Terpineol	Ames assay with and without S9 activation (rat liver)	*S. typhimurium* TA100, TA98, TA97a, TA102	Up to and including cytotoxic concentrations	Not mutagenic in TA100, TA98 and TA97a; 2-fold increase in TA102 with and without metabolic activation	Gomes-Carneiro et al. (1998)
	Rec-assay	*Bacillus subtilis* strains H 17 (rec+) and M 45 (rec−)	19 μg/disc	Not mutagenic	Oda et al. (1979)
α-Terpineol	Ames assay	*S. typhimurium* TA98, TA100, TA1535 and TA1538	3 μmol/plate in EtOH	Not mutagenic	Florin et al. (1980)
	Ames assay with and without metabolic activation	*S. typhimurium* TA 98, TA 1535, TA 1537 and TA 1538	Up to 10,000 μg or nl/plate	Not mutagenic	Heck et al. (1989)
	Ames assay with and without metabolic activation (rat liver)	*S. typhimurium* TA98, TA100, TA1535,TA1537 and TA1538	Up to 10,000 μg/plate	Not mutagenic	Lorillard Research Center (1983)
	Mouse lymphoma assay with and without metabolic activation	L5178Y TK+/− cells	250–300 μg or nl/ml	Not mutagenic	Heck et al. (1989)
	Mouse lymphoma assay with and without metabolic activation	L5178Y TK+/− cells	Up to 300 nl/ml	Not mutagenic	Lorillard Research Center (1982b)
p-Mentha-8-en-1-ol	Ames assay with S9 activation	*S. typhimurium* TA98, TA100	100 μL	Not mutagenic	Rockwell and Raw (1979)
	Host mediated assay, with and without beta-glucuronidase	*S. typhimurium* TA98, TA100	10 μL/plate of ether extracts from urine of 2 rats given 0.5 ml undiluted material p.o.	Weak mutagenic activity in TA100, but not in TA98	Rockwell and Raw (1979)
Vetiverol	Ames assay with and without S9 activation (rat liver), solvent: DMSO	*S. typhimurium* TA98, TA100, TA1535, TA1537 and TA1538	0–5000 μg/plate	Not mutagenic Cytotoxic at 5000 μg/plate	RIFM (1985k)
	Ames assay with and without S9 activation (rat liver), solvent: DMSO	*S. typhimurium* TA98, TA100, TA1535, TA1537 and TA1538	50–5000 μg/plate	Not mutagenic	RIFM (1985k)
Geranodyle	*S. typhimurium* mutagenicity assay	TA 98, TA 100, TA 1535 and TA 1537 with and without S9 factors	Up to 5000 μg/plate in DMSO	No mutagenicity	RIFM (1995e)
	Mutagenicity assay	*E. coli* WP2uvrA with and without S9 factors	Up to 5000 μg/plate in DMSO	No mutagenicity	RIFM (1995e)
	In vitro cytogenetic assay	Chinese hamster V79 cells	19.5–2500 μg/ml. Dimethyl sulfoxide (DMSO)	Not mutagenic	RIFM (2000e)

Table 5-2A
Mutagenicity and genotoxicity: *in vivo* studies/non-cyclic terpene alcohols

Material	Test system	Species	Dose or concentration	Results	References
Farnesol	Bone marrow micronucleus assay	Mouse	NA	Not genotoxic	Rupa et al. (2003)
Geraniol	Bone marrow micronucleus assay	Mouse	NA	Not genotoxic	Rupa et al. (2003)
Hydroxycitronellol	Bone marrow micronucleus assay	Mouse	516, 860, 1204 mg/kg body weight by single gavage	Not genotoxic	Wild et al. (1983)
Linalool	Bone marrow micronucleus assay	Mouse	500, 1000, 1500 mg/kg body weight by single gavage	Not genotoxic	RIFM (2001b)

α-terpineol, and vetiverol were non-mutagenic in standard bacterial tests (Ames test) with and without metabolic activation. α-Terpineol was negative in two mouse lymphoma tests. An isolated positive result reported for terpineol (unspecified isomer) in *Salmonella typhimurium* strain TA102 with and without metabolic activation by Gomes-Carneiro et al. (1998) is of doubtful significance as there was no clear dose–response and the increase was only twofold.

Table 5-2B
Mutagenicity and genotoxicity: *in vivo* and *ex vivo* studies/cyclic terpene alcohols

Material	Test system	Species	Dose	Results	References
D,L-Menthol	*Ex vivo* Comet assay	ddY Mouse	2000 mg/kg body weight p.o., sampling times 3, 8, 24 h after dosing	Not genotoxic	Sasaki et al. (2000)
L-Menthol	Bone marrow chromosome aberration test	Rat	1.45, 14.5, 145, 500, 3000 mg/kg as single oral dose, sacrifice 6, 24, 48 h after treatment;1.45, 14.5, 145, 1150 mg/kg body weight/day p.o. for 5 days, sacrifice 6 h after last dose	Not clastogenic	FDA (1975)
	Dominant lethal test	Rat	1.45, 14.5, 145, 500, 3000 mg/kg as single oral dose;1.45, 14.5, 145, 1150 mg/kg body weight/day p.o. for five days	Not mutagenic	FDA (1975)
Menthol racemic	*Ex vivo* DNA replicative synthesis assay	F344 rat (male)	750, 1450 mg/kg p.o.	Increase in replicative DNA synthesis	Uno et al. (1994)
	Ex vivo DNA replicative synthesis assay	B6C3F1 Mouse (male)	1000, 2000 mg/kg p.o.	Increase in replicative DNA synthesis	Miyagawa et al. (1995)
	Bone marrow micronucleus assay	B6C3F1 Mouse	Daily i.p. injections for 3 days (250, 500, 1000 mg/kg body weight/day)	Not clastogenic	Shelby et al. (1993)

Positive results were obtained in a non-validated test system (rec assay) with borneol (Yoo, 1986) and menthol (Yoo, 1986). In an *in vivo-in vitro*study designed to test for mutagenicity of the metabolites of citronellol, linalool and *p*-menth-8-en-1-ol, Sprague–Dawley rats were administered a single dose of 0.5 ml of citronellol, linalool or *p*-menth-8-en-1-ol by gavage, and the urine was collected for 24-h (Rockwell and Raw, 1979). The urine (500 μL) was hydrolyzed with β-glucuronidase. Hydrolyzed and unhydrolyzed urine samples, ether extracts of the urine, and aqueous fractions of the urine–ether extracts were then separately incubated with *S. typhimurium* strains TA98 and TA100 without S9 activation. Linalool, citronellol, *p*-menth-8-en-1-ol and all preparations of the urine of rats given linalool or citronellol showed no evidence of mutagenicity in either TA98 or TA100. However, urine extracts from rats given *p*-menth-8-en-1-ol showed weak mutagenic activity towards TA100, but not TA98. It was concluded by the study authors that compounds such as *p*-menth-8-en-1-ol "...appeared to require an *in vivo* metabolic activation to detect their mutagenic form".

4.3.2. In vitro chromosome aberration studies

Linalool, farnesol, α-bisabolol, geranodyle and L-menthol did not induce chromosome aberrations *in vitro* when incubated with Chinese hamster ovary or Chinese hamster fibroblast cells (CIR, 1999; FDA, 1975; Ishidate et al., 1984; Matsuoka et al., 1998; Murthy et al., 1991; RIFM, 1983b, 1995e; Rupa et al., 2003; Sofuni et al., 1985). For D,L-menthol, questionable results were reported in assays without metabolic activation (Galloway et al., 1998; Hilliard et al., 1998; Sofuni et al., 1985). In assays with metabolic activation, D,L-menthol was not genotoxic (Hilliard et al., 1998; Ishidate et al., 1984; Ivett et al., 1989). As D,L-menthol has not shown genotoxic effects *in vivo* (see below), the questionable results in the *in vitro* assays are considered to be of minor relevance.

With geraniol, tested up to toxic levels, the results were inconclusive as an increase in the number of cells with structural aberrations was observed in one of two experiments with metabolic activation (Rupa et al., 2003). As geraniol has been tested by the same authors also in a micronucleus test *in vivo*, in which it showed no evidence of a genotoxic activity (Rupa et al., 2003), it appears that the inconsistently observed *in vitro* genotoxicity is not expressed *in vivo* and is not of relevance.

4.3.3. Indicator studies

D,L- and D-Menthol induced no genotoxic effects in the Comet assay using Chinese hamster ovary and lung cells (CHO, V79 cells) or human lymphocytes (Hartmann and Speit, 1997; Kiffe et al., 2003).

4.3.4. In vivo studies

The four non-cyclic materials (farnesol, geraniol, hydroxycitronellol, linalool) and the cyclic terpene alcohol L-menthol were non-genotoxic in the mouse bone marrow micronucleus test (RIFM, 2001b; Rupa et al., 2003; Shelby et al., 1993; Wild et al., 1983). L-Menthol was not mutagenic in the dominant lethal test and a bone marrow chromosome aberration test (FDA, 1975). No indication of genotoxicity was obtained in the *ex vivo* Comet assay with D,L-menthol (Sasaki et al., 2000). Positive results in the *ex vivo* DNA replicative synthesis assay with rat and mouse hepatocytes are explained by the known activity of D,L-menthol to induce hepatic enzyme systems (Uno et al., 1994; Miyagawa et al., 1995).

4.3.5. Summary of the genotoxicity data

The non-cyclic and cyclic terpene alcohols were inactive in bacterial tests and mammalian cell systems. With the exception of geraniol and D,L-menthol, which showed inconclusive results, the terpene alcohols did not induce chromosome aberrations in mammalian cells *in vitro*. All four non-cyclic terpene alcohols, including geraniol, and the cyclic terpene alcohol which were tested in the *in vivo* mouse micronucleus and/or the *in vivo* chromosome aberration test were not genotoxic *in vivo*.

Based on a weight of evidence evaluation of the available in *vitro* and *in vivo* mutagenicity and genotoxicity assays on non-cyclic and cyclic terpene alcohols, this group of substances would not be expected to exhibit genotoxicity *in vivo* at the intended use levels.

4.4. Carcinogenicity (see Tables 6A and 6B)

No bioassays that meet current standards are available for the non-cyclic terpene alcohols. Promotion of dermal carcinogenicity by linalool was investigated by Roe and Field (1965), and a study on the ability of linalool to induce lung tumors in a susceptible mouse strain was reported by Stoner et al. (1973) (see Tables 6A and 6B).

The cyclic menthol (racemic mixture) showed no evidence of carcinogenic activity in 2-year NTP studies on rats and mice (NCI, 1979). The ability of *p*-menth-8-en-1-ol and α-terpineol to induce lung tumors in a susceptible mouse strain was investigated by Stoner et al. (1973).

4.4.1. Non-standard carcinogenicity studies

Linalool (20% in acetone) elicited a weak tumor promoting response in strain 101 mice when tested with the carcinogen dimethylbenz[*a*]anthracene (DMBA) (Roe and Field, 1965).

Linalool and the cyclic terpene alcohols, *p*-menth-1-en-8-ol (α-terpineol) and *p*-menth-8-en-1-ol, were tested by intraperitoneal

Table 6A
Carcinogenicity studies/non-cyclic terpene alcohols

Material	Method	Dose	Species	Results	References
Non-standard carcinogenicity studies					
Linalool	DMBA induced mouse skin tumor model	20% in acetone once a week for 13 weeks, starting 3 weeks after single DMBA application	Inbred strain 101 mouse	Weak tumor promoting response	Roe and Field (1965)
	Pulmonary tumor induction by weekly i.p. injection for 8 weeks; sacrifice at 24 weeks after first injection	3 times weekly for 8 weeks in tricaprylin; cumulative doses 600 and 3000 mg/kg body weight	A/HE mouse	No significant difference in lung tumor incidence as compared to controls	Stoner et al. (1973)

DMBA: dimethylbenz[*a*]anthracene.

Table 6B
Carcinogenicity studies/cyclic terpene alcohols

Material	Method	Dose	Species	Results	References
D,L-Menthol	103 weeks	0, 2000, 4000 ppm in diet (equivalent to 0, 300 or 600 mg/kg body weight/day)	B6C3F1 mouse (50/sex/dose)	Not carcinogenic	NCI (1979)
	103 weeks	0, 3750, 7500 ppm in diet (equivalent to 0, 188 or 375 mg/kg body weight/day)	F344 rat (50/sex/dose)	Not carcinogenic	NCI (1979)
Non-standard carcinogenicity studies					
Menthol	Pulmonary tumor induction by weekly i.p. injection for 8 weeks, sacrifice at 20 weeks after first injection	3 times weekly for 8 weeks in tricaprylin; cumulative doses 500 and 2000 mg/kg body weight	A/HE mouse (20/dose)	No significant difference in lung tumor incidence as compared to controls	Stoner et al. (1973)
α-Terpineol	Pulmonary tumor induction by weekly i.p. injection for 8 weeks; sacrifice at 20 weeks after first injection	3 times weekly for 8 weeks in tricaprylin; cumulative doses 960 and 1900 mg/kg body weight	A/HE mouse (20/dose)	No significant difference in lung tumor incidence as compared to controls	Stoner et al. (1973)
p-Mentha-8-en-1-ol	Pulmonary tumor induction by weekly i.p. injection for 8 weeks; sacrifice at 24 weeks after first injection	3 times weekly for 8 weeks in tricaprylin; cumulative doses 960 and 1900 mg/kg body weight	A/HE mouse (20/dose)	No significant difference in lung tumor incidence as compared to controls	Stoner et al. (1973)

DMBA: dimethylbenz[*a*]anthracene.

injection for their ability to induce primary lung tumors in female A/He mice, a strain susceptible to carcinogen-induced lung tumorigenesis (Stoner et al., 1973). The maximum tolerated dose (MTD) and 20 per cent of the MTD (cumulative doses of 600 and 3000 mg/kg for linalool and 1900 and 9600 mg/kg for both α-terpineol and *p*-menth-8-en-1-ol) induced no increase in pulmonary tumors.

4.4.2. Summary of the carcinogenicity data

A long-term oral study using the NTP protocol conducted in rats and mice using D,L-menthol provided no evidence of carcinogenicity. Non-standard carcinogenicity studies in mice using α-terpineol, *p*-mentha-8-en-1-ol and menthol also provided no evidence of carcinogenicity. Given the information on metabolism and detoxification and the lack of structural alerts for carcinogenicity and the evidence that they are non-genotoxic, it is considered reasonable to conclude that the cyclic terpene alcohols are without carcinogenic potential. There are no long-term studies that evaluated directly the carcinogenicity of linalool. However, based on the conclusion of no significant genotoxic potential, weak, if any, tumor promoting activity, the high NOAELs observed in subchronic studies, the information on metabolism and detoxification and the lack of structural alerts for carcinogenicity, it is considered reasonable to conclude that linalool and the non-cyclic terpene alcohols have no significant potential for carcinogenicity under the recommended current conditions of use as fragrance ingredients (Bickers et al., 2003).

In summary, the available data provide no evidence to indicate that the non-cyclic or cyclic terpene alcohols considered here are carcinogenic. Given the genetic toxicity data and the well-characterized metabolism of these substances and closely related compounds, one may conclude that the non-cyclic and cyclic terpene alcohols are unlikely to possess carcinogenic activity under conditions of use as fragrance ingredients.

4.5. Reproductive and developmental toxicity (see Tables 7A and 7B)

A small number of reliable reproductive and developmental toxicity studies have been conducted on the non-cyclic and cyclic terpene alcohols (RIFM, 1989c; RIFM, 2006b) (see Tables 7A and 7B).

Linalool, in coriander oil, was investigated for reproductive toxicity in groups of 10 virgin Crl CD rats administered 0, 250, 500, or 1000 mg/kg body weight/day of coriander oil containing 72.9% linalool by mass (RIFM, 1989c). The test material was given by gavage once daily, 7 days prior to cohabitation, through cohabitation (maximum of 7 days), gestation, delivery, and a 4-day post-parturition period. The duration of the study was 39 days. Maternal and offspring indices were monitored. There were statistically significant decreases in maternal body weight and food consumption, gestation index, length of gestation, and litter size at 1000 mg/kg body weight/day. Slight, non-significant reductions in maternal body weight, food consumption, gestation index and length of gestation were found at 500 mg/kg body weight/day. Pups had a decrease viability at 1000 mg/kg body weight/day. The authors concluded that there were no effects observed in the dams at 250 mg/kg body weight/day of coriander oil, and in the offspring at the 250 and 500 mg/kg body weight/day levels. They concluded that the maternal NOAEL was 250 mg/kg body weight/day and the developmental NOAEL was 500 mg/kg body weight/day. These values correspond to 183 mg/kg body weight/day and 365 mg/kg body weight/day of linalool.

Table 7A
Reproductive and developmental toxicity studies/non-cyclic terpene alcohols

Material	Method	Concentration(s)/dose	Species	Results	References
Farnesol	Intraamniotic inj.	0.75 mg on gd 3	Rat	Increase in skin barrier ontogenesis	Hanley et al. (1999)
Linalool (72.9% in coriander oil)	Coriander oil, dissolved in corn oil was administered by gavage to female CD virgin rats (10/dose) 7 days prior to a 7-day cohabitation period with male rats, and continued through day 25 of presumed gestation (for rats that did not deliver a litter), or until day 4 of lactation	0 (vehicle), 250, 500 or 1000 mg coriander oil/kg body weight/day	Rat	*Maternal* NOAEL: 250 mg coriander oil/kg body weight/day (corresponding to 183 mg linalool/kg body weight/day) In all dose groups excess salivation; 500 mg/kg body weight/day: food consumption decreased, body weight decreased, gestation index decreased, length of gestation decreased (all effects not statistically significant) 1000 mg/kg body weight/day: food consumption decreased, body weight decreased, gestation index decreased, length of gestation decreased urine-stained abdominal fur, ataxia and/or decreased motor function, maternal body weight gain during the premating period decreased, litter size decreased *Offspring* NOAEL: 500 mg coriander oil/kg body weight/day (corresponding to 365 mg linalool/kg body weight/day) 1000 mg/kg body weight/day: 16.3% decrease in delivered live litter size, indicative of *in utero* deaths, and a statistically significant increase in pup mortality on day 1, with associated pup morbidity were observed	RIFM (1989c)
Linalool	25 presumed pregnant rats were dosed *via* gavage on gestational days 7–17	0 (vehicle), 250, 500 or 1000 mg/kg body weight/day in corn oil	Crl:CD® (SD) IGS BR VAF/PLUS® rats	*Maternal* Pregnancy occurred in 22, 23, 20, and 22 dams in the 0, 250, 500, or 1000 mg/kg body weight/day groups, respectively There were no test substance-related abnormal clinical signs or gross lesions 1000 mg/kg body weight/day: body weight gains reduced (11%; not stat. sign.) during the dosing period (increased during post-dosing period). Absolute and relative feed consumption values significantly reduced (7%) for the dosing period NOAEL: 500 mg/kg body weight/day LOAEL: 1000 mg/kg body weight/day (reduction in body weight gain, reduced feed consumption) *Offspring* No litter parameters affected. No gross external, soft tissue, or skeletal fetal alterations NOAEL: 1000 mg/kg body weight/day (highest tested dose)	RIFM (2006b)

The developmental toxicity of linalool was investigated in 25 presumed pregnant SD rats dosed *via* gavage on gestational days 7 through 17 with linalool in corn oil at 0, 250, 500, or 1000 mg/kg body weight/day (RIFM, 2006b). There were no test substance-related abnormal clinical signs or gross lesions. Body weight gains were non-statistically reduced (11%) in the 1000 mg/kg body weight/day group during the dosing period and were increased over the vehicle control after the dosing period. Absolute and relative feed consumption values were significantly reduced (7%) in the 1000 mg/kg group for the dosing period. No litter parameters were affected, and no gross external, soft tissue or skeletal fetal alterations were found in any group. The maternal NOAEL is 500 mg/kg body weight/day. The developmental NOAEL is 1000 mg/kg body weight/day.

The developmental toxicity of α-bisabolol was investigated in pregnant rats dosed daily *via* gavage on days 6–15 of gestation, with α-bisabolol (98% purity) at 0.250, 0.500, 1.0, and 3.0 ml/kg body weight (~equivalent to 250, 500, 1000 or 3000 mg/kg body weight). (The 3.0 ml/kg dose was used to test maternal toxicity.) Control groups received 1% tylosis mucus or 1% carboxyethyl cellulose gel and were used for the maternal range-finding aspect of the study. Fetuses were removed on day 20 and examined. No effects on pre-natal development were observed at doses up to 1.0 ml/kg. At the highest dose, a significant reduction in fetal number and subsequent increase in resorption rate was observed. No deformities were noted. Also at the highest dose, slight sedation, ataxia, reduced feed intake, and reduction of body weight gain were observed in the dams. The authors concluded that the lowest maternal and developmental toxic doses were between 1.0 and 3.0 ml/kg body weight (CIR, 1999; Habersang et al., 1979). A similarly designed study was conducted in New Zealand rabbits. Pregnant rabbits received 0.3, 1.0, or 3.0 mL/kg (~equivalent to 300, 1000 or 3000 mg/kg) α-bisabolol by stomach tube on days 6–15 of gestation. A control group received 3 ml of 1% tylosis mucus. Fetuses were removed on day 30 and examined. No adverse effects on either prenatal development or on the dams were noted at doses up to 1.0 ml/kg. A reduction in the number of surviving fetuses was noted at the highest dose. No deformities were noted. Slight sedation and reduced body weight gains were noted in the dams at the highest dose level. The lowest toxic oral dose for both fetuses and dams was concluded to be between 1.0 and 3.0 ml α-bisabolol (CIR, 1999; Habersang et al., 1979).

In a fetal rat skin *in vitro* study of nuclear hormone receptors that regulate fetal epidermal development, Hanley et al. (1997) reported that all-*trans* farnesol, an isoprenoid product of the mevalonate pathway, significantly accelerated barrier ontogenesis, resulting in a reduction in transepidermal water loss, while mevalonate, 25-OH cholesterol, squalene, *cis*-farnesol, and nerolidol had no effect. In a subsequent study, Hanley et al. (1999) injected farnesol (0.75 mg per amniotic sac) and other activators of nuclear hormone receptors into the amniotic fluid of fetal rats on gestational day 17 and evaluated barrier function on day 19. While vehicle-treated fetal rats displayed no altered epidermal development compared to naïve controls, a measurable barrier was induced by the intra-amniotic administration of farnesol.

L-Menthol was not embryo- or feto-toxic and displayed no teratogenic properties in gavage studies in various species (rat, mouse, rabbit, and hamster) at maternally non-toxic dose levels

Table 7B
Reproductive and developmental toxicity studies/cyclic terpene alcohols

Material	Method	Dose	Species	Results	References
α-Bisabolol	Developmental toxicity study by oral route (gavage)	250, 500, 1000, and 3000 mg/kg body weight/day on gd 6–15; purity 98%, controls received 1% aqueous tylose or 1% aqueous carboxy methyl cellulose	Rat (Wistar or SD, number not specified)	250, 500, 1000 mg/kg body weight/day: no effect on prenatal development or on dams (NOAEL for both developmental and maternal toxicity: 980 mg/kg body weight/day) 3000 mg/kg body weight/day: significant reduction in fetal number and subsequent increase in resorption rate (no details reported) No deformities. Maternal toxicity (slight sedation, ataxia, feed intake decreased, body weight gain decreased (LOAEL for both developmental and maternal toxicity: ca. – 2940 mg/kg body weight/day)	Habersang et al. (1979)
	Developmental toxicity study by oral route (gavage)	300, 1000, and 3000 mg/kg body weight/day on gd 6–18; purity 98%; controls received 3 ml of 1% aqueous tylose/kg body weight/day	New Zealand Rabbit (number not specified)	300, 1000 mg/kg body weight/day: no effect on prenatal development or on dams (NOAEL for both developmental and maternal toxicity: 980 mg/kg body weight/day) 3000 mg/kg body weight/day: reduction in number of live fetuses; no dead or deformed fetuses. Dams slightly sedated, body weight gain↓ (LOAEL for both developmental and maternal toxicity: ca. 2940 mg/kg body weight/day)	Habersang et al. (1979)
Menthol (unspecified isomer)	Developmental toxicity study by oral route (gavage)	2, 10, 47 and 218 mg/kg body weight/day on gd 6–15	Wistar rat	No effect on maternal and fetal survival, or on number of abnormalities in soft or skeletal tissues. No clinical signs of maternal toxicity (NOAEL for maternal and developmental toxicity: 218 mg/kg body weight/day)	FDA (1973)
	Developmental toxicity study by oral route (gavage)	1.85, 8.6, 40 and 185 mg/kg body weight/day on gd 6–15	CD-1 Mouse	No effect on maternal and fetal survival, or on number of abnormalities in soft or skeletal tissues. No clinical signs of maternal toxicity (NOAEL for maternal and developmental toxicity: 185 mg/kg body weight/day)	FDA (1973)
	Developmental toxicity study by oral route (gavage)	4.25, 19.8, 92 and 425 mg/kg body weight/day on gd 6–18	Rabbit	No effect on fetal survival, or on number of abnormalities in soft or skeletal tissues. 2, 3, 1 and 0 animals died in the 4.25, 19.8, 92 and 25 mg/kg body weight/day groups, respectively, as a result of the administration procedure (NOAEL for maternal and developmental toxicity: 425 mg/kg body weight/day)	FDA (1973)
	Developmental toxicity study by oral route (gavage)	4, 21, 98 and 405 mg/kg body weight/day on gd 6–10	Hamster	No effect on maternal and fetal survival, or on number of abnormalities in soft or skeletal tissues. No clinical signs of maternal toxicity (NOAEL for maternal and developmental toxicity:405 mg/kg body weight/day)	FDA (1973)

gd: gestation day.

(185–425 mg/kg body weight/day; highest doses tested) (FDA, 1973).

No studies on the reproductive toxicity of other non-cyclic and cyclic terpene alcohols are available. However, histopathological examinations of the reproductive organs of male and female rats in repeated dose studies of farnesol (Horn et al., 2005) and D,L-menthol (NCI, 1979) showed no adverse effects.

4.6. Skin irritation (see Table 8-1 A, B and 8-2 A, B)

4.6.1. Human studies

The non-cyclic and cyclic terpene alcohols have been well-studied for their potential to produce skin irritation in humans.

No irritation was observed in predictive tests with undiluted citronellol or with 12% farnesol after single applications (Basketter et al., 2004; RIFM, 1975g, 1976c, 1977c, 1978e). No irritation was observed with the highest tested concentrations, i.e., 20% linalool (Fujii et al., 1972), 10% tetrahydromyrcenol (RIFM, 1972c), 10% hydroxycitronellol (RIFM, 1972d), 5% rhodinol (RIFM, 1971c, 1972d), 4% myrcenol (RIFM, 1972d), 4% tetrahydrolinalool (RIFM, 1976a), 4% ocimenol (RIFM, 1974c), 4% nerolidol (RIFM, 1973g) and 4% tetrahydromuguol (RIFM, 1974d). Irritation was observed with 10% 6,7-dihydrogeraniol after repeated application (RIFM, 1989b, 1988c). As for the cyclic terpene alcohols, no irritation after a single application was observed with the highest tested concentrations for the following materials: undiluted α-terpineol

(Basketter et al., 2004), 20% borneol (Fujii et al., 1972; RIFM, 1972d, 1973i), 20% isopulegol (RIFM, 1999c), 20% santalol (RIFM, 1972d), 20% terpineol (Fujii et al., 1972), 10% hydroabietyl alcohol (RIFM, 1972d), 10% *iso*-borneol (RIFM, 1977c), 10% 6,7-dihydroterpineol (RIFM, 1972d), 8% cedrol (RIFM, 1973g), 10% *cis*-*p*-menthan-7-ol (RIFM, 1975h), 8% menthol (D,L- and L-; RIFM, 1973g, 1974d), 5% α-bisabolol (DeGroot (1994) as cited in CIR (1999)), 5% 4-carvomenthenol (RIFM, 1977c), 4% caryophyllene alcohol (RIFM, 1973g), 4% carveol, dihydrocarveol and *p*-mentha-1,8-dien-7-ol (RIFM, 1972d, 1977c,g), 4% fenchyl alcohol (RIFM, 1976a).

Mild irritation was found with repeated applications of cedrenol (6.25% in EtOH, RIFM, 1964c) and myrtenol (8% in petrolatum (petrolatum).; RIFM, 1986b, 1987e). Irritation was also elicited by 6-isopropyl-2-decahydronaphthalenol at 10% after a single application (RIFM, 1978e, 1979e). Vetiverol (8%) produced 1 irritant reaction in a maximization test (MAX) (RIFM, 1976a).

Menthol, at concentrations as low as 0.5%, can elicit sensory reactions such as stinging and cooling (Marriott et al., 2005; Green and Shaffer, 1992). In a few cases, all in children younger than 1 year, menthol applied to the nostrils or near the nose caused reflex apnea (OECD, 2003).

Further details of these and other studies of dermal irritation are provided in Tables 8-1A and 8-1B.

4.6.2. Animal studies

Most of the non-cyclic and cyclic terpene alcohols have been tested in animal models of primary skin irritation using rabbits.

If applied undiluted under semi-occlusive conditions (i.e., in accordance with current testing guidelines), practically all non-cyclic materials exhibited slight to moderate irritation with geraniol, geranyl linalool and 6,7-dihydrogeraniol having the most

Table 8-1A
Skin irritation studies in humans/non-cyclic terpene alcohols

Material	Method	Concentration	Subjects	Results	References
D,L-Citronellol	24-h patch test, two times in a week	25% in 3:1 EtOH:DEP	12 volunteers	25% in 3:1 EtOH:DEP. No irritation edematous reactions in 2 subjects to the vehicle were observed	RIFM (2002a)
		25% in 3:1 DEP:EtOH		25% in 3:1 DEP:EtOH: No irritation	
	24-h patch test, two times in a week	30% in 3:1 DEP:EtOH 40% in 3:1 DEP:EtOH	22 volunteers	No irritation	RIFM (2003a)
	48 h occluded patch test	32% in acetone	50 volunteers	Irritation observed	Motoyoshi et al. (1979)
	4 h occluded patch test	0.2 ml undiluted aliquot	30 volunteers	No reaction	Basketter et al. (2004)
	48-h occluded patch test	20% in petrolatum or unguentum hydrophilicum	35 volunteers	No irritation	Fujii et al. (1972)
	24-72 h occluded patch test	2% in unguentum simplex or unguentum hydrophilicum	30 volunteers	No irritation	Fujii et al. (1972)
Dehydrolinalool	48 h, occlusive (pre-test for a maximization study)	20% in petrolatum	31 volunteers	No irritation	RIFM (1977c)
6,7-Dihydrogeraniol	24-h patch, three days a week for three weeks	10% (w/v) in EtOH/DEP (75:25)	109 healthy volunteers	Irritation was observed in 19/109	RIFM (1989b)
6,7-Dihydrogeraniol	24-h patch, three days a week for three weeks	10% (w/v) in EtOH/DEP (75:25)	106 human volunteers	Irritation was observed in 57/106. 39 persisted for more than 48 h	RIFM (1988c)
Farnesol	Induction phase of HRIPT	5% in petrolatum	103 healthy volunteers	No irritation	RIFM (2000c)
	Induction phase of HRIPT	5% in petrolatum	101 healthy volunteers	No irritation	RIFM (2000b)
	Induction phase of HRIPT	5% in 3:1 DEP:EtOH	108 volunteers	No irritation	RIFM (2004d)
	48 h, occlusive (pre-test for a maximization study)	12% in petrolatum	25 healthy volunteers	No irritation (0/25)	RIFM (1977c)
	48 h, occlusive (pre-test for a maximization study)	12% in petrolatum	26 healthy volunteers	No irritation (0/26)	RIFM (1977c)
	48 h, occlusive (pre-test for a maximization study)	12% in petrolatum	35 healthy volunteers	No irritation (0/35)	RIFM (1978e)
	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	25 healthy volunteers	No irritation (0/25)	RIFM (1977f)
	48 h, occlusive (pre-test for a maximization study)	12% in petrolatum	5 healthy volunteers	No irritation (0/5)	RIFM (1974c)
	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	25 healthy volunteers	No irritation (0/25)	RIFM (1976c)
	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	25 healthy volunteers	No irritation (0/25)	RIFM (1976c)
	48 h, occlusive (pre-test for a maximization study)	12% in petrolatum	5 healthy volunteers	No irritation (0/5)	RIFM (1975g)
	48 h, occlusive (pre-test for a maximization study)	12% in petrolatum	5 healthy volunteers	No irritation (0/5)	RIFM (1975g)
	48 h, occlusive (pre-test for a maximization study)	12% in petrolatum	25 healthy volunteers	No irritation (0/25)	RIFM (1975g)
	48 h, occlusive (pre-test for a maximization study)	12% in petrolatum	25 healthy volunteers	No irritation (0/25)	RIFM (1975g)

Table 8-1A (*continued*)

Material	Method	Concentration	Subjects	Results	References
Geraniol	4 h closed patch test	0.2 ml undiluted aliquot	28 volunteers	5 positive reactions	Basketter et al. (2004)
	4 h closed patch test	0.2 ml undiluted aliquot	25 volunteers	2 positive reactions	York et al. (1996)
	Patch test, read at 24, 48 and 72 h after removal	20% in petrolatum	49 volunteers	No irritation	RIFM (1977d)
	Closed patch test on the back, 48 h exposure	20% in petrolatum or unguentum hydrophilicum	29 volunteers	No irritation	Fujii et al. (1972)
	Closed patch test on the inner arm, 24–72 h exposure	2% in unguentum simplex or unguentum hydrophilicum	30 volunteers	No irritation	Fujii et al. (1972)
	Closed patch test on the inner arm, 24–48 h exposure	0.5% in EtOH or a non-irritative cream base	84 dermatitis patients	No irritation	Fujii et al. (1972) and Takenaka et al. (1986)
	Patch test, read at 48 and 72 h after removal	5, 10, 20% in petrolatum	383 dermatitis patients	Number of irritation increased at $\geqslant$10%	Yoshikawa (1996)
	Closed patch test 48 h	32% in acetone	50 male volunteers	Severe irritation	Motoyoshi et al. (1979)
	Induction phase of HRIPT	2% in 3:1 DEP:EtOH	100 volunteers	No irritation	RIFM (2000a)
	Induction phase of HRIPT	5 + 0.5% Tocopherol in 3:1 DEP:EtOH	109 volunteers	Irritation Observed	RIFM (2002b)
	Induction phase of HRIPT	10% in 3:1 DEP:EtOH	112 volunteers	No irritation	RIFM (2004d)
	Induction phase of HRIPT	12.5% in EtOH	41 volunteers	No irritation	RIFM (1964b)
Geranyl dihydrolinalool[a]	48 h, occlusive (pre-test for a maximization study)	1% in petrolatum	26 healthy volunteers	No irritation	RIFM (1982c)
Geranyl linalool	48 h, occlusive (pre-test for a maximization study)	1% in petrolatum	29 healthy volunteers	No irritation	RIFM (1982c)
Hydroxycitronellol	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	5 healthy volunteers	No irritation	RIFM (1972d)
Linalool	Closed patch test on the back, 48 h exposure	20% in petrolatum or unguentum hydrophilicum	28 volunteers	No irritation	Fujii et al. (1972)
	Closed patch test on the inner arm, 24–72 h exposure	2% in unguentum simplex or unguentum hydrophilicum	30 volunteers	No irritation	Fujii et al. (1972)
	Closed patch test on the inner arm, 24–48 h exposure	0.4% in EtOH or a non-irritative cream base	84 dermatitis patients	No irritation	Fujii et al. (1972)
	Patch test on the back, 48 h exposure, read at 30 minutes after removal and at 72, 96, 120 h	32% in acetone	50 volunteers	Mild irritation	Motoyoshi et al. (1979)
	48 h, occlusive (pre-test for a maximization study)	4% in petrolatum	32 healthy volunteers	No irritation	RIFM (1976a)
	Closed patch test on the back or forearm for 24–48 h, results read 30 minutes after removal	0.05–0.5% (in a base cream or in 99% EtOH)	84 subjects	No irritation	Takenaka et al. (1986)
trans-3,7-Dimethyl-1,6-octadien-3-ol l	48 h, occlusive (pre-test for a maximization study)	8% in petrolatum	5 healthy volunteers	No irritation	RIFM (1972d)
Myrcenol	48 h, occlusive (pre-test for a maximization study)	4% in petrolatum	5 healthy volunteers	No irritation	RIFM (1972d)
Nerol	Closed patch test on the back or forearm for 24–48 h, results read 30 minutes after removal	0.05–0.5% (in a base cream or in 99% EtOH)	314 subjects	2 subjects with an erythema (+), and 8 subjects with a slight erythema (±)	Takenaka et al. (1986)
	48 h, occlusive (pre-test for a maximization study)	4% in petrolatum	5 healthy volunteers	No irritation	RIFM (1972d)
Nerolidol	48 h, occlusive (pre-test for a maximization study)	4% in petrolatum	5 healthy volunteers	No irritation	RIFM (1973g)
Rhodinol	Induction phase of HRIPT	5% in vaseline	40 healthy volunteers	Irritation observed in 18/40 volunteers	RIFM (1971b)
	48 h, occlusive (pre-test for a maximization study)	5% in unknown vehicle	10 healthy volunteers	No irritation	RIFM (1971c)
	48 h, occlusive (pre-test for a maximization study)	5% in petrolatum	5 healthy volunteers	No irritation	RIFM (1972d)
	closed patch test on the back or forearm for 24–48 h, results read 30 minutes after removal	0.05–0.5% (in a base cream or in 99% EtOH)	75 subjects	No irritation	Takenaka et al. (1986)
Ocimenol	48 h, occlusive (pre-test for a maximization study)	4% in petrolatum	5 healthy volunteers	No irritation	RIFM (1974c)
Tetrahydrolinalool	48 h, occlusive (pre-test for a maximization study)	4% in petrolatum	32 healthy volunteers	No irritation	RIFM (1976a)
	Closed patch test on the back or forearm for 24–48 h, results read 30 minutes after removal	0.05–0.5% (in a base cream or in 99% EtOH)	46 subjects	No irritation	Takenaka et al. (1986)

(*continued on next page*)

Table 8-1A (*continued*)

Material	Method	Concentration	Subjects	Results	References
Tetrahydromuguol	48 h, occlusive (pre-test for a maximization study)	4% in petrolatum	24 healthy volunteers	No irritation	RIFM (1974d)
Tetrahydromyrcenol	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	29 healthy volunteers	No irritation	RIFM (1982c)

[a] This material is not one of the materials being reviewed as it is not used in fragrances, but it is included in this table because it is structurally related.

Table 8-1B
Skin irritation studies in humans/cyclic terpene alcohols

Material	Method	Concentration	Subjects	Results	References
α-Bisabolol	48 h, closed patch (pre-test for a maximization study)	0.1% in commercial product	25 volunteers	No irritation	Ivey Labs (1992), as cited in CIR (1999)
	Patch Test	5% in petrolatum	1–20 patients	No irritation	DeGroot (1994) as cited in CIR (1999)
Borneol	Closed patch test on the back, 48 h exposure	20% in petrolatum or unguentum hydrophilicum	35 volunteers	No reaction in 34. Very slight reaction in 1	Fujii et al. (1972)
	Closed patch test on the inner arm, 24–72 h exposure	2% in unguentum simplex or unguentum hydrophilicum	30 volunteers	No irritation	Fujii et al. (1972)
	Closed patch test on the back or forearm for 24–48 h, results read 30 minutes after removal	0.05–0.5% (in a base cream or in 99% EtOH)	40 subjects	1 subject with a slight erythema (±)	Takenaka et al. (1986)
L-Borneol	48 h, occlusive (pre-test for a maximization study)	8, 20% in petrolatum	5 healthy volunteers	No irritation	RIFM (1972d)
	48 h, occlusive (pre-test for a maximization study)	20% in petrolatum	23 healthy volunteers	No irritation	RIFM (1973i)
iso-Borneol	Closed patch test on the back or forearm for 24–48 h, results read 30 minutes after removal	0.05–0.5% (in a base cream or in 99% EtOH)	40 subjects	No irritation	Takenaka et al. (1986)
	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	35 healthy volunteers	No irritation	RIFM (1977c)
Carveol	48 h, occlusive (pre-test for a maximization study)	4% in petrolatum	5 healthy volunteers	No irritation	RIFM (1972d)
p-Mentha-1,8-dien-7-ol	48 h, occlusive (pre-test for a maximization study)	4% in petrolatum	5 healthy volunteers	No irritation	RIFM (1977f)
4-Carvomenthenol	48 h, occlusive (pre-test for a maximization study)	5% in petrolatum	25 healthy volunteers	No irritation	RIFM (1977c)
Caryophyllene alcohol[a]	48 h, occlusive (pre-test for a maximization study)	4% in petrolatum	5 healthy volunteers	No irritation	RIFM (1973g)
Cedrenol	0.5 ml, 9 semi-open patch applications (induction phase of HRIPT)	6.25% in EtOH	38 healthy volunteers	Mild irritation	RIFM (1964c)
	48 h, occlusive (pre-test for a maximization study)	8% in petrolatum	5 healthy volunteers	No irritation	RIFM (1974c)
Cedrol	48 h, occlusive (pre-test for a maximization study)	8% in petrolatum	5 healthy volunteers	No irritation	RIFM (1973g)
Dihydrocarveol	48 h, occlusive (pre-test for a maximization study)	4% in petrolatum	25 healthy volunteers	No irritation	RIFM (1977c)
Dihydro-α-terpineol	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	5 healthy volunteers	No irritation	RIFM (1972d)
Fenchyl alcohol	48 h, occlusive (pre-test for a maximization study)	4% in petrolatum	24 healthy volunteers	No irritation	RIFM (1976a)
Hydroabietyl alcohol	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	5 healthy volunteers	No irritation	RIFM (1972d)
6-Isopropy-2-decahydronaphthalenol	0.5 ml, 10 closed patch applications (induction phase of HRIPT)	2% in dimethylphthalate	54 healthy volunteers	No irritation	RIFM (1973n)
	0.2 g, 10 closed patch applications (induction phase of HRIPT)	10% in unspecified vehicle	57 healthy volunteers	3 irritant reactions	RIFM (1979e)
	48 h, occlusive (maximization study)	10% in petrolatum	33 healthy volunteers	5 irritant reactions	RIFM (1978e)
	48 h, occlusive (pre-test for a maximization study)	4% in petrolatum	25 healthy volunteers	No irritation	RIFM (1979d)
Isopulegol	Closed patch test for 48 h, results read 24 and 48 h after removal	10%, 20% in lanolin	30 volunteers (15m/15f)	No irritation	RIFM (1999c)
cis-*p*-Menthan-7-ol	9 applications during induction phase of HRIPT	10% in petrolatum	50 healthy volunteers	No irritation	RIFM (1975h)
	9 applications during induction phase of HRIPT	20% in petrolatum	50 healthy volunteers	No irritation	RIFM (1975i)
	9 applications during induction phase of HRIPT	15% in diethyl phthalate	102 healthy volunteers	1/102 irritant reactions	RIFM (2005c)

Table 8-1B (*continued*)

Material	Method	Concentration	Subjects	Results	References
Menthol	48 h, occlusive (pre-test for a maximization study)	8% in petrolatum	5 healthy volunteers	No irritation	RIFM (1973g)
	Rubbed briskly over nasolabial fold	0.5% in water	58 volunteers	⩾20% sensory reactions (stinging, cooling)	Marriott et al. (2005)
	Closed patch test on the back or forearm for 24–48 h, results read 30 minutes after removal	0.05–0.5% (in a base cream or in 99% EtOH)	133 subjects	2 subjects with a slight erythema (±)	Takenaka et al. (1986)
L-Menthol	48 h, occlusive (pre-test for a maximization study)	8% in petrolatum	24 healthy volunteers	No irritation	RIFM (1974d)
	Closed patch (Teflon ring) for several minutes	2.5 ml of 30% (w/v) solution (in 80% aqueous EtOH)	9 volunteers	Sensory irritation (burning, coldness, stinging)	Green and Shaffer (1992)
Myrtenol	48 h, occlusive (pre-test for a maximization study)	8% in petrolatum	24 healthy volunteers	No irritation	RIFM (1985i)
	48 h, occlusive (pre-test for a maximization study)	8% in petrolatum	26 healthy volunteers	No irritation in pre-test, two irritant reactions in MAX	RIFM (1986b)
	48 h, occlusive (pre-test for a maximization study)	8% in petrolatum	23 healthy volunteers	No irritation in pre-test, one irritant reaction in MAX	RIFM (1987e)
cis-2-Pinanol	48 h, occlusive (pre-test for a maximization study)[a]	20% in petrolatum	30 healthy volunteers	No irritation	RIFM (1979b)
Santalol	48 h, occlusive (pre-test for a maximization study)	20% in petrolatum	5 healthy volunteers	No irritation	RIFM (1972d)
Terpineol	48 h closed patch test	0.12% in 1% soap solution	8 healthy volunteers	No irritation	RIFM (1961)
	Closed patch test on the back, 48 h exposure	20% in petrolatum or unguentum hydrophilicum	45 volunteers	No irritation	Fujii et al. (1972)
	Closed patch test on the inner arm, 24–72 h exposure	2% in unguentum simplex or unguentum hydrophilicum	30 volunteers	No irritation	Fujii et al. (1972)
	Induction HRIPT	12.5% in EtOH	37 volunteers	No irritation	RIFM (1964c)
α-Terpineol	4 h closed patch test	0.2 ml undiluted aliquot	30 volunteers	No irritation	Basketter et al. (2004)
Vetiverol	48 h, occlusive (pre-test for a maximization study)	8% in petrolatum	30 healthy volunteers	No reactions (1 irritant reaction in the MAX)	RIFM (1976a)
Sclareol	48 h, semi-occlusive (HRIPT induction)	3% in alcohol SDA 39C	35 volunteers	No Irritation	RIFM (1975a)
	48 h, semi-occlusive (HRIPT induction)	3% in petrolatum	39 volunteers	No irritation	RIFM (1975b)
	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	23 volunteers	No Irritation	RIFM (1979b)
	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	26 volunteers	No irritation	RIFM (1981a)
	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	28 volunteers	No irritation	RIFM (1986b)
	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	29 volunteers	No irritation	RIFM (1979b)

[a] This material is not one of the materials being reviewed as it is not used in fragrances, but it is included in this table because it is structurally related.

marked effects. No or only very slight effects were observed at concentrations between 0% and 10% (Motoyoshi et al., 1979; RIFM, 1978-1986; RIFM, 1987; RIFM, 1988e; RIFM, 1987g; RIFM, 1985f).

Similar but less severe effects were found with the cyclic terpene alcohols. Only very slight effects were noted with α-bisabolol.

Further details of these and other studies of dermal irritation are provided in Tables 8-2A and 8-2B.

4.6.3. Summary of the skin irritation data

The potential for irritation by most of the terpene alcohols assessed in this report has been well characterized in both humans and in laboratory animals.

The human studies performed show occasional evidence of irritation at or close to current levels of use in the case of citronellol, geraniol, nerol, borneol, cedrenol, and menthol. Predictive tests with undiluted citronellol in volunteers gave no indication of irritancy (Basketter et al., 2004).

The animal data indicate that most of the terpene alcohols are likely to be skin irritants when topically applied at neat concentrations. For the most part only minimal evidence of skin irritation was associated with concentrations in the range of 0.5–5.0%.

4.7. Mucous membrane irritation (see Tables 9-A and 9-B)

In comparison to skin irritation, the potential for the terpene alcohols to induce eye irritation has been studied on fewer representatives of this class of compounds.

Corneal involvement and marked conjunctival irritation were observed with undiluted 3,7-dimethyloct-1-en-ol. Moderate irritation reactions were observed with undiluted citronellol, 6,7-dihydrogeraniol, farnesol, geraniol, and nerol (RIFM, 1985c; RIFM, 1976e; RIFM, 1979c; RIFM, 1995b; RIFM, 1963b; RIFM, 1999e; RIFM, 1963; Troy, 1977). Slight effects were noted with geranyl linalool, linalool, nerolidol, and tetrahydrolinalool. At concentrations between 3% and 10% no or very slight irritation was observed for dehydrolinalool and linalool (RIFM, 1978f; RIFM, 1967a; RIFM, 1992b; RIFM, 1967b; Troy, 1977).

Undiluted α-bisabolol and *cis*-*p*-menthan-7-ol elicited slight effects on the eye of rabbits (CIR, 1999; RIFM, 1978g). Terpineol, at 12.5%, was a mild irritant (RIFM, 1963), and cedrenol, at 6.25%, was a moderate eye irritant (RIFM, 1963a). Severe corneal and iris effects were caused by a 50% solution of vetiverol in Tween 80 (RIFM, 1984c); however, the contribution of the solvent to the severity of these effects is unknown.

Table 8-2A
Skin irritation studies in animals/non-cyclic terpene alcohols

Material	Method	Concentration	Species	Results	References
D,L-Citronellol	Buehler pre-test	0.50%, 1.0%, 2.5%, 5.0%, 10%, 25%, 50% in DEP or 100%	Guinea pigs	Irritation observed	RIFM (1992c)
	24–48 h patch test	100%	Guinea pigs	Irritation observed	Motoyoshi et al. (1979)
	24-48 h patch test	100%	Pitman Moore miniature swine	Irritation observed	Motoyoshi et al. (1979)
	Draize irritation test	100%	Rabbits	No irritation	Troy (1977)
	4 h, semi-occlusive, 0.5 ml as a single application	100%	Rabbit (n = 3)	Well defined skin irritation following dosing. Significant irritation remained after 7 days and recovery had generally occurred within 14 days	RIFM (1989e)
	4 h, semi-occlusive, 0.5 ml as a single application	100%	Rabbit (n = 4)	Irritant (mean score for erythema 2.0 and for edema 2.0)	RIFM (1985b)
	4 h, semi-occlusive, 0.5 ml as a single application	100%	Rabbit (n = 3)	Irritant (mean score for erythema 2.0 and for edema 2.2)	RIFM (1984a)
	Irritation evaluated as a part of LD_{50} study	100%	Rabbits	Irritation observed	RIFM (1973a)
	24–48 h patch test	100%	Rabbits	Irritation observed	Motoyoshi et al. (1979)
L-Citronellol	Single application on intact and abraded skin, 0.5 ml, 24 h under occlusive dressing, readings at 24 h and at 72 h	1% in propylene glycol	Rabbit (n = 6)	Very slight erythema in four animals at 24 h. No observable reaction in 6/6 at 72 h. PII: 0.3	RIFM (1973l)
Dehydrolinalool	Single application on intact and abraded skin, 0.5 ml, 24 h under occlusive dressing, readings at patch removal and at 72 h	100% and 3%, 10% and 30% in peanut oil	Rabbit (n = 6)	Undiluted: very slight erythema in all rabbits, persisted at 72 h 30%: very slight erythema in all rabbits, no effects in 4 animals at 72 h 3%, 10%: no irritation	RIFM (1992b)
	Single application for 5 or 120 minutes, readings at 24 and 72 h and 8 days	100%	Rabbit (n = 2)	Application for 5 minutes caused very slight erythema, no effects at day 8. Application for 2 h caused very slight to slight erythema in both animals and slight edema in one animal; very slight erythema still present at day 8	RIFM (1978c)
	Single application on intact and abraded skin, 0.5 ml, 24 h under occlusive dressing, readings at 24 h, 72 h and 8 days	Undiluted	Rabbit (n = 6)	Moderate to severe erythema in all rabbits, still present at study end; moderate edema, still present in 2 animals at study end	RIFM (1978c)
	Single application on intact skin, 0.5 ml, 4 h under occlusive dressing, readings at 4 h, 1 day, 2 days and 8 days	Undiluted	Rabbit (n = 4)	slight erythema in all rabbits, slight and very slight erythema and edema still present at 8 days	RIFM (1978d)
	Irritation evaluated as a part of LD_{50} study	Undiluted	Rabbit (n = 10)	Severe to moderate erythema in all the rabbits	RIFM (1977a)
6,7-Dihydrogeraniol	4 h, semi-occlusive, 0.5 g or ml as a single application	Undiluted	Rabbit (n = 6)	Irritant. Primary irritation index: 5.6	RIFM (1985f)
3,7-Dimethyloct-6-en-3-ol	4 h, semi-occlusive, 0.5 ml or ml as a single application	Undiluted	Rabbit (n = 3)	Not irritant (mean score for erythema 0.2 and for edema 0.0)	RIFM (1988b)
3,7-Dimethyl-1-octanol	4 h, semi-occlusive, 0.5 ml or ml as a single application	Undiluted	Rabbit (n = 3)	Irritant (mean score for erythema 2.0 and for edema 1.0)	RIFM (1989a)
Farnesol	Single application on intact and abraded skin, 0.5 ml, 24 h under occlusive dressing, readings at 25 h, 72 h and 7 days	100%	Rabbit (n = 6)	Slightly irritant (very slight and slight erythema, cleared by 7 days; all scores for edema 0)	RIFM (1979c)
	4 h, semi-occlusive, 0.5 ml as a single application	100%	Rabbit (n = 3)	Very slight to severe erythema and very slight to severe edema in all animals. not fully reversible within 15 days	RIFM (1995c)
Farnesol	Irritation evaluated as a part of LD_{50} study	100%	Rabbit (n = 10)	Irritation observed	RIFM (1974b)
Farnesol	Irritation evaluated as a part of LD_{50} study	10% in vaseline	Rat (n = 10)	No irritation	RIFM (1983f)

Geraniol	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit ($n = 3$)	Irritant (mean score for erythema 2.0 and for edema 1.7)	RIFM (1984a)
	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit ($n = 3$)	Irritant (mean score for erythema 2.1 and for edema 1.3)	RIFM (1985b)
	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit ($n = 8$), several studies	Moderate response	RIFM (1978-1986)
	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit ($n = 3$)	Well defined erythema with very slight to moderate edema; still present at 72 h, PII: 3.8	RIFM (1987c)
	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit ($n = 3$)	Very slight to moderate erythema with very slight to slight edema; hyper-keratosis, desquamation; PII: 2.2	RIFM (1987f)
	Primary irritation Test	Undiluted	Rabbit ($n = 6$)	Severe irritation observed	Motoyoshi et al. (1979)
	Primary irritation Test	Undiluted	Rabbit ($n = 9$)	No irritation	RIFM (1977)
	Primary irritation test	3%, 10%, 30%, 100% in EtOH	Guinea pig	Irritation at 30%, 100%	RIFM (1977a)
	Primary irritation test	Undiluted	Mini pig ($n = 6$)	No irritation	Motoyoshi et al. (1979)
	Primary irritation Test	Undiluted	Rat ($n = 10$)	Irritation observed	RIFM (1980b)
Geranyl dihydrolinalool[a]	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit ($n = 4$)	slightly irritant (mean score for erythema 1.4 and for edema 0.9)	RIFM (1987a)
Geranyl linalool	Single application on intact and abraded skin, observations at 24 and 72 h	Undiluted	Rabbit ($n = 6$)	Well-defined erythema and slight edema, erythema still present at 72 h	RIFM (1978f)
	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit ($n = 4$)	Irritant (mean score for erythema 2.2 and for edema 2.1)	RIFM (1988e)
Hydroxycitronellol	Single application on intact and abraded skin, 5 ml/kg, 24 h under occlusive dressing, readings at patch removal	Undiluted	Rabbit ($n = 4$)	Mild erythema at 24 h	RIFM (1973h)
Linalool	Single application on intact and abraded skin, observations at 24 and 72 h 5% in DEP: very slight erythema in one rabbit at 24 h at both abraded and intact sites, no effects at 72 h	Undiluted and 5% in DEP	Rabbit ($n = 3$ per dose)	Undiluted: very slight to well-defined erythema in all rabbits at 24 h, very slight erythema in one rabbit at 72 h at both the intact and abraded skin sites	RIFM (1967a)
	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit ($n = 3$)	Slightly irritant (mean score for erythema 1.9 and for edema 1.4)	RIFM (1984a)
	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit ($n = 3$)	Irritant (mean score for erythema 2.0 and for edema 1.4)	RIFM (1985b)
	Single application on intact and abraded skin, 0.5 ml, 24 h under occlusive dressing, readings at patch removal and at 72 h	Undiluted and 3%, 10% and 30% in peanut oil	Rabbit ($n = 6$)	Undiluted: very slight erythema in all rabbits, persisted at 72 h 30%: very slight erythema in all rabbits, no effects in 4 animals at 72 h 3%, 10%: no irritation	RIFM (1992b)
trans-3,7-Dimethyl-1,6-octadien-3-ol l l	Single application on intact and abraded skin, 5 ml/kg, 24 h under occlusive dressing, readings at patch removal	Undiluted	Rabbit ($n = 4$)	Moderate erythema at 24 h	RIFM (1973h)
Myrcenol	Irritation evaluated as a part of LD_{50} study	Undiluted (5 g/kg)	Rabbit ($n = 10$)	Moderate erythema and edema in all rabbits until d 3. Moderate to slight erythema (6/10) and edema (6/10) persisted until day 7	RIFM (1972a)
Nerol	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit ($n = 3$)	PII 2.0 (very slight erythema in 1/3 at 1 h, very slight to well-defined erythema with or without very slight edema in 3/3 at 24, 48 and 72 h, cleared by 7 days)	RIFM (1987b)
Nerol	Irritation evaluated as a part of LD_{50} study	Undiluted (5 g/kg)	Rabbit	Slight to moderate erythema and edema	RIFM (1972a)
Nerol	Primary irritation test	Undiluted	Rabbit	No irritation	Troy (1977)
Nerol	Primary irritation test (Buehler pre-test)	0.5, 1, 2.5, 5, 10, 25, 50% in DEP or undiluted	Guinea pig	Slight irritation at all doses	RIFM (1992e)
Nerolidol	Single application on intact and abraded skin, 0.5 ml, 24 h under occlusive dressing, readings at 24 an 48 h	Undiluted and 5% in DEP	Rabbit ($n = 3$)	Undiluted: well-defined erythema, still present at study end, slight edema; 5% in DEP: very slight edema in one animal, cleared by 48 h	RIFM (1967b)
Rhodinol	24 h occlusive, readings at day 1, day 7 and day 14	Undiluted (1.25, 2.5, 5 g/kg)	Rabbit ($n = 4$/dose)	Moderate erythema and edema	RIFM (1973a)

(*continued on next page*)

Table 8-2A (*continued*)

Material	Method	Concentration	Species	Results	References
Tetrahydrolinalool	Single application on intact and abraded skin, observations at 24 and 72 h	Undiluted and 5% in DEP	Rabbit ($n = 3$ per dose)	Undiluted: very slight erythema in all rabbits at 24 h, very slight erythema in two rabbits at 72 h at both the intact and abraded skin sites 5% in DEP: very slight erythema in one rabbit at 24 h at both abraded and intact sites, no effects at 72 h	RIFM (1967a)
Tetrahydromyrcenol	24 h occlusive, readings at day 1, day 7 and day 14	Undiluted (5 g/kg)	Rabbit ($n = 10$)	D1: moderate to severe erythema (2/10), moderate to slight edema (8/10), very slight edema (2/10) D7: moderate erythema, eschar (9/10) and slight edema (10/10); D14:erythema with flaking skin persisted until day 14	RIFM (1982b)

[a] This material is not one of the materials being reviewed as it is not used in fragrances, but it is included in this table because it is structurally related.

Menthol, in dilutions as low as 0.5%, was reported to be irritating to the human nasal mucous membrane. In rabbits, degenerative and destructive changes were found in the nasal mucosa after repeated spray application of menthol at concentrations of 1% and 5%, respectively (Fox, 1930).

Additional information about the mucosal irritation potential of terpene alcohols is provided in Tables 9-A and 9-B.

4.8. Respiratory irritation

Respiratory irritation was assessed in mice by recording their respiratory rate when exposed to citronellol, geraniol, linalool, or nerol for 1 minute using a nebulizer for aerosolization in a 2600 ml chamber (Troy, 1977). Mild to moderate decreases in the respiratory rate were observed with geraniol and nerol; the ED_{25} (dose at which there is a 25% reduction in the respiratory rate) was calculated to be 570 and 590 μg/L for geraniol and nerol, respectively. The ED_{25} for citronellol was 990 μg/L, indicating a slight effect, while linalool had a marked effect with an ED_{25} of 350 μg/L.

4.9. Skin sensitization

4.9.1. Human studies (see Tables 10-1A, 10-1B, 10-1C and 10-1D)

Historical human data exist for both the Human Repeated Insult Patch Test (HRIPT) and Human Maximization Test (HMT) methods, and most of the non-cyclic and many of the cyclic terpene alcohols under review.

No data from predictive tests were available for the non-cyclic alcohols 3,7-dimethyloct-6-en-3-ol, 2,6-dimethyloct-3,5-dien-2-ol, 3,7-dimethyl-4,6-octadien-3-ol, and 3,7-dimethyloct-7-en-1-ol, and for the cyclic alcohols β-caryophyllene alcohol, elemol, neomenthol, octahydro-7,7,8,8-tetramethyl-2,3b-methanol-3bH-cyclopenta(1, 3)cyclopropa(1,2) benzene-4-methanol, patchouli alcohol, 2(10)-pinen-3-ol, *p*-menth-8-en-1-ol, and thujanol.

Citronellol (25% in DEP:EtOH), dehydrolinalool (20% in petrolatum), 3,7-dimethyl-1-octanol (8% in petrolatum), geranyl linalool (1% in petrolatum), hydroxycitronellol (10% in petrolatum), linalool (20% in petrolatum), *trans*-3,7-Dimethyl-1,6-octadien-3-ol (8% in petrolatum), myrcenol (4% in petrolatum), nerol (4% in petrolatum), nerolidol (4% in petrolatum), ocimenol (4% in petrolatum), tetrahydrolinalool (4% in petrolatum), tetrahydromuguol (4% in petrolatum) and tetrahydromyrcenol (10% in petrolatum) showed no evidence of a sensitizing effect in the predictive studies. The following cyclic terpenes showed no evidence of a sensitizing effect: α-bisabolol (0.1% in petrolatum), *iso*-borneol (10% in petrolatum), carveol (4% in petrolatum), *p*-mentha-1,8-dien-7-ol (4% in petrolatum), 4-carvomenthenol (5% in petrolatum), cedrenol (8% in petrolatum), dihydrocarveol (4% in petrolatum), diydroterpineol (10% in petrolatum), fenchyl alcohol (4% in petrolatum), isopulegol (8% in petrolatum), *cis*-*p*-menthan-7-ol (15% in petrolatum), D,L-menthol (8% in petrolatum), L-menthol (8% in petrolatum), santalol (20% in petrolatum), terpineol (12.5% in petrolatum) and vetiverol (8% in petrolatum).

Sensitization reactions were observed in predictive tests with geraniol (6% in petrolatum), farnesol (undiluted), and rhodinol (3,7-dimethyl-7-octen-1-ol; 5% in petrolatum), and with the cyclic alcohols L-borneol (20% in petrolatum), cedrol (8% in petrolatum), hydroabietyl alcohol (10% in petrolatum), 6-isopropyl-2-decahydronaphthalenol (10% in petrolatum) and impure sclareol (10% in petrolatum). Reactions with L-borneol (20% in petrolatum) were observed in one human maximization test (HMT) were attributed to a spillover effect involving benzylidene acetone. Another HMT conducted at the same concentration produced no reactions. Cedrol (8% in petrolatum) caused 2 reactions in an HMT, however, when the same sample was retested in another HMT, no reactions

Table 8-2B
Skin irritation studies in animals/cyclic terpene alcohols

Material	Method	Concentration	Species	Results	References
α-Bisabolol	4 h, semi-occlusive	Undiluted	Rabbit (n = 3)	Very slight erythema at 4 h; by 24 h, the reaction increased to well-defined erythema in two rabbits, and very slight edema in one; by 72 h very slight erythema was noted only in one rabbit. At 7 days scaling in all	BASF (1989) as cited in CIR (1999)
Borneol	Mouse Inner Ear Assay, 5 μl were applied under open conditions, observations every 15 minutes until maximum erythema observed	5, 2.5, 1.25, 0.625, 0.3125, 0.16 μg/5 μl	Mouse (n = 12/group)	Irritant reactions were observed at all dose levels	Saeed and Sabir (1994)
L-Borneol	24 h occlusive, readings at patch removal and daily until day 7 after application	Undiluted (2 g/kg)	Rabbit (n = 10)	Slight to moderate erythema on day 1 (6/10), day 2 (3/10) and day 3 (1/10), cleared by day 4; slight edema on day 1 (1/10), cleared by day 2	RIFM (1972a)
iso-Borneol	24 h occlusive, readings at patch removal	Undiluted (5 g/kg)	Rabbit (n = 5)	Mild to moderate erythema (5/5), moderate edema (5/5)	RIFM (1977a)
L-Carveol	Irritation evaluated as part of an associated LD_{50}study	Undiluted	Rabbit (n = 6)	Irritant reactions were observed	RIFM (1972b)
	Irritation evaluated as part of an associated FCAT	10, 5%, 1% and 0.1% in olive oil	Guinea pigs	Irritation was observed	Karlberg et al. (1992)
p-Mentha-1,8-dien-7-ol	Irritation evaluated as part of an associated LD_{50} study	Undiluted	Rabbit(n = 10)	Severe erythema (10/10), moderate (2/10) and severe edema (8/10) was observed	RIFM (1977a)
	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit (n = 4)	Slightly irritant (mean score for erythema 2.0 and for edema 1.3)	RIFM (1988e)
Cedrol	24 h occlusive, readings at patch removal	Undiluted (5 g/kg)	Rabbit (n = 6)	mild (3/6) to moderate erythema (3/6), mild (3/6) to moderate edema (1/6)	RIFM (1977a)
Dihydrocarveol	24 h occlusive, readings at patch removal	Undiluted (5 g/kg)	Rabbit (n = 10)	moderate to severe erythema (8/10), moderate to severe edema (8/10)	RIFM (1977a)
Dihydro-α-terpineol	24 h occlusive, readings at patch removal	Undiluted (5 g/kg)	Rabbit (n = 7)	Slight redness in 3/7, moderate redness in 4/7, moderate edema in 7/7	RIFM (1973a)
Menthol, racemic	Single application on intact and abraded skin, 5 ml/kg, 24 h under occlusive dressing, readings at patch removal	Undiluted	Rabbit (n = 4)	Mild erythema at 24 h, no edema	RIFM (1973h)
Sclareol	Primary irritation test	3% in petrolatum	Rabbit (n = 3)	No irritation	RIFM (1975c)
	Primary irritation test	3% in alcohol SDA39C	Rabbit (n = 3)	No irritation	RIFM (1975d)
	Irritation evaluated as part of an associated LD_{50} study	100%	Rabbit	Irritation observed	RIFM (1979a)
Fenchyl Alcohol	Irritation evaluated as part of an associated LD_{50} study	100%	Rabbit(n = 2)	Moderate erythema and edema	RIFM (1976b)
4-Carvomenthenol	Irritation evaluated as part of an associated LD_{50} study	100%	Rabbit(n = 4)	Moderate erythema and edema	RIFM (1977a)
Myrtenol	6 h under occlusion with 0.3 ml	0.5–100%	Guinea pigs	No Irritation from 0.5% to 2.5% Irritation from 5% to 100%	RIFM (1987d)
	6 h under occlusion with 0.3 ml	0.5–75	Guinea pigs	No Irritation from 0.5% to 10% Irritation from 25% to 75%	RIFM (1987d)
α-Terpineol	4 h, semi-occlusive, 0.5 g or ml as a single application	100%	Rabbit	Irritating (mean score for erythema 2.0 and for edema 2.4)	RIFM (1984a)
	4 h, semi-occlusive, 0.5 g or ml as a single application	100%	Rabbit (n = 4)	Irritating (mean score for erythema 2.2 and for edema 2.6)	RIFM (1985b)
	4 h, semi-occlusive, 0.5 g or ml as a single application	50% in DEHP and 100%	Rabbit (n = 4)	50%: slightly irritating (mean score for erythema 1.7 and for edema 0.8) 100%: irritating (mean score for erythema 1.9 and for edema 2.1)	RIFM (1986a)
	Mouse Inner Ear Assay, 5 μl were applied under open conditions, observations every 15 minutes until maximum erythema observed	20, 10, 5, 2.5, 1.25, 0.625, 0.3125, 0.15625 and 0.078125 μg/5μl	Mouse (n = 12/group)	Irritation observed ID50 = 0.847 μg/5 μl IU (irritant units)=0.625(24 h)and >10 (48 h)	Saeed and Sabir (1994)
				Irritating	Fentem et al. (2001)
cis-Verbenol[a]	Draize test, occlusive treatment for 24 h, abraded and intact skin	0.5 g undiluted sample, moistened with 0.9% saline	Rabbit (n = 6)	On day 7, exfoliation was observed in 4/6 animals. The primary irritation index was 1.92. Therefore the test material was classified as a non-irritant	RIFM (1991b)

(*continued on next page*)

Table 8-2B (*continued*)

Material	Method	Concentration	Species	Results	References
Vetiverol	4 h, semi-occlusive, 0.5 ml as a single application	100%	Rabbit ($n = 8$)	Slight to slight/moderate effects 24 h after treatment and mainly slight effects 72 h after treatment	RIFM (1984h)
	Irritation evaluated as part of an associated LD_{50} study	100%	Rabbit	Irritation was observed	RIFM (1977a)
	Preliminary intradermal-irritation test	0.1%, 0.25%, 0.5%, 1% and 2% in 0.01% dobs/saline	Guinea pig	1%: very faint erythema 2%: definitive irritation reactions	RIFM (1984h)
	Preliminary topical-irritation test	5%, 10% and 25% in 0.01% dobs/saline	Guinea pig	5%: highest non-irritating concentration Irritation observed at 10% and 25%	RIFM (1984c)
	Preliminary intradermal irritation	0.1%, 0.25%, 0.5%, 1% and 2% in 0.01% dobs/saline	Guinea pig	2%: definitive irritation reactions	RIFM (1984g)
	Preliminary topical irritation test	5%, 10% and 25% in polyethylene glycol (PEG)/acetone	Guinea pig	5%: highest non-irritating concentration. Irritation at 10% and 25%	RIFM (1984d)
	Irritation evaluated as part of an associated phototoxicity study	Range of concentrations	Rats	3%: minimal irritating concentration	RIFM (1984f)
Geranodyle	4-h semi-occlusive	Not reported	Rabbits	Slight irritation	RIFM (1987g)
	Induction phase photoirritation	100%, 30%, 10%, 3% and 1% in EtOH and 2% DMSO	Guinea pigs	10%: maximum non-irritation concentration Irritation observed at 30% and above	RIFM (1985l)
	Primary irritation phototoxicity	40%, 20% and 10% in acetone	Guinea pigs	No irritation	RIFM (1995d)

[a] This material is not one of the materials being reviewed as it is not used in fragrances, but it is included in this table because it is structurally related.

were observed. Questionable reactions were obtained with myrtenol (8%) that were attributed to irritation.

Because of their sensitization potential, 6,7-dihydrogeraniol, hydroabietyl alcohol and 6-isopropyl-2-decahydronaphthalenol (IFRA, 1989, 2004) are prohibited for use in fragrance materials by the International Fragrance Association (IFRA) code. Restrictions for use apply to farnesol and geraniol (considered weak sensitizers) (IFRA, 2006, 2007; QRA Expert Group, 2006). The studies reported for geraniol in the literature are often vague with respect to the description of the material used (synthetic or pure geraniol, or geranium oil). Hence, the high incidences of positive reactions reported by some investigators (Brites et al., 2000) may be due to impurities. Different qualities of sclareol also have different sensitization potential; high purity sclareol is not a sensitizer (RIFM, 1979b, 1981a, 1986b, 1975a). Sclareol used as a fragrance ingredient should therefore have a minimum purity of 98% (IFRA, 2005).

The allergenic activity of terpenes may be affected by autoxidation (Sköld et al., 2002a,b; Sköld et al., 2004). To investigate the role of oxidation products in linalool sensitization, 1511 consecutive dermatitis patients in six European dermatological clinics were patch tested with linalool, oxidized linalool, and linalool hydroperoxide. Non-oxidized linalool was a very weak sensitizer, however the oxidation mixtures and linalool hydroperoxide were strong sensitizers. Of the patients tested, 1.3% showed reactions to oxidized linalool, 1.1% to linalool hydroperoxide; 2/3 of the patients reacting positive to oxidized terpenes had fragrance related contact allergy and/or positive history for adverse reactions to fragrances (Matura et al., 2005; Sköld et al., 2005). Sköld et al. (2006) reported that 25/1511 patients (1.7%) reacted to oxidized linalool. Based on the autoxidation potential of linalool, the IFRA Standard states that this material should only be used when peroxide levels are kept low ($\leqslant$20 mmol/l) through the use of an antioxidant.

Based on the absence of structural features that indicate a sensitization potential, the results obtained with structurally closely related analogues in predictive testing, and the results from diagnostic patch testing and/or human experience, the following materials are not considered to present a relevant sensitization capability: 3,7-dimethyloct-6-en-3-ol, 3,7-dimethyloct-7-en-1-ol, β-caryophyllene alcohol, elemol, neomenthol, patchouli alcohol, 2(10)-pinen-3-ol, octahydro-7,7,8,8-tetramethyl-2,3b-methanol-3bH-cyclopenta(1,3)cyclopropa(1,2)benzene-4-methanol, *p*-menth-8-en-1-ol, and thujanol. Positive reactions to menthol isomers have been reported in the literature; given the widespread use of this material in consumer goods, the reported incidences are small and the sensitization potential of this material (all isomers) is therefore considered weak.

2(10)-Pinen-3-ol, 2,6-dimethyloct-3,5-dien-2-ol do not have structural alerts for topical effects (Ford et al., 2000). However, 3,7-dimethyl-4,6-octadien-3-ol, exhibits structural features indicative of a potential sensitizing effect and should, therefore, be regarded as a potential skin sensitizer.

Additional information on the studies performed in humans is provided in Table 10-1A for non-cyclic alcohols and Table 10-1B for the cyclic alcohols.

4.9.1.1. Cross sensitization. Cross sensitization between geraniol and limonene, and between farnesol and santalol have been reported (Audicana and Bernaola, 1994; Hausen et al., 1989).

4.9.1.2. Diagnostic patch test studies. Positive reactions in diagnostic patch tests on dermatitis patients have been reported for geraniol (at concentrations $\geqslant$1% in petrolatum), nerol (5% in petrolatum), neroli-dol (1% in petrolatum), citronellol ($\geqslant$1% in petrolatum), hydroxycitronellol (7% in petrolatum) and, in very few cases, for linalool (10% and 20% in petrolatum) and rhodinol (5%, unknown vehicle).

Table 9-A
Mucous membrane irritation studies/non-cyclic terpene alcohols

Material	Method	Results	References
Citronellol	0.1 ml undiluted	irritating (Draize scores of 40, 13, 5, 2 and 0 at day 1, day 2, day 3, day 4, day 7)	Troy (1977)
L-Citronellol	0.1 ml, 1% in propylene glycol, 6 animals	Temporary mild conjunctival reactions in 5 animals, no observable effects in one animal	RIFM (1973j)
Dehydrolinalool	0.1 ml, undiluted and 3%, 10% and 30% in peanut oil, observations at 1 h and at 1, 2, 3, 4, and 7 days; 6 animals/dose	Undiluted: moderate conjunctival irritation with slight corneal involvement in 5 rabbits, corneal effects still present in 2 rabbits at study end 30%: slight conjunctival irritation in 5 rabbits, cleared by day 4 10%: very slight conjunctival irritation in all rabbits, cleared by day 1 3%: no irritation	RIFM (1992b)
	0.1 ml, undiluted, observations at 24, 48 and 72 h and after 8 days; 6 animals	Undiluted: slight conjunctival irritation with slight corneal and iris involvement in all rabbits, corneal and conjunctival effects still present in all rabbits and iritis in one animal at study end	RIFM (1978c)
6,7-Dihydrogeraniol	0.1 ml, undiluted, 6 animals	Primary irritation index: 18.1, all effects reversible within 8 days	RIFM (1985c)
3,7-Dimethyloct-1-en-3-ol	0.1 ml, undiluted, 1 animal	Irritation observed (mean scores for redness 3.0, conjunctivae 2.7), cornea and iris effects not reversible at the end of the observation period, i.e., at 8 days	RIFM (1988a)
Farnesol	0.1 ml, 0.3% in soybean oil, 6 animals	Slight swelling and redness by 8 h; cleared by 24 h	RIFM (1976e)
	0.1 ml, undiluted, observations at 1 h and day 1, day 2, day 3, day 4, day 7, day 14 and Day 21, 6 animals	Moderate conjunctival irritation with chemosis in all animals, cleared in 2 rabbits by day 14. Corneal and iris effects still present in one animal at day 21, very slight chemosis in 2 animals at day 21	RIFM (1979c)
	0.1 ml, undiluted, 3 animals	Hyperemia in two animals, slight to moderate redness and swelling in all animals, all effects healed by day 5	RIFM (1995b)
Geraniol	0.1 ml, 5% in 95% alcohol SDA39C, 3 animals	No corneal or iris effects. Mild vessel injection of conjunctivae with slight chemosis, all effects cleared by the 4th day	RIFM (1963b)
	0.1 ml, undiluted	irritating (Draize scores of 26, 19, 8, 4 and 1 at day 1, day 2, day 3, day 4, and day 7)	Troy (1977)
	0.1 ml, undiluted	Slight corneal opacity and iris effects, not reversible within 21 days; mean score for erythema 2.4 and edema 1.5	RIFM (1999e)
	0.1 ml, 12.5% vehicle unknown SDA39C, 3 animals	Irritation with chemosis and discharge, cleared by day 7	RIFM (1963a,b) RIFM (1963)
Geranyl linalool	0.1 ml undiluted, 6 animals	Very slight redness, cleared by 72 h in 5 animals	RIFM (1978f)
Linalool	0.1 ml, undiluted and 5% in DEP, observations at 0, 1, 2, 4, 24, 48 and 72 h, 3 animals/dose, eyes not washed	Undiluted: very slight corneal opacity and very slight to moderate conjunctival irritation with chemosis and discharge in all 3 rabbits. Effects were still present at 72 h 5% in DEP: very slight conjunctival irritation in all 3 rabbits at instillation, which cleared in 2 rabbits by 1 h and in the third rabbit by 2 h	RIFM (1967a)
	0.1 ml, undiluted and 3%, 10% and 30% in peanut oil, observations at 1 h and at 1, 2, 3, 4, and 7 days; 6 animals/dose	Undiluted: moderate conjunctival irritation with slight corneal involvement in all 6 rabbits, cleared by day 7 30%: slight conjunctival irritation in 5 rabbits, cleared by day 4 10%: very slight conjunctival irritation in all rabbits, cleared by day 1 3%: no irritation	RIFM (1992b)
	0.1 ml undiluted	irritating (Draize scores of 27, 16, 10, 6 and 0 at day 1, day 2, day 3, day 4, day 7)	Troy (1977)
Nerol	0.1 ml undiluted	irritating (Draize scores of 31, 21, 15, 5 and 1 at day 1, day 2, day 3, day 4, day 7)	Troy (1977)
Nerolidol	0.1 ml undiluted and 5% in DEP, 3 animals	Undiluted: very slight redness, cleared by 2 h, 5% in DEP: no effects	RIFM (1967b)
Tetrahydrolinalool	0.1 ml, undiluted and 5% in DEP, observations at 0, 1, 2, 4, 24, 48 and 72 h, 3 animals/dose, eyes not washed	Undiluted: very slight corneal opacity in one animal at 24, 48 and 72 h, and very slight to moderate conjunctival irritation with chemosis and discharge in all 3 rabbits. Effects were still present at 72 h 5% in DEP: very slight conjunctival irritation in all 3 rabbits at instillation, which cleared in 2 rabbits by 1 h and in the third rabbit by 4 h	RIFM (1967a)

Positive diagnostic patch test results were also obtained for hydroabietyl alcohol (1%, 10%, 40% in petrolatum), isopulegol (0.1%, 1%, 5% in petrolatum), menthol (1%, 2%, 5% in petrolatum), santalol (1%, 2%, 5%, 10% in petrolatum), and in very few cases for α-terpineol (5%, 10%). Synthetic and natural santalol (from sandalwood) caused erythematous reactions in 1.4–3.5% of subjects at concentrations of 0.05–0.5% (Takenaka et al., 1986).

Yoshikawa (1996) patch-tested 383 dermatitis patients with natural and synthetic geraniol (purity 98.7% and 98.1%, respectively) at 20%, 10% and 5% in white petrolatum and found that reactions increased markedly at concentration higher than 10%; Yoshikawa (1996) also discussed the role of impurities in the elicitation of irritation. Occasional evidence of irritation at or close to current levels of use was found with citronellol (negligible to slight dermal irritation at test concentrations between 0.5% and 40%, mainly in dermatitis patients (RIFM, 2002a, 2003a; Fujii et al., 1972; Takenaka et al., 1986)) and with nerol at test concentrations between 0.05% and 0.5% (Takenaka et al., 1986).

Additional information on diagnostic patch test studies is provided in Table 10-1C for non-cyclic alcohols and Table 10-1D for the cyclic alcohols.

4.9.2. Animal studies (see Tables 10-2A and 10-2B)

Information on the individual animal studies is provided in Table 10-2A for non-cyclic alcohols and in Table 10-2B for the cyclic alcohols. By and large, the results from animal studies support the

Table 9-B
Mucous membrane irritation studies/cyclic terpene alcohols

Material	Method	Results	References
α-Bisabolol	0.1 ml, undiluted, 3 animals	No corneal or iris effects; well-defined conjuntival redness at 1, 24, and 48 h, all effects cleared by 72 h	BASF (1989) as cited in CIR (1999)
Cedrenol	0.1 ml, 6.25% in EtOH 39 C, 3 animals	No corneal or iris effects, moderate conjuntival irritation, all effects cleared by day 4	RIFM (1963a)
6-Isopropyl-2-decahydronaphthalenol	0.1 ml, 0.5% in propylene glycol, 3 animals	No irritation	RIFM (1973m)
cis-p-Menthan-7-ol	0.1 g, 6 animals	Slight irritation, all effects healed by 96 h	RIFM (1978g)
Menthol	Undiluted, 1 and 5% in not specified vehicle	Injuries were graded 9 on a scale of maximum 10 (no details reported)	Carpenter and Smyth (1946)
	1%, 5% in paraff. liquidum, sprayed for 9 months	1%: degenerative changes in nasal mucosa 5%: destructive changes in nasal mucosa	Fox (1930)
	0.5% in dilution	Caused swelling of the mucous membrane in humans	Fox (1930)
L-Menthol	0.7% in butyl stearate in EtOH	Irritant effects observed	Goldemberg (1979)
Sclareol	3% in petrolatum	No irritation	RIFM (1975e)
	3% in alcohol SDA39C	Irritant effects (moderate conjunctival irritation with corneal involvement which cleared on the 10th day)	RIFM (1975f)
Terpineol	12.5% in 87.5% EtOH	Mean Draize score = 12/110 Mild conjunctival irritation. All eyes clear by day 7	RIFM (1964d)
Vetiverol	10 μL, undiluted and 50% in Tween 80, 2 animals	Undiluted: small loss of corneal epithelium with slight conjunctivitis healing by day 4. The second eye showed moderate effects with slight effects persisting to day 22 50%: almost total loss of corneal epithelium, moderate corneal swelling and iritis. Pannus at day 5. Persistent moderate lesions until day 22	RIFM (1984c)
Geranodyle	30% in 4% carboxymethyl cellulose	No irritation	RIFM (1987i)
	10% in olive oil	No irritation	RIFM (2000f)

conclusions drawn from human experience or predictive testing in humans (see Section 4.9.1.).

No sensitization reactions were elicited in guinea pig tests by tetrahydrolinalool at concentrations up to 20%. No sensitization reactions were elicited in guinea pig tests with D,L-citronellol or L-citronellol in concentrations up to 10%. D,L-Citronellol was positive in the murine local lymph node assay (LLNA) at a concentration of 50% (EC3 not determined). Of the tested cyclic alcohols, L-carveol, cedrol, geranodyle, isopulegol, and α-terpineol were all negative in guinea pig sensitization tests. It is notable that no sensitization reactions were obtained in a guinea pig MAX with the sensitizer 6,7-dihydrogeraniol.

Mixed results were obtained with geraniol (not sensitizing in Buehler and six MAXs, sensitizing in three MAXs, in the open epicutaneous test, and in the LLNA with mice). The EC3 values appeared to be dependent on the vehicle used and were between 5.6% and 25.8%.

Pure and oxidized linalool were tested for their sensitizing capacity using guinea pig or LLNAs (Basketter et al., 2002; Sköld et al., 2002a,b, 2004). Linalool gave no or only very weak reactions, while hydroperoxides and other oxidation products sensitized the animals. One of the major oxidation products of linalool was isolated and identified as 7-hydroperoxy-3,7-dimethyl-octa-1,5-dien-3-ol.

Weak reactions were found in guinea pig tests with nerolidol and farnesol. Nerolidol was weakly positive in an adjuvant test, and negative in an OET and a Draize sensitization tests. Farnesol was positive in only one out of four MAXs and weakly positive in another adjuvant test. The OET was negative and the EC3 in a LLNA was determined to be 5.5%.

With the cyclic alcohols, positive reactions were obtained with hydroabietyl alcohol in a modified adjuvant test, with L-menthol in the Draize test after two cycles of sensitization treatment, and with santalol and vetiverol in MAXs. Reactions induced by myrtenol in a Buehler test at a test concentration of 10%, but not at 1or 3%, were thought to be irritant in nature as they were not apparent after rechallenge.

4.9.3. Summary of the skin sensitization data

The sensitizing potential for most of the terpene alcohols has been well characterized in humans. For many materials, supporting data exist from animal experiments.

The following materials appear not to have a sensitizing effect: dehydrolinalool, 3,7-dimethyl-1-octanol, geranyl linalool, linalool, *trans*-3,7-Dimethyl-1,6-octadien-3-ol, myrcenol, nerol, nerolidol, ocimenol, tetrahydrolinalool, tetrahydromuguol, tetrahydromyrcenol, bisabolol, *iso*-borneol, carveol, *p*-mentha-1,8-dien-7-ol, caryophyllene alcohol, 4-carvomenthenol, cedrenol, dihydrocarveol, dihydroterpineol, fenchyl alcohol, isopulegol, *cis-p*-menthan-7-ol, menthol, geranodyle, pure sclareol, terpineol and α-terpineol, and octahydro-7,7,8,8-tetramethyl-2,3b-methanoL-3bH-cyclopenta(1,3) cyclopropa(1,2)benzene-4-methanol.

Sensitization reactions were observed in predictive tests with geraniol, 6,7-dihydrogeraniol (3,7-dimethyl-2-octen-1-ol), farnesol, and rhodinol (3,7-dimethyl-7-octen-1-ol), and with the cyclic alcohols L-borneol, cedrol, hydroabietyl alcohol, 6-isopropyl-2-decahydronaphthalenol and impure sclareol. Additionally, citronellol and hydroxycitronellol, nerolidol, oxidized linalool, L-menthol, santalol, and vetiverol were allergenic in animals. Questionable reactions were obtained with myrtenol in both human and animal tests. There are IFRA Standards prohibiting the use of 6,7-dihydrogeraniol (3,7-dimethyl-2-octen-1-ol), hydroabietyl alcohol and 6-isopropyl-2-decahydronaphthalenol. Additionally, linalool and sclareol have IFRA Standard Specifications (IFRA, 1989, 2004). IFRA Standards (IFRA, 2006, 2007) restricting the use of geraniol, D,L-citronellol, rhodinol (3,7-dimethyl-7-octen-1-ol) and farnesol are based on the QRA approach (QRA Expert Group, 2006). In spite of the widespread use of menthol, the incidence of positive reactions is very small, and its sensitizing potential is therefore considered low. Due to their sensitizing effects, 6,7-dihydrogeraniol, hydroabietyl alcohol and isopropyl-2-decahydronaphthalenol have been prohibited for use in fragrance materials. Restrictions exist for farnesol.

As the quality of the material may influence the sensitization potential, restrictions with regard to the required purity exist for farnesol, linalool and sclareol.

No suitable test results from analogue materials were available for some materials. 2(10)-Pinen-3-ol, and 2,6-dimethyloct-3,5-dien-2-ol do not have structural alerts for topical effects (Ford et al., 2000). Based on structural elements that indicate a potential for sensitization, 3,7-dimethyl-4,6-octadien-3-ol, should be regarded as a potential sensitizer until tested.

Table 10-1A
Skin sensitization studies in humans/non-cyclic terpene alcohols

Material	Method	Concentration(s)	Subjects	Results	References
D,L-Citronellol	HRIPT	25% in 3:1DEP:EtOH	101 healthy volunteers	No sensitization reactions; the etiology of the edematous reactions in two subjects during the induction phase is unknown	RIFM (2005a)
	MAX	6% (vehicle not reported)	25 volunteers	No sensitization reactions	Greif (1967)
Dehydrolinalool	MAX	20%	31 healthy volunteers	No sensitization reactions	RIFM (1977c)
6,7-Dihydrogeraniol	MAX	10% in DEP	24 healthy volunteers	1 positive reaction (1/24)	RIFM (1985g)
	HRIPT	10% in EtOH/DEP (75:25)	53 healthy volunteers	3 positive reactions	RIFM (1988c)
	HRIPT	10% in EtOH/DEP (75:25); re-challenge with 10% and 1%, each in EtOH/DEP as above	109 healthy volunteers; re-challenge with 3 subjects	3 positive reactions (3/109); re-challenge with 10% resulted in positive reactions in all 3 sensitized subjects; re-challenge with 1% induced a positive reaction in one of the three subjects	RIFM (1989b)
3,7-Dimethyl-1-octanol	MAX	8% in petrolatum	25 healthy volunteers	No sensitization reactions	RIFM (1973g)
Farnesol	HRIPT	5% in petrolatum	103 healthy volunteers	No sensitization reactions	RIFM (2000c)
	HRIPT	5% in petrolatum + 0.2% tocopherol	101 healthy volunteers	No sensitization reactions	RIFM (2000b)
	HRIPT	5% in 3:1 DEP:EtOH	108 volunteers	No sensitization reactions	RIFM (2004d)
	MAX	Undiluted	25 healthy volunteers	4 positive reactions	RIFM (1974c)
	MAX	Undiluted	25 healthy volunteers	7 positive reactions	RIFM (1975g)
	MAX	Undiluted	25 healthy volunteers	No sensitization reactions	RIFM (1975g)
	MAX	12% in petrolatum	25 healthy volunteers	No sensitization reactions	RIFM (1975g)
	MAX	12% in petrolatum	25 healthy volunteers	2 positive reactions	RIFM (1975g)
	MAX	10% in petrolatum	25 healthy volunteers	6 positive reactions	RIFM (1976c)
	MAX	10% in petrolatum	25 healthy volunteers	No sensitization reactions	RIFM (1976c)
	MAX	12% in petrolatum	25 healthy volunteers	No sensitization reactions	RIFM (1977c)
	MAX	12% in petrolatum	26 healthy volunteers	No sensitization reactions	RIFM (1977c)
	MAX	10% in petrolatum	25 healthy volunteers	4 positive reactions	RIFM (1977c)
	MAX	12% in petrolatum	35 healthy volunteers	No sensitization reactions	RIFM (1978e)
	MAX	12% in petrolatum	25 healthy volunteers	No sensitization reactions	RIFM (1977c)
	MAX	12% in petrolatum	26 healthy volunteers	No sensitization reactions	RIFM (1977c)
	MAX	12% in petrolatum	25 healthy volunteers	4 positive reactions	RIFM (1977c)
	MAX	12% in petrolatum	35 healthy volunteers	No sensitization reactions	RIFM (1978e)
Geraniol	HRIPT	10% in 3:1 DEP:EtOH	112 healthy volunteers	3 questionable reactions	RIFM (2004a)
	HRIPT	5% in 3:1 DEP:EtOH	109 healthy volunteers	1 questionable reaction, no reaction in this subject at re-challenge	RIFM (2002b)
	HRIPT	2% in 3:1 DEP:EtOH	110 healthy volunteers	No sensitization reactions	RIFM (2000a)
	HRIPT	5% in EtOH (95%)	40 healthy volunteers	No sensitization reactions	RIFM (1964b)
	HRIPT	12.5% in EtOH	41 volunteers	No sensitization reactions	RIFM (1964a)
	MAX	6% in petrolatum	25 volunteers	No sensitization reactions	Greif (1967) and Marzulli and Maibach (1980)
	MAX	5% in petrolatum	25 volunteers	20 positive reactions	Malten et al. (1984)
	MAX	6% in petrolatum	24 volunteers	No sensitization reactions	RIFM (1979b)
	MAX	6% in petrolatum	26 volunteers	1 positive reaction	RIFM (1979b)
	Modified Draize test	10% in petrolatum	104 volunteers	No sensitization reactions	Marzulli and Maibach (1980)
	Modified Draize test	10% in alcohol	73 volunteers	2 positive reactions	Marzulli and Maibach (1980)
Geranyl dihydrolinalool[a]	MAX	1% in petrolatum	26 volunteers	No sensitization reactions	RIFM (1982c)
Geranyl linalool	MAX	1% in petrolatum	29 volunteers	No sensitization reactions	RIFM (1982c)
Hydroxycitronellol	MAX	10% in petrolatum	25 volunteers	No sensitization reactions	RIFM (1972d)
Linalool	MAX	20% in petrolatum	25 volunteers	No sensitization reactions	RIFM (1970b)
	MAX	8% (vehicle not reported)	25 volunteers	No sensitization reactions	Greif (1967)
	MAX	20% (vehicle not reported)	25 volunteers	No sensitization reactions	Ishihara et al. (1986)
trans-3,7-Dimethyl-1,6-octadien-3-ol	MAX	8% in petrolatum	25 healthy volunteers	No sensitization reactions	RIFM (1972d)
Myrcenol	MAX	4% in petrolatum	25 healthy volunteers	No sensitization reactions	RIFM (1972d)
Nerol	MAX	4% in petrolatum	25 healthy volunteers	No sensitization reactions	RIFM (1972d)
Nerolidol	MAX	4% in petrolatum	25 healthy volunteers	No sensitization reactions	RIFM (1973g)
Ocimenol	MAX	4% in petrolatum	25 healthy volunteers	No sensitization reactions	RIFM (1974c)
Rhodinol	HRIPT	5% in vaseline, re-challenge with 5% in petrolatum	40 healthy volunteers	12 positive reactions; re-challenge positive in 5/9	RIFM (1971b)
	MAX	5% in unknown vehicle	25 healthy volunteers	No sensitization reactions	RIFM (1971c)
	MAX	5% in petrolatum	25 healthy volunteers	No sensitization reactions	RIFM (1972d)
Tetrahydrolinalool	MAX	4% in petrolatum	32 healthy volunteers	No sensitization reactions	RIFM (1976a)
Tetrahydromuguol	MAX	4% in petrolatum	24 healthy volunteers	No sensitization reactions	RIFM (1974d)
Tetrahydromyrcenol	MAX	10% in petrolatum	29 healthy volunteers	Questionable reaction was observed in 3/29 subjects, however after retesting, no (0/29) reactions were observed	RIFM (1982c)

MAX: maximization test.
[a] This material is not one of the materials being reviewed as it is not used in fragrances, but it is included in this table because it is structurally related.

Table 10-1B
Skin sensitization studies in humans/cyclic terpene alcohols

Material	Method	Concentration(s)	Subjects	Results	References
α-Bisabolol	MAX	0.1% in commercial product	25 volunteers	No sensitization reactions	Ivey Labs (1992) as cited in CIR (1999)
L-Borneol	MAX	20% in petrolatum	25 volunteers	2 positive reactions	RIFM (1972d)
	MAX	8% in petrolatum	25 volunteers	No sensitization reactions	RIFM (1972d)
	MAX	20% in petrolatum	23 volunteers	No sensitization reactions	RIFM (1973i)
iso-Borneol	MAX	10% in petrolatum	35 volunteers	No sensitization reactions	RIFM (1977c)
Carveol	MAX	4% in petrolatum	25 volunteers	No sensitization reactions	RIFM (1972d)
p-Mentha-1,8-dien-7-ol	MAX	4% in petrolatum	25 volunteers	No sensitization reactions	RIFM (1977f)
4-Carvomenthenol	MAX	5% in petrolatum	25 volunteers	No sensitization reactions	RIFM (1977c)
	MAX	5% in petrolatum	21 volunteers	1 questionable reaction, probably irritant (no reaction after re-challenge)	RIFM (1977c)
Caryophyllene alcohol[a]	MAX	4% in petrolatum	25 volunteers	No sensitization reactions	RIFM (1973g)
Cedrenol	HRIPT	6.25% in EtOH SD39C	38 healthy volunteers	No sensitization reactions	RIFM (1964c)
	MAX	8% in petrolatum	25 volunteers	No sensitization reactions	RIFM (1974c)
Cedrol	MAX	8% in petrolatum	25 volunteers	2 positive reactions	RIFM (1973g)
	MAX	8% in petrolatum	25 volunteers	No sensitization reactions	RIFM (1973g)
Dihydrocarveol	MAX	4% in petrolatum	25 volunteers	No sensitization reactions	RIFM (1977c)
Dihydro-α-terpineol	MAX	10% in petrolatum	25 volunteers	No sensitization reactions	RIFM (1972d)
Fenchyl alcohol	MAX	4% in petrolatum	24 volunteers	No sensitization reactions	RIFM (1976a)
Hydroabietyl alcohol	HRIPT	10% in petrolatum	200 volunteers	11 positive re actions (5.5%)	Rapaport (1980)
	MAX	10% in petrolatum	25 volunteers	3 positive reactions	RIFM (1972d)
	MAX	10, 40% in petrolatum	40%: 26 and,10%: 35 cosmetic dermatitis patients	1+ and 1++ positive reaction at 10%, no reactions at 40%	Malten et al. (1984)
6-Isopropy L-2-decahydronaphthalenol	HRIPT	2% in dimethylphthalate	54 healthy volunteers	No sensitization reactions	RIFM (1973n)
	HRIPT	10% (vehicle not reported)	57 volunteers	2 positive reactions	RIFM (1979e)
	MAX	10% in petrolatum	33 healthy volunteers	4 sensitization and 5 irritant reactions	RIFM (1978e)
	MAX	4% in petrolatum	25 healthy volunteers	3 positive reactions	RIFM (1979d)
Isopulegol	MAX	8% in petrolatum	25 healthy volunteers	No sensitization reactions	RIFM (1971c) and Klecak (1985)
cis-*p*-Menthan-7-ol	HRIPT	15% in 75% DEP/25% EtOH	102 volunteers	No sensitization reactions	RIFM (2005c)
	HRIPT	20% in petrolatum	50 volunteers	No sensitization reactions	RIFM (1975h)
	HRIPT	10% in petrolatum	50 volunteers	No sensitization reactions	RIFM (1975h)
D,L-Menthol	MAX	8% in petrolatum	25 healthy volunteers	No sensitization reactions	RIFM (1973g)
L-Menthol	MAX	8% in petrolatum	24 healthy volunteers	No sensitization reactions	RIFM (1974d)
Myrtenol	MAX	8% in petrolatum	24 volunteers	1 positive reaction	RIFM (1985i)
	MAX	8% in petrolatum	26 volunteers	1 positive reaction and 1 irritant reaction	RIFM (1985i)
	MAX	8% in petrolatum	23 volunteers	several questionable reactions, one irritant reaction; no evidence of sensitization reactions	RIFM (1987e)
cis-2-Pinanol[a]	MAX	20% in petrolatum	30 healthy volunteers	No sensitization reactions	RIFM (1979b)
Santalol	MAX	20% in petrolatum	25 volunteers	No sensitization reactions	RIFM (1972d)
α-Santalol	MAX	20% in petrolatum	Not reported	No sensitization reactions	Klecak (1979, 1985)
Sclareol	MAX	10% in petrolatum	29 healthy volunteers	Sensitization observed (1/29)	RIFM (1979b)
	MAX	10% in petrolatum	29 healthy volunteers	Sensitization observed (3/26)	RIFM (1979b)
	MAX	10% in petrolatum	23 healthy volunteers	No sensitization reactions	RIFM (1981a)
	MAX	10% in petrolatum (Sclareol Russian)	28 healthy volunteers	No sensitization reactions	RIFM (1986b)
	HRIPT	3% in alcohol SDA 39C(recrystall.)	35 subjects	No sensitization reactions	RIFM (1975a)
	HRIPT	3% in petrolatum (recrystall.)	39 subjects	No sensitization reactions	RIFM (1975a)
Terpineol	HRIPT	12.5% in 87.5% EtOH	37 subjects	No sensitization reactions	RIFM (1964e)
	MAX	12% in alcohol	25 volunteers	No sensitization reactions	Greif (1967)
Vetiverol	MAX	8% in petrolatum	30 volunteers	No sensitization reaction in 30 volunteers, 1 irritant reaction	RIFM (1976a)
	HRIPT	8% (vehicle not specified)	Not specified	No sensitization reactions	Klecak (1985)

[a] This material is not one of the materials being reviewed as it is not used in fragrances, but it is included in this table because it is structurally related.

4.10. Phototoxicity and photoallergenicity (see Tables 11A and 11B)

Limited data were available with regard to the phototoxicity and photoallergenicity of terpene alcohols (see Tables 11A and 11B). From human or animal studies reliable data were available on the phototoxicity of the non-cyclic terpene alcohols, farnesol, geraniol, tetrahydrolinalool, and tetrahydromuguol, and on the cyclic alcohols isopulegol, vetiverol, and santalol. Only farnesol, and the cyclic alcohols, α-bisabolol and vetiverol were tested for their photoallergenic potential.

No phototoxic reactions were seen in groups of 10 human volunteers exposed to 5.5% tetrahydromuguol, followed by irradiation with UVA (RIFM, 1981c; Weinberg and Springer, 1981).

In photo-patch tests in 111 dermatitis patients, geraniol (at 5% in petrolatum) did not elicit any photoallergic reactions (Nagareda et al., 1992). Several hundred dermatitis patients were subjected to

Table 10-1C
Diagnostic patch test studies in humans/non-cyclic terpene alcohols

Material	Method	Concentration(s)	Subjects	Results	References
D,L-Citronellol	Patch test	1% and 5% in petrolatum	100 patients	1%: 1 positive reaction 5%: 2 positive reactions	Frosch et al. (1995)
	Patch test	2% and 5% in vaseline	45 patients with melanosis, 120 with cosmetic dermatitis, 78 with dermatitis, 26 controls	2%: no reactions 5%: no reactions in controls and melanosis patients, 2/120 (1.7%) and 1/78 positive (1.3%)	Ishihara et al. (1979)
	Patch test	5% in petrolatum	658 subjects	2 positive reactions	Heydorn et al. (2003)
	Patch test	5% in petrolatum	315 subjects	No sensitization reactions	Heydorn et al. (2002)
	Patch test	5% in petrolatum	218 fragrance sensitive patients	19 positive reactions (8.7%)	Larsen et al. (2002)
	Patch test	2% in petrolatum	119 subjects with cosmetic allergy	2 positive reactions	De Groot et al. (1988)
	Patch test	1% in petrolatum	1855 subjects	7 positive reactions	Frosch et al. (2002a,b)Frosch et al. (2002)
	Patch test	0.5%, 1% in petrolatum	1701 subjects	0.5%: 2 positive reaction 1%: 4 positive reactions	Frosch et al. (2005)
L-Citronellol	Patch test	5% in Vaseline	101 patients, 10 controls	No sensitization reactions	Ishihara et al. (1979)
	Patch test	5% in unknown vehicle	95 patients, 14 controls	No sensitization reactions	Ishihara et al. (1981)
	Patch test	5% in unknown vehicle	95 patients, 20 controls	No sensitization reactions	Nishimura et al. (1984); Itoh et al., 1986, 1988
	Patch test	5% in petrolatum	178 fragrance sensitive patients	10 positive reactions (5.6%)	Larsen et al. (2001)
	Patch test	5% in vaseline	193 patients, 21 controls	No sensitization reactions	Ishihara et al. (1979)
	Patch test	5% in unknown vehicle	95 patients, 14 controls	No sensitization reactions	Ishihara et al. (1981)
	Patch test	5% in unknown vehicle	95 patients, 20 controls	No sensitization reactions	Nishimura et al. (1984); Itoh et al., 1986, 1988
Farnesol	Patch test	5% in petrolatum	1855 patients	10 positive reactions (0.5%)	Frosch et al. (2002a)
	Patch test	20% in petrolatum	573 patients	7 positive reactions (1.22%)	Hirose et al. (1987)
	Patch test	5% in petrolatum	102 patients	4 positive reactions (3.92%)	Hausen (2001)
	Patch test	4% in petrolatum	182 dermatitis patients	1.1% positive reactions	Malten et al. (1984)
	Patch test	5 % in lanolin	2021 dermatology patients	22 positive reactions (1.1%)	Schnuch et al. (2004)
	Patch test	1 % in lanolin	111 subjects sensitive to balsam of Peru	8 positive reactions (7.2%)	Goossens and Merckx (1997)
	Patch test	not reported	1483 patients	1.1% positive reactions	Sugiura et al. (2000)
	Patch test	2%, 5%, 10% in petrolatum	466 contact dermatitis patients	1.5% positive reactions	Yamamoto (1986)
Geraniol	Patch test	not reported	713 patients with cosmetic dermatitis	8 positive reactions	Adams and Maibach (1985)
	Patch test	not reported	19,546 patients	Positive reactions in 0.3%	Angelini et al. (1997)
	Patch test	1% in petrolatum	226 patients	19 positive reactions (8.4%)	Brites et al. (2000)
	Patch test	not reported	5202 patients, of which 309 with cosmetic dermatitis	11 positive reactions (0.2%); 1.3% in cosmetic dermatitis patients	Broeckx et al. (1987)
	Patch test	1% in petrolatum	934 patients with cosmetic dermatitis	40/609 (6.6%) female and 27/325 (8.3%) male patients had positive reactions	Buckley et al. (2000)
	Patch test	2% in petrolatum	2461dermatitis patients	7 positive reactions (0.28%)	Calnan et al. (1980)
	Patch test	10% in petrolatum	179 patients with cosmetic allergy	11 positive reactions (6.1%)	De Groot et al. (1985)
	Patch test	5% in petrolatum	119 patients with cosmetic allergy	2 positive reactions(1.68%)	De Groot et al. (1988)
	Patch test	5% in unknown vehicle	55 cosmetic dermatitis, 159 dermatitis patients and 42 controls	1/55 (1.8%) and 4/159 (2.5%) positive reactions, no reactions in controls	Ishihara et al. (1981)
	Patch test	5% in unknown vehicle	680 patients, 115 controls	3 positive reactions (0.44%), no reactions in controls	Itoh et al. (1986)
	Patch test	5% in unknown vehicle	756 patients, 122 controls	3 positive reactions (0.4%), no reactions in controls	Itoh et al. (1988)
	Patch test	1% in petrolatum	182 dermatitis patients	1.6% positive reactions	Malten et al. (1984)
	Patch test	5% in petrolatum	111 patients with contact dermatitis	1 positive reaction(0.9%)	Nagareda et al. (1992)
	Patch test	5% in unknown vehicle	522 patients	3 positive reactions(0.57%)	Nishimura et al. (1984)
	Patch test	3% in petrolatum	1200 patients with contact dermatitis	4 positive reactions (0.3%)	Santucci et al. (1987)
	Patch test	1% in petrolatum	1500 patients with contact dermatitis	4 positive reactions (0.3%)	Santucci et al. (1987)
	Patch test	not reported	170 patients	No sensitization reactions	Sugai (1996)
	Patch test	not reported	1483 patients	0.3% positive reactions	Sugiura et al. (2000)

(*continued on next page*)

Table 10-1C *(continued)*

Material	Method	Concentration(s)	Subjects	Results	References
Hydroxycitronellol	Patch test	7% in petrolatum	216 fragrance sensitive patients	13 positive reactions (6%)	Larsen et al. (2002)
Linalool	Patch test	30% in petrolatum	179 patients with cosmetic allergy	No reactions	De Groot et al. (1985)
	Patch test	10% in petrolatum	119 patients with cosmetic allergy	1 positive reaction	De Groot et al. (1988)
	Patch test	20% in petrolatum	1825 patients	3 positive reactions (0.2%)	De Groot et al. (2000)
	Patch test	1% and 5% in petrolatum	100 patients	Both 1% and 5% produced one questionable reaction	Frosch et al. (1995)
	Patch test	5% in unknown vehicle	162 patients, 16 controls	No sensitization reactions	Itoh et al. (1988)
	Patch test	5% in petrolatum	218 fragrance sensitive patients	No sensitization reactions	Larsen et al. (2002)
	Patch test	not reported	1511 dermatitis patients	20 positive reactions to oxidized linalool (1.3%), 16 positive reactions to linalool hydroperoxide (1.1%); non-oxidized linalool was a very weak sensitizer	Matura et al. (2005) and Sköld et al. (2005)
	Patch test	not reported	1511 dermatitis patients	25 positive reactions to oxidized linalool (1.7%)	Sköld et al. (2006)
	Patch test	10% in petrolatum	70 patients with contact dermatitis, 19 patients with eyelid dermatitis	No reactions in contact dermatitis patients, one subject (1/19) with eyelid dermatitis had a positive reaction	Nethercott et al., 1989
	Patch test	5% in petrolatum	1200 patients with contact dermatitis	No reactions	Santucci et al. (1987)
Nerol	Patch test	5% in petrolatum	218 fragrance sensitive patients	13 positive reactions (6%)	Larsen et al. (2002)
Nerolidol	Patch test	1% in petrolatum	2273 dermatitis patients	3 positive reactions	Hausen (2001)
Rhodinol	Patch test	5% in unknown vehicle	130 patients	No sensitization reactions	Nishimura et al. (1984)
	Patch test	5% in unknown vehicle	202 patients, 26 controls	1 positive reaction (0.5%) in dermatitis patients, no reactions in controls	Itoh et al. (1986, 1988)

a photo-patch test with santalol (unspecified isomer) at concentrations between 2% and 10% in petrolatum. There were no photoallergic reactions observed (Hashimoto et al., 1990; Nagareda et al., 1992, 1996, Sugai, 1980, 1996).

In guinea pigs, farnesol (10% in petrolatum) and geranodyle (up to 10% in DMSO and EtOH and 40% in acetone) were not phototoxic. Tetrahydrolinalool elicited no reactions at concentrations up to 30% in acetone (RIFM, 1983d, 1985l, 1995d, 1999b).

Isopulegol was found not to be phototoxic in guinea pigs treated with 10%, 30% or 50% solutions in propylene glycol:acetone and irradiated with 14 J/cm^2 for 70 minutes (RIFM, 1994d). In rats, no phototoxicity was observed with vetiverol (3% in EtOH), irradiated for 72 minutes with 15 J/cm^2 UVA (RIFM, 1984f).

Farnesol and the cyclic alcohols, α-bisabolol, geranodyle and vetiverol were tested for their photoallergenicity in reliable photoallergenicity tests with guinea pigs (CIR, 1999; RIFM, 1983e, 1984e, 1985m). Farnesol was not photoallergenic in guinea pigs induced with 10% in petrolatum and a 30 s UV exposure and challenged with the same treatment after a resting period of 21 days (RIFM, 1983e). No photoallergic reactions were found in guinea pigs treated with 3% or 15% α-bisabolol in EtOH and olive oil and irradiated on several days for induction, and challenged with 3% or 15% α-bisabolol(CIR, 1999).

Vetiverol induced photoallergenicity in guinea pigs induced with 30% and 10 J/cm^2 UVA, and challenged 14 days later with 10% (in dimethylacetamide:acetone: EtOH) and irradiation. As reactions were elicited only at the highest challenge concentration (10%), and not at 1% or 0.1%, the authors of this study concluded that the photoallergenic potential of vetiverol was weak (RIFM, 1984e).

UV spectra have been obtained for 13 non-cyclic terpene alcohols (citronellol, dehydrolinalool, 3,7-dimethyl-1-octanol, farnesol, geraniol, hydroxycitronellol, linalool, myrcenol, nerol, nerolidol, rhodinol, tetrahydrolinalool, tetrahydromuguol) and 19 cyclic terpene alcohols (borneol, 1-borneol, L-carveol, 4-carvonmenthenol, cedrenol, cedrol, dihydro-α-terpineol, fenchyl alcohol, geranodyle, isoborneol, isopulegol, *p*-mentha-1,8-dien-7-ol, *cis*-*p*-menthan-7-ol, *p*-menth-1-en-8-ol (S), menthol, terpineol, α-terpineol, 4-thujanol, vetiverol). In general, they did not absorb UVB light (290–320 nm). They all absorbed UV light peaking in the UVC range (<290 nm) and returning to baseline at about 300 nm (see Tables 11C and 11D). Based on the UV spectra and review of phototoxic/photoallergy data, terpene alcohols would not be expected to elicit phototoxicity or photoallergy under the current conditions of use as a fragrance ingredient.

4.11. Miscellaneous studies

Nerolidol showed no ability to bind to the rat uterine estrogen receptor (Blair et al., 2000). In a study to investigate the potential estrogenic activity of a number of essential oil constituents (Howes et al., 2002), estrogenic activity was detected for geraniol at high concentrations in a bioassay using recombinant yeast cells expressing the human estrogen receptor. Geraniol and nerol were able to displace [3H]17-β-estradiol from isolated α- and β-human estrogen receptors at concentrations in the order of 10^4 to 10^5 times higher than 17-β-estradiol. None of these compounds showed estrogenic or anti-estrogenic activity in the estrogen-responsive human cell line Ishikawa Var 1 at levels below their cytotoxic concentrations, and none showed activity in a yeast screen for androgenic and anti-androgenic activity.

In ovariectomized mice, transdermal citral and geraniol showed no ability to stimulate the estrogenic responses of uterine hyper-

Table 10-1D
Diagnostic patch test studies in humans/cyclic terpene alcohols

Material	Method	Concentration(s)	Subjects	Results	References
Hydroabietyl alcohol	Patch test	10% in petrolatum	1641 patients	21 positive reactions (1.3%)	Bruze (1986)
	Patch test	10% in petrolatum	1825 patients	17 positive reactions (0.9%)	De Groot et al. (2000)
	Patch test	10% in petrolatum	174 patients	No sensitization reactions	Kanerva et al. (1997)
	Patch test	10% in petrolatum	223 nurses with dermatoses	1 positive reaction (0.4%)	Kiec-Swierczynska and Krecisz (2000)
	Patch test	40% in petrolatum	182 dermatitis patients	5.3% positive reactions	Malten et al. (1983, 1984)
	Patch test	10% in petrolatum	2573 patients	38 positive reactions (1.5%)	Fregert and Gruvberger (1984)
	Patch test	not reported	128 patients	3 positive reactions (2.3%)	Trattner et al. (2002)
Menthol (unspecified isomer)	Patch test	1% in petrolatum	330 patients with leg ulcers or eczema	6.1% positive reactions	Blondeel et al. (1978)
	Patch test	5% in yellow paraffin	877 dermatitis patients	1.0% positive reactions (male 0.9%, females 1.1%)	Rudzki and Kleniewska (1971)
	Patch test	5% in yellow paraffin	1070 dermatitis patients	0.9% positive reactions	Rudzki and Kleniewska (1971)
	Patch test	5% in petrolatum	1200 patients with contact dermatitis	1 positive reaction (0.08%)	Santucci et al. (1987)
L-Menthol	Patch test	1% in petrolatum	220 dermatitis patients	2 positive reactions (0.9%)	JCDRG (1981)
	Patch test	5% in petrolatum	512 patients with intra-oral complaints	11 positive reactions (2.1%)	Morton et al. (1995)
4-Carvomenthenol	Patch test	5% in petrolatum	318 patients	No reactions	Paulsen and Andersen (2005)
Santalol	Patch test	10% in petrolatum	123 patients with facial dermatoses	7 positive reactions (5.7%)	Hayakawa et al. (1983)
	Patch test	1%, 2%, 10% in petrolatum	310, 305 and 306 patients with facial dermatoses	0.3%, 0.6%, 1.5% positive reactions at 1%, 2%, 10% in petrolatum, respectively	Sugai (1980)
	Patch test	2% in petrolatum	1244 patients	37 positive reactions (3%)	Sugai (1982)
	Patch test	1%, 2%, 10% in petrolatum	527 patients with facial dermatoses	0.6%, 0.6%, 1.5% positive reactions at 1%, 2%, 10% in petrolatum, respectively	Sugai (1984)
	Patch test	Not reported	716 patients	11 positive reactions (1.5%)	Sugai (1986)
	Patch test	5% in petrolatum	106 patients	1 positive reactions (0.9%)	Sugai (1996)
	Patch test	0.05–0.5% in cream base or EtOH (sample 1)	427 patients	15/427 (3.52%)	Takenaka et al. (1986)
	Patch test	0.05–0.5% in cream base or EtOH (sample 2)	214 patients	3/214 (1.41%)	Takenaka et al. (1986).
	Patch test	5% in petrolatum	178 fragrance sensitive patients	2 positive reactions (1.1%)	Larsen et al. (2001)
	Patch test	2% in petrolatum	3123 patients with cosmetic dermatitis	47 positive reactions (1.5%)	Utsumi et al. (1992)
	Patch test	2% in petrolatum	133 patients with cosmetic dermatitis	2 positive reactions (1.5%)	Nagareda et al. (1992)
	Patch test	2% in petrolatum	141 patients with cosmetic dermatitis	1 positive reaction (0.7%)	Nagareda et al. (1996)
	Patch test	2% in petrolatum	237 patients with cosmetic dermatitis	3 positive reactions (1.27%)	Hashimoto et al. (1990)
α-Santalol	Patch test	10% 2% 1% (α and β santalol in white petrolatum)	327 patients	5/327 (1.5%) 2/327 (0.6%) 2/327 (0.6%)	MJCDRG (1984)
Terpineol	Patch test	1% and 5% in petrolatum	100 patients	No sensitization reactions	Frosch et al. (1995)
Terpineol	Patch test	0.05–0.5% in base cream or 99% EtOH	312 subject	4 positives, 3 questionable reactions	De Groot et al. (1985)
Terpineol (mixed isomers)	Patch test	15% in petrolatum (together with 10% of terpinyl acetate)	179 patients with cosmetic allergy	No sensitization reactions	De Groot et al. (1985)
α-Terpineol	Patch test	5% in petrolatum	1606 patients with contact dermatitis	1/1606 positive reactions plus 11 questionable reaction	Frosch et al. (2002b)
	Patch test	5% in petrolatum	1200 patients with contact dermatitis	2 positive reactions (0.2%)	Santucci et al. (1987)

trophy or an acute increase in uterine vascular permeability. These results show that very high concentrations of some essential oil constituents appear to have the potential to interact with estrogen receptors, but the biological significance of this is uncertain. The causal relationship between the use of geraniol and gynaecomastia that has been implied by Abramovici and Sandbank (1988) therefore remains unclear.

Linalool, isopulegol and α-terpineol were evaluated for potential immunotoxicity *in vivo* and showed no suppression of antibody-forming cells or the primary antibody response (Gaworski et al., 1994; Vollmuth et al., 1989; Lorillard Research Center, 1982a).

4.12. Environmental toxicity

There are environmental data in the RIFM/FEMA Database for materials within the cyclic and non-cyclic terpene alcohols group. These include biodegradation, acute *Daphnia* and fish studies, and algal population growth inhibition data. Data are available for 30 materials. Overall, these materials appear to be readily biodegradable and their acute aquatic toxicities are typically >1 mg/L.

As several of these materials have both biogenic as well as other commercial sources, their identification in the environment

Table 10-2A
Skin sensitization studies in animals/non-cyclic terpene alcohols

Material	Method	Concentration(s)	Species	Results	References
Citronellol	Buehler test	Challenge: 25%, 7.5% and 2.5% (w/v) in diethyl phthalate (DEP)	Guinea pig (20 in test group, 10 in control group)	No reactions indicating a sensitization	RIFM (1992c)
	2.5%, 5%, 10%, 25% and 50% (w/v) in 1:3 EtOH:DEP	CBA mice	2.5%, 5%, 10%, 25%: No sensitization 50%: positive reaction		RIFM (2005b)
	MAX	Induction and challenge with 10% (vehicle not specified)	Guinea pig	No reactions	Ishihara et al. (1986)
L-Citronellol	Non-adjuvant test	Induction with 2.5% and 5% aqueous solutions (10 × 0.2 ml. occlusive patch), Challenge with 2.5% in water	Guinea pig (10 in test group)	No sensitization reactions (0/10)	RIFM (1973k)
	Non-adjuvant test	Induction with intradermal injection of a mixture containing 0.00005% L-citronellol and 6 other ingredients (including cinnamic alcohol) in cream, 10 times over 3 weeks, challenge by intradermal injection	Guinea pig	Sensitization in 3/8 (not assignable to L-citronellol)	RIFM (1962a)
	Bühler test	Induction with closed patch topical application of 25% in DEP for 6 h once a week for 3 weeks; challenge: 1%, 3%, 10% in DEP	Guinea pig (20 in test group, 10 in control group)	No sensitization reactions (0/20, 0/20, 0/20 at 1%, 3%, and 10% in DEP)	RIFM (1993a)
Dihydrogeraniol	MAX	Induction with 5% in olive oil (intradermal) and undiluted (percutaneous), challenge: 80% in olive oil	Guinea pig	No sensitization reactions (0/19)	RIFM (1985h)
Farnesol	LLNA	5, 10%, 25% in acetone:olive oil (4:1)	CBA/Ca Mouse	Potential sensitizer (EC3: 5.5)	RIFM (2004c)
	Modified FCA method	Challenge: 3%	Guinea pig (10)	Weak sensitizing capacity (mean response 0.10)	Hausen et al. (1992)
	MAX	25% in petrolatum	Guinea pig	No sensitization	RIFM (1995a)
	MAX	10% in petrolatum	Guinea pig	No sensitization	RIFM (1983c)
	MAX	Induction: 10% Challenge: 10%	Guinea pig	Moderate sensitizer (score 0.7)	Ishihara et al. (1986)
	OET	Challenge with 2%	Guinea pig (6–8/group)	No sensitization	Klecak (1985)
Geraniol	LLNA	Not reported	Not reported	No sensitization	Basketter and Kimber (1997)
	LLNA	25, 50% in 1:3 EtOH:DEP	CBA/Ca Mouse	Potential sensitizer (EC3: 11.4%)	RIFM (2003c)
	LLNA	Up to 50%	CBA/Ca Mouse	Inconclusive	RIFM (2003d)

	LLNA	30%, 50% in 3:1 EtOH:DEP	CBA/Ca Mouse	Sensitizing (EC3: 25.85%)	RIFM (2001c)
	LLNA	30%, 50% in 1:3 EtOH:DEP	CBA/Ca Mouse	Sensitizing (EC3: 20.43%)	RIFM (2001d)
	LLNA	30%, 50% in DEP	CBA/Ca Mouse	Sensitizing (EC3: 11.78%)	RIFM (2001e)
	LLNA	10%, 30%, 50% in EtOH	CBA/Ca Mouse	Sensitizing (EC3: 5.64%)	RIFM (2001f)
	Draize sensitization test	Challenge with 10%	Guinea pig	No sensitization	Klecak et al. (1977)
	Modified Draize test	0.05% injection challenge, 10% application challenge concentration	Guinea pig	No sensitization	Sharp (1978)
	OET	Induction undiluted, 30% and 10%, Challenge with 10%	Guinea pig (6–8/group)	Moderate sensitizer	RIFM (1977e)
	OET	Challenge with 3% and 10%	Guinea pig (6–8/group)	3%: no sensitization10%: sensitizing	Klecak et al. (1977)
	OET	Challenge with 6%	Guinea pig (6–8/group)	No sensitization	Klecak (1979)
	OET	Challenge with 2%	Guinea pig (6–8/group)	No sensitization	Klecak (1985)
	Buehler test	25%, 7.5%, 2.5% in DEP	Guinea pig	No sensitization (0/20)	RIFM (1992d)
	Modified Freund's complete adjuvant method	Not reported	Guinea pig	Weak sensitizer (mean response 0.6)	Hausen and Vieluf (1997)
	Freund's complete adjuvant test (FCAT)	Challenge with 10%	Guinea pig	Sensitizing	Klecak et al. (1977)
	MAX	Epidermal induction with 50%, challenge with 10% in 70% acetone/30% PEG 400 (3 tests) and acetone alone (4th test)	Guinea pig	Not sensitizing in first three tests, marginal sensitizer in the fourth test	RIFM (1989g)
	MAX	Challenge with 10%	Guinea pig	Sensitization	Klecak et al. (1977)
	MAX	Induction: 10%Challenge: 10%	Guinea pig	Moderate sensitizer (score 0.5)	Ishihara et al. (1986)
	MAX	Induction: 10%	Guinea pig	Sensitization observed	Ishihara, 1986
Hydroxycitronellol	Mouse Ear Swelling Test	50% in EtOH	Mouse	Sensitization in 20% of animals	Gad et al. (1986)
Linalool	LLNA	Undiluted and 0%, 25%, 50% in acetone: olive oil (4:1), purified linalool	CBA/Ca Mouse	Weak sensitizing capacity (EC3: 55%)	Basketter et al. (2002)
	LLNA	Undiluted and 0%, 25%, 50% in acetone:olive oil (4:1)	CBA/Ca Mouse	Weak sensitizing capacity (EC3: 30%)	Basketter et al. (2002, 2003)
	LLNA	Purified linalool in acetone: olive oil (4:1)	CBA/Ca Mouse	Weak sensitizing capacity(EC3: 46%)	Sköld et al. (2002a,b, 2004)
	LLNA	Auto-oxidized linalool in acetone:olive oil (4:1)	CBA/Ca Mouse	Sensitizing (EC3 between 1.6% and 9.4%)	Sköld et al. (2002a,b, 2004)
	Modified Draize test	0.05% injection challenge, 10% application challenge concentration (vehicle not specified)	Guinea pig	No reactions	Sharp (1978)
	OET	29% (vehicle not specified)	Guinea pig	No reactions	Klecak (1979)
	MAX	Induction and challenge with 10% (vehicle not specified)	Guinea pig	No reactions	Ishihara et al. (1986)
Nerol	Buehler test	25%, 7.5%, 2.5% in DEP	Guinea pig	No sensitization (0/20)	RIFM (1992e)
	OET	Challenge: 4%	Guinea pig	No sensitization	Klecak (1985)

(*continued on next page*)

Table 10-2A (*continued*)

Material	Method	Concentration(s)	Species	Results	References
Nerolidol	OET	Challenge: 4%	Guinea pig	No sensitization	Klecak (1979)
	Modified Draize method	Induction: 1%, Challenge: 1 and 20%	Guinea pig	No sensitization	Sharp (1978)
	Modified FCA method	Challenge: 3%	Guinea pig (10)	Weak sensitizing capacity (mean response 0.28)	Hausen et al. (1992)
Tetrahydrolinalool	MAX	Induction with 10% in Freund's complete adjuvant (intradermal and percutaneous), challenge: 5%, 10%, 20% and 40% in acetone	Guinea pig (5/group; 2/control group)	No sensitization was observed at 5% and 10%. At 20 and 40% reactions were observed in 1/5 and 3/5 animals, respectively	RIFM (1999b)

is not necessarily indicative of sources from fragrance compounds. For example, Helming et al. (1999a,b) identified borneol, terpineol and fenchyl alcohol as biogenic volatile organic compounds emitted naturally at three continental vegetative sites in the United States.

Hence if the results from materials studied to date are indicative of the group then there are no grounds for environmental concern with respect to cyclic and non-cyclic terpene alcohol compounds as currently used in fragrance compounds.

5. Summary

The materials assessed in this report have close structural relationships and similar biochemical and toxicity profiles. They generally participate in the same pathways of metabolic detoxication.

The terpene alcohols are dermally absorbed, and a significant amount can be retained briefly within the epidermis, dermis, and subcutaneous tissue. Some have a penetration enhancing effect *in vitro*.

Few data are available from which to characterize the oral bioavailability of the terpene alcohols. For the assessment of potential oral exposures, bioavailability is therefore assumed to be 100%.

Based on the data reviewed, the terpene alcohols are expected to undergo extensive conjugation and metabolism by well-characterized pathways, primarily in the liver, to form more polar compounds that are excreted mainly in the urine and to a lesser extent in the feces. They form generally innocuous end products: primary alcohols are metabolized to corresponding aldehydes and acids, and ultimately to CO_2, and secondary alcohols are conjugated with glucuronide and excreted. Unsaturated alcohols may undergo further oxidation at the point of unsaturation or be oxidized to the corresponding acid prior to conjugation and excretion in the urine. A few materials, however, may generate α,β-unsaturated metabolites or hydroperoxides.

The acute dermal toxicity of the terpene alcohols is very low, with LD_{50} values in rabbits reported to be greater than 2000 mg/kg body weight. The acute oral toxicity is likewise low with LD50 values generally greater than 1000 mg/kg body weight.

Dermal repeated dose toxicity studies have been conducted only with linalool and α-bisabolol and indicated, apart from local effects, a low magnitude of systemic toxicity with NOAELs of 250 and 200 mg/kg body weight/day, respectively. Slight effects on body weight and food consumption were observed at a dose level of 1000 mg/kg body weight/day.

The liver and kidneys were the only target organs affected in oral repeated dose toxicity studies. The magnitude of systemic toxicity is considered to be low with NOAELs generally greater than 50 mg/kg body weight/day. Hence, it can be assumed that efficient detoxication mechanisms are in place to prevent significant toxicity.

Terpene alcohols have been extensively tested in genotoxicity studies *in vitro*. Ames and other bacterial mutation data demonstrate no mutagenic activity of this group of compounds. A few positive results have been obtained in chromosome aberration studies *in vitro*, but these materials showed no evidence of genotoxicity *in vivo*. The relevance of the positive findings is, therefore, limited.

Reproductive and developmental toxicity data are limited but give no indication of a relevant adverse effect on reproductive function or the developing organism. NOAELs for maternal and developmental toxicity are far in excess of current human exposure levels and raise no safety concern.

At concentrations likely to be encountered by consumers, these chemicals are considered non-irritating to human skin. Their

Table 10-2B
Skin sensitization studies in animals/cyclic terpene alcohols

Material	Method	Concentration(s)	Species	Results	References
L-Carveol	Modified FCA test (closed challenge testing)	Induction: 3 intradermal injections with 5% carveol or carvone in olive oil; Challenge: 0.2%, 1.0%, 5.0% in olive oil (24 h occlusive patch)	Guinea pig (Dunkin-Hartley, female, 14/group)	No significant response (3/14 positive reactions); animals sensitized to carvone reacted when challenge tested with 5% carveol (probably due to oxidation of small amounts of carveol to carvone)	Karlberg et al. (1992)
4-Carvo-menthenol	OET	Induction and challenge: 5% (vehicle not specified)	Guinea pig (minimum of 6 animals)	No reactions	Klecak (1985)
Cedrol	OET	Induction and challenge: 8% (vehicle not specified)	Guinea pig (minimum of 6 animals)	No reactions	Klecak (1979, 1985)
	MAX	Induction: 10%Challenge: 10%	Guinea pig	No reactions	Ishihara et al. (1986)
Hydroabietyl alcohol	Modified FCA method	3 intradermal inductions, open topical challenge with 1%, 5%, and 10% in acetone	Guinea pig (10/group)	Sensitizing at all tested concentrations (mean response 1.21)	Hausen et al. (1989)
	OET	Induction and challenge: 10% (vehicle not specified)	Guinea pig (minimum of 6 animals)	No reactions	Klecak (1985)
Isopulegol	MAX	Induction: 10% in propylene glycol:acetone (1:1) Challenge: 5%, 10%, 20%, 40% in propylene glycol:acetone (1:1)	Guinea pig (5/group)	No reactions	RIFM (1994d)
	OET	Induction and challenge: 8% (vehicle not specified)	Guinea pig (minimum of 6 animals)	No reactions	Klecak (1985)
L-Menthol	MAX	Induction: 10% Challenge: 10%	Guinea pig	No reactions	Ishihara et al. (1986)
	Modified Draize test	0.1% injection challenge, 10% application challenge concentration	Guinea pig	Sensitizing after two sensitization treatments	Sharp (1978)
Myrtenol	Buehler test	Induction: undiluted Challenge: 10%, 3%, 1% in DEP	Guinea pig	1 positive reaction (1/19) at 10%, no reactions at 3% and 1%. No reactions at re-challenge with 10%	RIFM (1987d)
Santalol	MAX	Induction: 10% Challenge: 10%	Guinea pig	Mild sensitizer	Ishihara et al. (1986)
α-Santalol	OET	Induction: 20%, Challenge: 6% in EtOH, acetone, vaseline and/or other vehicle	Guinea pig (minimum of 6 animals)	No reactions	Klecak (1979)
	OET	Induction and challenge: 20% (vehicle not specified)	Guinea pig (minimum of 6 animals)	No reactions	Klecak (1985)
Terpineol	OET	Induction and challenge: 12% (vehicle not specified)	Guinea pig (minimum of 6 animals)	No reactions	Klecak (1979)
	MAX	Intradermal: 10% in CA, 10% w/v in Freund's/CA and saline (1:1) Topical: 10% in CA Challenge: 5%, 10%, 20%, 40% (acetone)	Guinea pig	No reactions	RIFM (1999f)
α-Terpineol	MAX	Induction: 10% Challenge: 10%	Guinea pig	No reactions	Ishihara et al. (1986)
	Modified FCA test (closed challenge testing)	Induction with Tea Tree Oil, Challenge: 10% α-terpineol	Guinea pig (n = 10)	No reaction at 24 (0/10) and 48 h (0/10)	Hausen et al. (1999)
cis-Verbenol[a]	Buehler test (modified)	Induction: 9 × topical treatment with 25% w/v in white mineral oil (occlusive) Challenge; 5% w/v in white mineral oil	Male Hartley guinea pig	No reactions	RIFM (1992a)
Vetiverol	MAX	Intradermal induction with 2%, topical induction with 25%, and challenge with 5% (in acetone/PEG 400)	Guinea pig	Weak sensitizer (3/10 animals positive)	RIFM (1984d)
	MAX	Intradermal induction with 2%, topical induction with 25%, and challenge with 5% (in acetone/PEG 400)	Guinea pig	Weak sensitizer (3/10 animals positive)	RIFM (1984g)
	OET	Induction and challenge: 8% (vehicle not specified)	Guinea pig (minimum 6 animals)	No reactions	Klecak (1985)
Geranodyle	Guinea pig MAX	75% geranodyle v/v in arachis oil BP	Guinea pigs	No sensitization	RIFM (1999g)
	Guinea pig MAX	Up to 40% in acetone	Guinea pigs	No sensitization	RIFM (1995d)

[a] This material is not one of the materials being reviewed as it is not used in fragrances, but it is included in this table because it is structurally related.

Table 11A
Phototoxicity and photoallergenicity/non-cyclic terpene alcohols

Material	Method	Concentration	Species	Results	References
Farnesol	0.5 ml daily for 2 weeks plus 320 nm UV exposure for 30 s	10% in petrolatum	Guinea pig	Not phototoxic	RIFM (1983d)
	Single application of 0.5 ml plus 320 nm UV exposure for 30 s; after resting time of 21 days the same treatment was repeated	10% in petrolatum	Guinea pig	No photoallergenicity	RIFM (1983e)
Geraniol	Photo patch test	5% in petrolatum	111 patients with cosmetic dermatitis	No reactions	Nagareda et al. (1992)
Tetrahydrolinalool	5 animals, UV irradiation at 320–400 nm for 70 minutes; observations at 24 and 48 h	5%, 10%, 30% and 50% in acetone	Guinea pig (Hartley; female)	5%, 10%, 30%: no phototoxicity 50%: dermal irritation in one animal (without UV irradiation)	RIFM (1999b)
Tetrahydromuguol	Semi-occlusive patch for 24 h, followed by irradiation for 12 minutes (150 W, 290–400 nm, covered by a UVB filter), readings at 24 and 48 h, 10 healthy adults	5.5%	Human	Not phototoxic	RIFM (1981c) and Weinberg and Springer (1981)

Table 11B
Phototoxicity and photoallergenicity/cyclic terpene alcohols

Material	Method	Concentration	Species	Results	References
α-Bisabolol	Photosensitization protocol with 5 animals/group, UV irradiation at 240–540 nm, positive control tetrachlorosalicylanilide	Induction with 3% and 15% (v/v) in EtOH + 15 min irradiation on 5 Days + 2 days with olive oil as vehicle, challenge with 3% and 15% in commercial soap solution	Guinea pig	Not a sensitizer after UV	BASF (1981) as cited in CIR (1999)
Isopulegol	5 animals/group, UV irradiation at 320–400 nm for 70 minutes with 14 J/cm^2; observations at 24 and 48 h	10%, 30%, 50% in propylene glycol:acetone (1:1)	Guinea pig	No reactions	RIFM (1994d)
Santalol	Photo patch test	2% in petrolatum	237 patients with cosmetic dermatitis	No reactions	Hashimoto et al. (1990)
	Photo patch test	2% in petrolatum	133 patients with cosmetic dermatitis	No reactions	Nagareda et al. (1992)
	Photo patch test	2% in petrolatum	141 patients with cosmetic dermatitis	No reactions	Nagareda et al. (1996)
	Photo patch test	1%, 2%, 10% in petrolatum	310, 305, 306 patients with facial dermatoses	No reactions	Sugai (1980)
	Photo patch test	5% in petrolatum	106 patients	No reactions	Sugai (1996)
Vetiverol	Phototoxicity test 15 J/cm^2 UVA for 72 minutes	3% in EtOH, 0.1 ml	Rat (10/group)	Not phototoxic	RIFM (1984f)
	Photoallergy test 10 J/cm^2 UVA	Induction (topical): 30% + UVA Challenge (topical) 10%, 1%, 0.1% ± UVA; vehicle: dimethylacetamide:acetone:EtOH (4:3:3)	Guinea pig, injected with FCA	At the highest challenge concentration 5/12 photoallergic after one course of induction treatment	RIFM (1984e)
Geranodyle	Phototoxicity	10% in 2% DMSO and EtOH	Guinea pigs	Non-phototoxic	RIFM (1985j)
	Phototoxicity	10%, 20% and 40% in acetone	Guinea pigs	Non-phototoxic	RIFM (1995d)
	Photoallergy	10% in EtOH	Guinea pigs	Non-phototoxic	RIFM (1985k)

potential for eye irritation under the present maximum use concentrations is considered minimal.

Cases of sensitization, mostly in dermatitis patients, have been reported for many of the assessed terpene alcohols. Due to their sensitizing effects, 6,7-dihydrogeraniol, hydroabietyl alcohol and isopropyl-2-decahydronaphthalenol have been prohibited for use in fragrance materials. Restrictions exist for farnesol, geraniol, citronellol and rhodinol (3,7-dimethyl-7-octen-1-ol). Sclareol and linalool must comply with specific purity criteria if used as fragrance materials. No test results were available for some materials. 2(10)-Pinen-3-ol and 2,6-dimethyloct-3,5-dien-2-ol do not have structural alerts for topical effects (Ford et al., 2000). Based on structural elements that indicate a potential for sensitization, 3,7-dimethyl-4,6-octadien-3-ol, should be regarded as a potential sensitizer until tested.

Based on the UV spectra and review of phototoxic/photoallergy data, terpene alcohols would not be expected to elicit phototoxicity or photoallergy under the current conditions of use as a fragrance ingredient.

Table 11C
Summary of UV spectra data – non-cyclic terpene alcohols

Material	UV spectra range of absorption (nm)
Citronellol	Peaked at 220–230 nm
Dehydrolinalool	Peaked at 200–210 nm
3,7-Dimethyl-1-octanol	Peaked at 200–210 nm
Farnesol	Peaked at 220–230 nm
Geraniol	Peaked at 220–230 nm
Geranyl dihydrolinalool[a]	Peaked at 200–220
Hydroxycitronellol	Peaked at 220–230
Linalool	Peaked at 220–250
Myrcenol	Peaked at 200–230 nm
Nerol	Peaked at 220–240 nm
Nerolidol (isomer unspecified)	Peaked at 220–250 nm
Rhodinol	Peaked at 220–230 nm
Tetrahydrolinalool	Peaked at 220 nm
Tetrahydromuguol	Peaked at 210–230 nm

[a] This material is not one of the materials being reviewed as it is not used in fragrances, but it is included in this table because it is structurally related.

Table 11D
Summary of UV spectra data – cyclic terpene alcohols

Material	UV spectra range of absorption (nm)
Borneol	Peaked at 220–230 nm
1-Borneol	Peaked at 200–220 nm
laevo-Carveol	Peaked at 210–220 nm
4-Carvonmenthenol	Peaked at 220–230
Cedrenol	Peaked at 210–220 nm
Cedrol	Peaked at 220–240 nm
Dihydro-α-terpineol	Peaked at 220 nm
Fenchyl alcohol	Peaked at 220–240 nm
Geranodyle	Peaked at 210–220 nm
Isoborneol	Peaked at 220 nm
Isopulegol	Peaked at 220 nm
p-Mentha-1,8-dien-7-ol (*iso*-Carveol)	Peaked at 200–220 nm
cis-*p*-Menthan-7-ol	Peaked at 220–230 nm
p-Menth-1-en-8-ol (*S*)	Peaked at 200 nm
Menthol	Peaked at 220 nm
Terpineol	Peaked at 220 nm
α-Terpineol	Peaked at 200–220 nm
4-Thujanol	Peaked at 205–210 nm
Vetiverol	Peaked at 220–230 nm

6. Conclusion

The Panel is of the opinion that *there are safety concerns* with respect to sensitization by the following members of the group:

- 6,7-Dihydrogeraniol, hydroabietyl alcohol and 6-isopropyl-2-decahydro-naphthalenol are potent skin sensitizers. These materials are prohibited for use in fragrance materials by IFRA Standards.
- Farnesol is a weak sensitizer. Its use in fragrance materials is therefore restricted by IFRA Standards.
- Sclareol and linalool may contain impurities and/or oxidation products that are strong sensitizers. For use in fragrance materials, these compounds must comply with the purity criteria stated in their IFRA Standards.
- No sensitization test results were available for 2(10)-pinen-3-ol, 2,6-dimethyloct-3,5-dien-2-ol, and 3,7-dimethyl-4,6-octadien-3-ol. These materials should be regarded as potential sensitizers until tested.

There are *no safety concerns regarding the remaining materials* in this group under the present declared levels of use and exposure for the following reasons:

- The non-cyclic and cyclic terpene alcohols have a low order of acute toxicity.
- No significant toxicity was observed in repeated dose toxicity tests; it is concluded that these materials have dermal and oral NOAELs of 50 mg/kg body weight/day or greater.
- These materials were inactive in mutagenicity and genotoxicity tests.
- Based on data on metabolism it is concluded that members of this category exhibit similar chemical and biochemical fate. Although there is some indication for the production of reactive metabolites by some materials, these metabolites appear to be efficiently detoxicated and not expected to result in overt toxicity. There is no indication for the production of persistent metabolites.
- The results from materials studied to date are indicative of the group and there are no grounds for environmental concern with respect to cyclic and non-cyclic terpene alcohol compounds as currently used in fragrance compounds.
- Human dermatological studies show that, at current use levels, these materials are practically non-irritating.
- The sensitization potential is generally low.
- The margin of safety is generally greater than 100 times the maximum daily exposure.

Conflict of interest statement

This research was supported by the Research Institute for Fragrance Materials, an independent research institute that is funded by the manufacturers of fragrances and consumer products containing fragrances. The authors are all members of the Expert Panel of the Research Institute for Fragrance Materials, an independent group of experts who evaluate the safety of fragrance materials.

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