Food and Chemical Toxicology 48 (2010) S1–S42

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Review

A safety assessment of non-cyclic alcohols with unsaturated branched chain when used as fragrance ingredients ☆
The RIFM expert panel

D. Belsito [a], D. Bickers [b], M. Bruze [c], P. Calow [d], H. Greim [e], J.M. Hanifin [f], A.E. Rogers [g], J.H. Saurat [h], I.G. Sipes [i], H. Tagami [j]

[a] University of Missouri (Kansas City), c/o American Dermatology Associates, LLC, 6333 Long Avenue, Third Floor, Shawnee, KS 66216, USA
[b] Columbia University Medical Center, Department of Dermatology, 161 Fort Washington Avenue, New York, NY 10032, USA
[c] Malmo University Hospital, Department of Occupational and Environmental Dermatology, Sodra Forstadsgatan 101, Entrance 47, Malmo SE-20502, Sweden
[d] Roskilde University, Isafjordvej 66, Roskilde, DK 4000, Denmark
[e] Technical University of Munich, Institute for Toxicology and Environmental Hygiene, Hohenbachernstrasse 15-17, Freising-Weihenstephan D-85354, Germany
[f] Oregon Health Sciences University, Department of Dermatology, Mail Code CH16D, 3303 SW Bond Avenue, Portland, Oregon 97239-4501, USA
[g] Boston University School of Medicine, Department of Pathology and Laboratory Medicine, 715 Albany Street, L-804, Boston, MA 02118-2526, USA
[h] Hospital Cantonal Universitaire, Clinique et Policlinique de Dermatologie, 24, Rue Micheli-du-Crest, Geneve 14 1211, Switzerland
[i] Department of Pharmacology, University of Arizona, College of Medicine, 1501 North Campbell Avenue, P.O. Box 245050, Tucson, AZ 85724-5050, USA
[j] 3-27-1 Kaigamori, Aoba-ku, Sendai 981-0942, Japan

Contents

☆ All correspondence should be addressed to: A.M. Api, 50 Tice Boulevard, Woodcliff Lake, NJ 07677, USA. Tel.: +1 201 689 8089; fax: +1 201 689 8090.
E-mail address: amapi@rifm.org.

0278-6915/$ - see front matter
doi:10.1016/j.fct.2009.11.007

1. Chemical identity, regulatory status, and exposure

This report summarizes chemical and toxicological data relevant to the risk assessment of the use of some branched chain unsaturated non-cyclic alcohols as fragrance ingredients.

1.1. Rationale for grouping alcohols with unsaturated branched chain

The group consists of eight primary, nine primary allylic, four secondary, one secondary allylic, five tertiary and 15 tertiary allylic non-cyclic alcohols. The names and structures of the materials reviewed are shown in Table 1. Their common characteristic structural elements are one hydroxyl group per molecule, a C_4 to C_{16} carbon chain with one or several methyl or ethyl side chains and up to four non-conjugated double bonds. Of these materials, 24 have been previously reviewed in RIFM's Safety Assessment on Terpene Alcohols (Belsito et al., 2008). These substances are identified in Table 1. In addition, several non-cyclic branched chain alcohols used as examples here have been reviewed in other recent RIFM publications. Information on previously reviewed substances of this group is not presented again unless it is new or required to evaluate remaining fragrance ingredients.

Two members contain all the structural features listed above but do not contain a branched side chain ((2E,6Z)-nona-2,6-dien-1-ol, (Z)-2-penten-1-ol). It has been shown in the perfused rat liver that branching does not consistently alter the hepatotoxicity of C3 and C4-alcohols (of the alcohols under review 3-methyl-2-buten-1-ol and its unbranched homologue 2-buten-1-ol were tested, and the hepatotoxicity of both compounds was similar), which is evaluated as one of the critical effects (Strubelt et al., 1999; RIFM, 2002c). Therefore, both straight-chain alcohols ((2E,6Z)-nona-2,6-dien-1-ol, (Z)-2-penten-1-ol) can be evaluated together with branched chain alcohols. One member of the group, dihydromyrcenol, is a 1:1 mixture of the branched chain alcohol 2,6-dimethyl-7-octen-2-ol and its formate. It is an isomer of 7-octen-2-ol, 2-methyl-6-methylene-, dihydro derivative, which is also under review. Although studies on the metabolism of dihydromyrcenol are lacking, it is known that esters like formates are metabolized to the corresponding alcohol and formic acid (JECFA, 1998). Once taken up by the body, the formate of 2,6-dimethyl-7-octen-2-ol will be metabolized to 2,6-dimethyl-7-octen-2-ol and formic acid. Therefore, this mixture can be evaluated together with branched chain alcohols.

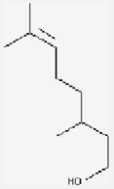
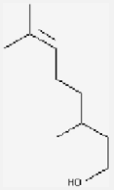
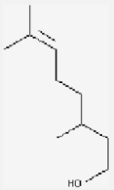
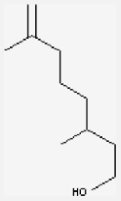
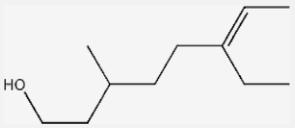
Due to their structural similarity, these alcohols also share common metabolic pathways (see below). As metabolism is crucial for toxicokinetics and toxicity, these alcohols are expected to have the same target organs (liver and kidney) as was shown for selected compounds. As the data base for these alcohols is limited, additional data on pharmacokinetics, metabolism, genotoxicity and systemic toxicity of the structurally related non-cyclic unsaturated branched alcohols, citronellol, dehydrolinalool, 6,7-dihydrolinalool, farnesol, geraniol, linalool, nerol, and nerolidol (cis and isomer unspecified), from an evaluation of terpene alcohols (Belsito et al., 2008) have been used.

Data for citronellol, geraniol, linalool, 3-methyl-2-buten-1-ol, nerol and phytol show that the alcohols share common metabolic pathways (see Section 3). The major pathways of metabolism and fate are:

- conjugation of the alcohol group with glucuronic acid,
- oxidation of the alcohol group,
- side-chain oxidation yielding polar metabolites, which may be conjugated and excreted or undergo further oxidation to an aldehyde, a carboxylic acid, and CO_2,
- hydrogenation of the double bonds,
- excretion of the unchanged parent compound.

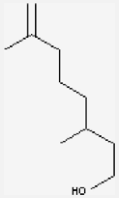
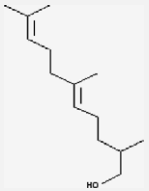
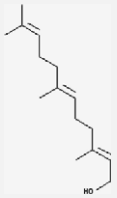
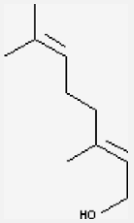
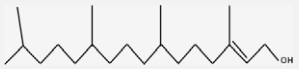
In most cases, metabolism yields innocuous metabolites. Some materials, however, may generate alpha, beta-unsaturated compounds, e.g. aldehydes formed from primary allylic alcohols, or un-

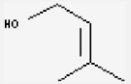
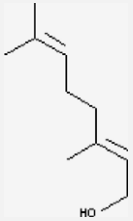
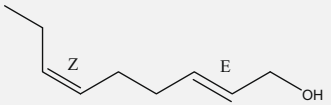
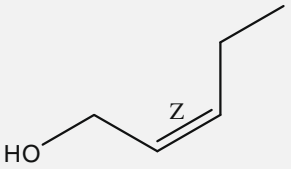
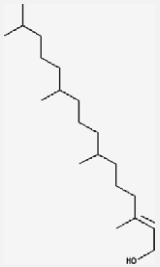
Table 1
Material identification, summary of volume of use, and dermal exposure.

Material	Synonyms	Structure	Worldwide metric tons[a]	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level[b]
Subgroup: primary					
***dl*-Citronellol**[c]					
$C_{10}H_{20}O$					
CAS# 106-22-9	• Citronellol		>1000	0.13	8.2
LogK_{ow}: 3.1 at 35 °C	• 3,7-Dimethyl-6-octen-1-ol				
Molecular weight: 156.27	• 6-Octen-1-ol, 3,7-dimethyl-				
Vapor pressure: 0.009 mm Hg at 20 °C[e]					
Water solubility: 105.5 mg/l at 25 °C[e]					
***l*-Citronellol**[c]					
$C_{10}H_{20}O$					
CAS# 7540-51-4	• (-)-3,7-Dimethyloct-6-en-1-ol		10–100	0.07	1.4
Henry's law: 0.0000568 atm m^3/mol at 25 °C[e]	• (S)-3,7-Dimethyl-6-octen-1-ol				
LogK_{ow}: 3.56[e]	• 6-Octen-1-ol, 3,7-dimethyl-, (S)-				
Molecular weight: 156.27					
Vapor pressure: 0.01 mm Hg at 20 °C[e]					
Water solubility: 105.5 mg/l at 25 °C[e]					
(+)-(R)-Citronellol[c]					
$C_{10}H_{20}O$					
CAS# 1117-61-9	• (+)-beta-Citronellol		10–100	0.0005[f]	0.02
Henry's law: 0.0000568 atm m^3/mol at 25 °C[e]	• (R)-3,7-Dimethyloct-6-en-1-ol				
LogK_{ow}: 3.56 [e]	• 6-Octen-1-ol, 3,7-dimethyl-, (R)-				
Molecular weight: 156.27					
Vapor pressure: 2.88 mm Hg at 25 °C[e]					
Water solubility: 105.5 mg/l at 25 °C [e]					
3,7-Dimethyloct-7-en-1-ol[c]					
$C_{10}H_{20}O$					
CAS# 141-25-3	• alpha-Citronellol		1–10	0.04	0.8
Henry's law: 0.0000481 atm m^3/mol at 25 °C[e]	• 7-Octen-1-ol, 3,7-dimethyl- (isomer unspecified)				
LogK_{ow} 3.63[e]					
Molecular weight: 156.69					
Vapor pressure: 0.000262 mm Hg at 25 °C[e]					
Water solubility: 181.5 mg/l at 25 °C[e]					
6-Ethyl-3-methyloct-6-en-1-ol					
$C_{11}H_{22}O$					
	• 6-Ethyl-3-methyloct-6-ene-1-ol				
	• 6-Ethyl-3-methyl-6-octen-1-ol				
CAS# 26330-65-4	• 3-Methyl-6-ethyl-6-octen-1-ol		1–10	0.0005[f]	0.02
Molecular weight 170.29	• 6-Octen-1-ol, 6-ethyl-3-methyl-				

(*continued on next page*)

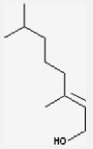
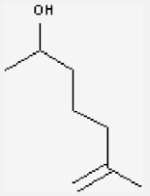
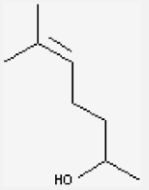
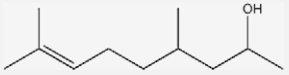
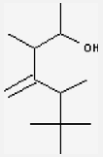
Table 1 (*continued*)

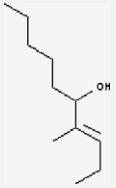
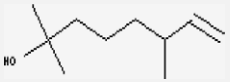
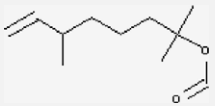
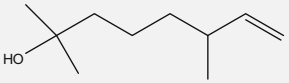
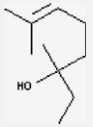
Material	Synonyms	Structure	Worldwide metric tons[a]	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level[b]
Rhodinol[c] $C_{10}H_{20}O$ CAS# 6812-78-8 Henry's law: 0.0000481 atm m^3/mol at 25 °C[e] Log K_{ow} 3.63 [e] Molecular weight: 156.69 Vapor pressure: 0.009 mm Hg at 20 °C[e] Water solubility: 181.5 mg/l at 25 °C[e]	• 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
2,6,10-Trimethylundeca-5,9-dienol $C_{14}H_{26}O$ CAS# 24048-14-4 Henry's law: 0.000183 atm m^3/mol 25 °C[e] Log K_{ow} 5.36 [e] Molecular weight: 210.61 Vapor pressure: 0.000176 mm Hg at 25 °C[e] Water solubility: 3.306 mg/l at 25 °C[e]	• Dihydroapofarnesol • 5,9-Undecadien-1-ol, 2,6,10-trimethyl-		0.01–0.1	0.02	0.04
Subgroup: primary allylic **Farnesol**[c] $C_{15}H_{26}O$ CAS# 4602-84-0 Henry's law: 0.000252 atm m^3/mol 25 °C[e] Log K_{ow}: 5.77[e] Molecular weight: 222.37 Vapor pressure: <0.001 mm Hg at 20 °C[e] Water solubility: 1.287 mg/l at 25 °C[e]	• 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
Geraniol[c] $C_{10}H_{18}O$ CAS# 106-24-1 Log K_{ow}: 3.47[e] Molecular weight: 154.25 Vapor pressure: 0.02 mm Hg at 20 °C[e] Water solubility: 255.8 mg/l at 25 °C[e]	• 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	5.3[d]
2-Hexadecen-1-ol, 3,7,11,15-tetramethyl- $C_{20}H_{40}O$ CAS# 7541-49-3 Log K_{ow} 8.32[e] Molecular weight: 296.54 Vapor pressure: 0.000000524 mm Hg 25 °C[e]	• 3,7,11,15-Tetramethyl-2-hexadecen-1-ol		<0.01	0.03	0.05

3-Methyl-2-buten-1-ol $C_5H_{10}O$ CAS# 556-82-1 Henry's law: 0.0000138 atm m3/mol 25 °C[e] Log K_{ow} 1.17[e] Molecular weight: 86.13 Vapor pressure: 1.4 mm Hg at 20 °C[e] Water solubility: 40940 mg/l at 25 °C[e]	• 2-Buten-1-ol, 3-methyl- • Prenol		1–10	0.0005	0.01
Nerol[c] $C_{10}H_{18}O$ CAS# 106-25-2 Henry's law: 0.0000589 atm m^3/mol 25 °C[e] Log K_{ow}: 3.47[e] Molecular weight: 154.25 Vapor pressure: 0.0159 mm Hg at 25 °C[e] Water solubility: 255.8 mg/l at 25 °C[e]	• 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
(2E,6Z)-Nona-2,6-dien-1-ol $C_9H_{16}O$ CAS# 28069-72-9 Log K_{ow} 2.87[e] Henry's law: 0.0000319 atm m^3/mol 25 °C[e] Molecular weight: 140.26 Vapor pressure: 0.0105 mm at Hg 25 °C[e] Water solubility: 963.8 mg/l at 25 °C[e]	• 2,6-Nonadien-1-ol, (E,Z)- • 2-trans-6-cis-Nonadien-1-ol		0.1–1	0.0003	0.05
(Z)-2-Penten-1-ol $C_5H_{10}O$ CAS# 1576-95-0 Henry's law: 0.0000117 atm m^3/mol 25 °C[e] Log K_{ow} 1.12[e] Molecular weight: 86.34 Vapor pressure: 0.0023 mm at Hg 25 °C[e] Water solubility: 45720 mg/l at 25 °C[e]	• 2-Penten-1-ol, (Z)- • cis-Pent-2-en-1-ol		0.001–0.01	0.0005[f]	0.02
Phytol $C_{20}H_{40}O$ CAS# 150-86-7 Henry's law: 0.000965 atm m^3/mol 25 °C[e] Log K_{ow} 8.32[e] Molecular weight: 296.54 Vapor pressure: <0.001 mm Hg 20 °C Water solubility: 0.00327 mg/l at 25 °C[e]	• 2-Hexadecen-1-ol, 3,7,11,15-tetramethyl-,[R-[R*,R*-(E)]]- • [R-[R*,R*-(E)]]-3,7,11,15-Tetramethyl- 2-hexadecen-1-ol		0.1–1	0.01	0.2

(*continued on next page*)

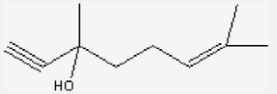
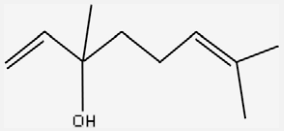
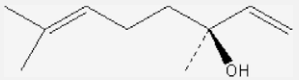
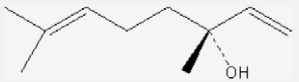
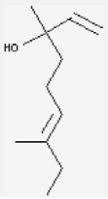
Table 1 (*continued*)

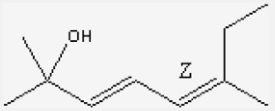
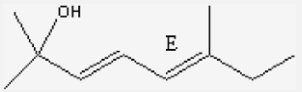
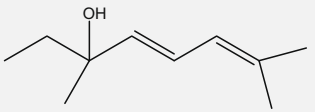
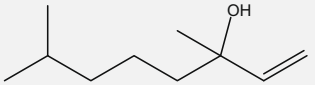
Material	Synonyms	Structure	Worldwide metric tons[a]	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level[b]
Tetrahydromuguol[c] $C_{10}H_{20}O$ CAS# 41678-36-8 Henry's law: 0.0000568 atm m^3/mol 25 °C[e] LogK_{ow} 3.56[e] Molecular weight: 156.27 Vapor pressure: 4.28 mm Hg at 25 °C[e] Water solubility: 211.8 mg/l at 25 °C[e]	• 3,7 & 2,6-Dimethyl-2-octenol • 3,7-Dimethylocten-2-ol • Tetrahydro allo-ocimenol		1–10	0.0005[f]	0.02
Subgroup: secondary					
Methylheptenol $C_8H_{16}O$ CAS# 1335-09-7 Henry's law: 0.0000273 atm m^3/mol 25 °C[e] LogK_{ow} 2.65[e] Molecular weight: 128.22 Vapor pressure: 0.0608 mm at Hg 25 °C[e] Water solubility: 1644 mg/l at 25 °C[e]	• Heptenol, methyl- • Methylheptenol		0.01–0.1	0.0005[f]	0.02
2-Methyl-2-hepten-6-ol $C_8H_{16}O$ CAS# 1569-60-4 Henry's law: 0.0000322 atm m^3/mol 25 °C[e] LogK_{ow} 2.57[e] Molecular weight: 128.15 Vapor pressure: 0.352 mm Hg at 25 °C[e] Water solubility: 1919 mg/l at 25 °C[e]	• 5-Hepten-2-ol, 6-methyl- • 6-Hydroxy-2-methyl-2-heptene • 6-Methylhept-5-en-2-ol		0.01–0.1	0.001	0.01
7-Nonen-2-ol, 4,8-dimethyl- $C_{11}H_{22}O$ CAS# 40596-76-7 Molecular weight: 170.3	• 4,8-Dimethylnon-7-en-2-ol • Homocitronellol		0.01–0.1	0.0005[f]	0.02
3,5,6,6-Tetramethyl-4-methyleneheptan-2-ol $C_{12}H_{24}O_4$ CAS# 81787-06-6 Henry's law: 0.0000847 atm m^3/mol 25 °C[e] LogK_{ow} 4.36[e] Molecular weight: 232.2 Vapor pressure: 0.038 mm Hg at 25 °C[e] Water solubility: 32.21 mg/l at 25 °C[e]	• 2-Heptanol, 3,5,6,6-tetramethyl-4-methylene-		0.01–0.1	0.0005[f]	0.02
Subgroup: secondary allylic					

4-Methyl-3-decen-5-ol $C_{11}H_{22}O$ CAS# 81782-77-6 Henry's law: 0.0000753 atm m^3/mol 25 °C[e] LogK_{ow}: 3.9 at 30 °C[e] Molecular weight: 170.96 Vapor pressure: 0.00595 mm at Hg 25 °C[e] Water solubility: 69.47 mg/l at 25 °C[e]	• 3-Decen-5-ol,4-methyl- • Undecavertol		100–1000	0.04	1.5
Subgroup: tertiary **Dihydromyrcenol** $C_{10}H_{20}O$ CAS# 18479-58-8 Henry's law: 0.0000407 atm m^3/mol 25 °C[e] LogK_{ow}: 3.0 at 30 °C Molecular weight: 156.27 Vapor pressure: 0.09 mm Hg at 20 °C[e] Water solubility: 252.2 mg/l at 25 °C[e]	• Dimyrcetol • 3,7-Dimethyl-1-octen-7-ol • 7-Octen-2-ol, 2,6-dimethyl-	 	>1000	0.33	6.8
7-Octen-2-ol, 2-methyl-6-methylene-, dihydro derivative $C_{10}H_{20}O$ CAS# 53219-21-9 Henry's law: 0.0000481 atm m^3/mol 25 °C[e] LogK_{ow}: 3.6[e] Molecular weight: 156.27 Vapor pressure: 0.2270 torr Water solubility: 869 mg/l (24 h & 72 h stirring)	• 2-Methyl-6-methyleneoct-7-en-2-ol,dihydro derivative; • 7-Octen-2-ol, 2-methyl-6-methylene-, dihydro deriv		100–1000	0.49	6.8
3,7-Dimethyloct-6-en-3-ol[c] $C_{10}H_{20}O$ CAS# 18479-51-1 Henry's law: 0.0000568 atm m^3/mol 25 °C[e] LogK_{ow} 3.52[e] Molecular weight: 156.69 Vapor pressure: 0.0528 mm Hg at 25 °C[e] Water solubility: 228.1 mg/l at 25 °C[e]	• 1,2-Dihydrolinalool • 6-Octen-3-ol, 3,7-dimethyl-		1–10	0.01	0.14
Myrcenol[c] $C_{10}H_{18}O$ CAS# 543-39-5 Henry's law: 0.0000292 atm m^3/mol 25 °C[e] LogK_{ow} 3.46[e] Molecular weight: 154.25 Vapor pressure: 0.05 mm Hg at 20 °C[e] Water solubility: 260.9 mg/l at 25 °C[e]	• 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-ol		1–10	0.0005[f]	0.02

(*continued on next page*)

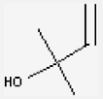
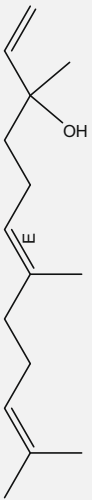
Table 1 (*continued*)

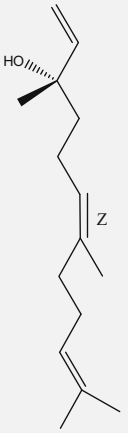
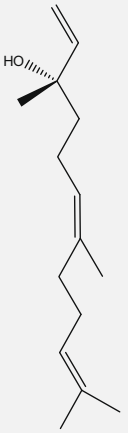
Material	Synonyms	Structure	Worldwide metric tons[a]	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level[b]
Ocimenol[c] $C_{10}H_{18}O$ CAS# 5986-38-9 Henry's law: 0.0000344 atm m^3/mol 25 °C[e] Log K_{ow} 3.38[e] Molecular weight: 154.25 Vapor pressure: 0.0117 mm Hg at 25 °C[e] Water solubility: 304.5 mg/l at 25 °C[e]	• 2,6-Dimethyl-5,7-octadien-2-ol • 5,7-Octadien-2-ol, 2,6-dimethyl-		0.01–0.1	0.0005[f]	0.02
Subgroup: tertiary allylic **Dehydrolinalool**[c] $C_{10}H_{16}O$ CAS# 29171-20-8 Log K_{ow}: 2.75[e] Molecular weight: 152.24 Vapor pressure: 0.1 mbar at 20 °C Water solubility: 2.45 g/l at 20 °C	• Dehydro-beta-linalool; • 3,7-Dimethyloct-6-en-1-yn-3-ol; • Linalool, dehydro-; • beta-Linalool, dehydro-; • 6-Octen-1-yn-3-ol, 3,7-dimethyl-		<0.01	0.0005[f]	0.02
Linalool[c] $C_{10}H_{18}O$ CAS# 78-70-6 Log K_{ow}: Log Pow = 2.9 Molecular weight: 154.25 Vapor pressure: 0.5027 torr; 0.2 mbar at 20 °C Water solubility: 1.45 g/l at 20 C	• Coriandrol; • 2,6-Dimethyl-2,7-octadien-6-ol; • 3,7-Dimethyl-1,6-octadien-3-ol; • 3,7-Dimethylocta-1,6-dien-3-ol; • Licareol; • Linalol; • Linalyl alcohol; • 1,6-Octadien-3-ol, 3,7-dimethyl-; • 2,7-Octadien-6-ol, 2,6-dimethyl-; • Petinerol		>1000	0.32	4.3
***d*-Linalool**[c] $C_{10}H_{18}O$ CAS# 126-90-9 Henry's law: 0.0000423 atm m^3/mol 25 °C[e] Log K_{ow}: 3.38[e] Molecular weight: 154.25 Vapor pressure: 0.00498 mm Hg at 25 °C[e] Water solubility: 683.7 mg/l at 25 °C[e]	• (S)-3,7-Dimethyl-1,6-octadien-3-ol • 3,7-Dimethylocta-1,6-dien-3-ol • 1,6-Octadien-3-ol, 3,7-dimethyl-, (S)-		<0.01	0.05	0.13
***l*-Linalool**[c] $C_{10}H_{18}O$ CAS# 126-91-0 Henry's law: 0.0000423 atm m^3/mol 25 °C[e] Log K_{ow}: 3.38[e] Molecular weight: 154.25 Vapor pressure: 0.00826 mm Hg at 25 °C[e] Water solubility: 683.7 mg/l at 25 °C[e]	• (R)-3,7-Dimethyl-1,6-octadien-3-ol • 3,7-Dimethylocta-1,6-dien-3-ol • 1,6-Octadien-3-ol, 3,7-dimethyl-, (R)-		10–100	0.07	0.31
3,7-Dimethyl-1,6-nonadien-3-ol $C_{11}H_{20}O$ CAS# 10339-55-6 Henry's law: 0.0000561 atm m^3/mol 25 °C[e] Log K_{ow}: 3.2 at 35 °C (cis isomer); 3.3 at 35 °C (trans isomer) Molecular weight: 168.28 Vapor pressure: 0.0177 mm Hg at 25 °C[e] Water solubility: 99.98 mg/l at 25 °C[e]	• Ethyl linalool • 1,6-Nonadien-3-ol, 3,7-dimethyl-		100–1000	0.18	3.6

(5Z)-2,6-Dimethylocta-3,5-dien-2-ol[c] $C_{10}H_{18}O$ CAS# 18675-16-6 Henry's law: 0.0000407 atm m^3/mol 25 °C[e] Log K_{ow} 3.3[e] Molecular weight: 154.53 Vapor pressure: 0.0366 mm Hg at25 °C[e] Water solubility: 355.4 mg/l at 25 °C[e]	• Muguol • 3,5-Octadien-2-ol, 2,6-dimethyl-, (5Z)-		0.1–1	0.0005[f]	0.02
(5E)-2,6-Dimethyl-3,5-octadien-2-ol[c] $C_{10}H_{18}O$ CAS# 18675-17-7 Henry's law: 0.0000407 atm m^3/mol 25 °C[e] Log K_{ow} 3.3[e] Molecular weight: 154.53 Vapor pressure: 0.0366 mm Hg at 25 °C[e] Water solubility: 355.4 mg/l at 25 °C[e]	• 3,5-Octadien-2-ol, 2,6-dimethyl-, (E,E)-		0.1–1	0.0005[f]	0.02
3,7-Dimethyl-4,6-octadien-3-ol[c] $C_{10}H_{18}O$ CAS# 18479-54-4 Henry's law: 0.0000407 atm m^3/mol 25 °C[e] Log K_{ow}:3.3[e] Molecular weight: 154.53 Vapor pressure: 0.0366 mm Hg at 25 °C[e] Water solubility: 355.4 mg/l at 25 °C[e]	• 4,6-Octadien-3-ol, 3,7-dimethyl		0.1–1	0.09	0.67
3,7-Dimethyloct-1-en-3-ol[c] $C_{10}H_{20}O$ CAS# 18479-49-7 Henry's law: 0.0000407 atm m^3/mol 25 °C[e] Log K_{ow}:3.47[e] Molecular weight: 156.69 Vapor pressure: 0.124 mm Hg at 25 °C[e] Water solubility: 252.2 mg/l at 25 °C[e]	• 6,7-Dihydrolinalool • 1-Octen-3-ol, 3,7-dimethyl-		10–100	0.0005[f]	0.02
Geranyl linalool[c] $C_{20}H_{34}O$ CAS# 1113-21-9 Henry's law: 0.000775 atm m^3/mol 25 °C[e] Log K_{ow} 7.97[e] Molecular weight: 276.47 Vapor pressure: 0.0000176 mm Hg at 25 °C[e] Water solubility: 0.006982 mg/l at 25 °C[e]	• 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		0.01–0.1	0.001	0.01

(*continued on next page*)

Table 1 (*continued*)

Material	Synonyms	Structure	Worldwide metric tons[a]	Dermal systemic exposure in cosmetic products (mg/kg/day)	Maximum skin level[b]
Isophytol $C_{20}H_{40}O$ CAS# 505-32-8 Henry's law: 0.000692 atm m^3/mol 25 °C[e] Log K_{ow}: 8.23[e] Molecular weight: 296.54 Vapor pressure: <0.001 mm Hg 20 °C Water solubility: 0.003893 mg/l at 25 °C[e]	• 1-Hexadecen-3-ol,3,7,11,15-tetramethyl- • 3,7,11,15-Tetramethyl-1-hexadecen-3-ol		1–10	0.01	0.44
2-Methyl-3-buten-2-ol $C_5H_{10}O$ CAS# 115-18-4 Henry's law: 0.00000988 atm m^3/mol 25 °C[e] Log K_{ow}: 1.08[e] Molecular weight: 86.13 Vapor pressure: 23.4 mm Hg at 25 °C[e] Water solubility: 48740 mg/l at 25 °C[e]	• 3-Buten-2-ol, 2-methyl- • 1,1,-Dimethyl-2-propenol		0.01–0.1	0.0005[f]	0.02
(E)-Nerolidol $C_{15}H_{26}O$ CAS# 40716-66-3 Henry's law: 0.000181 atm m^3/mol 25 °C[e] Log K_{ow} 5.68[e] Molecular weight: 222.72 Vapor pressure: 0.0000158 mm Hg 25 °C[e] Water solubility: 1.532 mg/l at 25 °C[e]	• 1,6,10-Dodecatrien-3-ol, 3,7,11-trimethyl-, (E)- • trans-Nerolidol • (E)-3,7,11-Trimethyldodeca-1,6,10- trien-3-ol		0.01–0.1	0.0005[f]	0.02

Nerolidol (*cis*)[c] $C_{15}H_{26}O$ CAS# 142-50-7 Henry's law: 0.000181 atm m^3/mol 25 °C[e] LogK_{ow} 5.68[e] Molecular weight: 222.72 Vapor pressure: 0.0000158 mm Hg at 25 °C[e] Water solubility: 1.532 mg/l at 25 °C[e]	• 1,6,10-Dodecatrien-3-ol, 3,7,11-trimethyl-, [S-(Z)]- • (+)-cis-Nerolidol • d-Nerolidol		0.01–0.1	0.01	0.02
Nerolidol (isomer unspecified)[c] $C_{15}H_{26}O$ CAS# 7212-44-4 Henry's law: 0.000181 atm m^3/mol 25 °C[e] LogK_{ow} 5.0 at 35 °C Molecular weight: 222.72 Vapor pressure: 0.1 mm Hg 20 °C[e] Water solubility: 1.532 mg/l at 25 °C[e]	• 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-ol,mixed isomers		10–100	0.03	2.02

[a] 2007 Volume of use survey (IFRA, 2007a).
[b] Skin levels were based on the assumption that the fragrance mixture is used at 20% in a fine fragrance.
[c] Materials have been previously reviewed by in RIFM's safety assessment of terpene alcohols (Belsito et al., 2008).
[d] Maximum concentration for IFRA QRA category 4 (eg. Hydroalcoholics for unshaved skin).
[e] Physical properties have been calculated.
[f] A default value of 0.02% was used to calculate dermal systemic exposure.

dergo oxidation to hydroperoxides. Such compounds can take part in a range of nucleophilic and electrophilic addition reactions with biological material. The respective parent compounds that are not well studied (2-isopropyl-5-methyl-2-hexene-1-ol, 2-methyl-2-buten1-ol, phytol, 3,7,11,15-tetramethyl-2-hexadecen1-ol, 6,10-dimethylundeca-1,5,9-trien-4-ol, 4-methyl-3-decen-5-ol, 2,2,8-trimethylnonen-3-ol) should undergo a more in-depth toxicity assessment. However, the primary allylic alcohol, 3-methyl-2-buten-1-ol, did not show a higher toxicity than nonallylic alcohols in the available studies (McGinty et al., submitted for publication).

The presence of a double bond may give rise to the metabolic formation of reactive and genotoxic epoxides although Ames tests did not indicate mutagenic activity, which would be expected if epoxides were formed in appreciable amounts, for any of the seven compounds tested (phytol; 3-methyl-2buten-1-ol; 7-nonen-2-ol,4,5-dimethyl-; 4-methyl-3-decen-5-ol; 3-7-dimethyl-1,6-nonadien-3-ol; 2-methyl-3-buten-2-ol; or isophytol).

1.2. Occurrence and use

The alcohols under review 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 risk assessment for use as fragrance ingredients. The scientific evaluation focuses on dermal exposure, which is considered to be the primary exposure route for fragrance materials. When 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 to be relevant based on the nature of the protocols, quality of the data and appropriate exposure. These data are presented below in tabular form.

Some of the alcohols assessed in this report have been evaluated and approved for use as flavor ingredients in foodstuffs. In the United States, 2-methyl-3-buten-2-ol and 2-methyl-2-hepten-6-ol have been approved for use as flavors by the Food and Drug Administration (FDA) in accordance with 21 CFR 172.515. 3-Methyl-2-buten-1-ol, 2-methyl-2-buten-1-ol and phytol are listed as food additives (FDA, 2007).

As judged by the International Joint FAO/WHO Expert Committee on Food Additives (JECFA), 3-methyl-2-buten-1-ol does not present a safety concern at current estimated intake levels (JECFA, 2004).

The annual worldwide use of the individual alcohols varies greatly and ranges from less than 0.1 to greater than 1000 metric tons. Compounds with use volumes greater than 100 metric tons are: 4-methyl-3-decen-5-ol, 3,7-dimethyl-1,6-nonadien-3-ol and dihydromyrcenol (IFRA, 2007c; Table 1).

1.3. Estimated consumer exposure

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

For some of the substances under review, consumer exposure from use of fragranced products was estimated by two methods (IFRA, 2007c):

(1) Assumed or reported maximum concentrations of the alcohols in fine fragrances coming into contact with skin were provided by RIFM for all alcohols, assuming that 20% of the fragrance oil is used in the final product. The highest maximum skin level concentration for all alcohols reported was dihydromyrcenol at 6.8%. The concentrations for the other three alcohols with use volumes of more than 10 metric tons per year were greater than 1% (Table 1).

(2) From a survey of the use of fragrance mixtures (including 11 of the substances under review) in 10 types of cosmetic products (body lotion, face cream, eau de toilette, fragrance cream, antiperspirant, shampoo, bath products, shower gels, toilet soap and hairspray), the daily systemic dose for consumers was calculated from the amount of applied cosmetic product, its application frequency, a retention factor to account for the length of time a product remains on the skin or for the likelihood of being washed off, the concentration of fragrance mixture in the product, the reported or assumed 97.5‰ of the concentration of the substance in the mixture and the consumer body weight of 60 kg. The daily systemic dose from each cosmetic product was calculated assuming 100% dermal uptake. To be conservative, it was assumed that a consumer is exposed simultaneously to all 10 cosmetic products. An explanation of how the data are obtained and how exposure was determined has been reported by Cadby et al. (2002) and Ford et al. (2000). The systemic doses from all 10 cosmetic products were summed and the sum for each substance is shown in Table 1. Maximum daily calculated exposures for these 11 substances range from 0.0003 to 0.33 mg/kg body weight/day for individual substances in users with high consumption of cosmetic products containing these materials. The highest exposures calculated were for dihydromyrcenol and 3,7-dimethyl-1,6-nonadien-3-ol (see Table 1).

Data on inhalation exposure during use of the substances are lacking. Estimations for systemic exposure to the materials under review are only available for the dermal exposure route.

2. Toxicokinetics

2.1. Dermal route of exposure

No data on dermal penetration of the compounds under review are available. Limited *in vivo* data and *in vitro* percutaneous studies in human skin preparations demonstrate that the terpene alcohols citronellol and linalool penetrate dermal tissues (Belsito et al., 2008). Due to the structural similarity it is expected that the materials considered in this review can also be absorbed through the skin. Interaction of skin components with perfume can slow its evaporation substantially compared with relatively free evaporation from an inert surface. The quantities of perfume ingredients available for absorption may be higher than expected based on their volatility (Belsito et al., 2008). Results from a study by Behan et al. (1996) show that after application of 75 μl of a model cologne perfume with a ten-ingredient mixture (each at 1% w/w), residual quantities on the skin after 60 min of free evaporation were 293 and 427 ng for 7-octen-2-ol, 2-methyl-6-methylene-, dihydro derivative and linalool, respectively. For the calculation of systemic exposure a worst-case assumption of 100% dermal absorption is used (see Section 1.3).

2.1.1. Human studies

Studies on the percutaneous absorption of citronellol and linalool in human skin *in vitro* and that of linalool *in vivo* have been described by Belsito et al. (2008).

Linalool was absorbed from a 1500 mg massage oil containing 2% lavender oil with approximately 25% linalool and 30% linalyl acetate through the skin of a male volunteer. Nineteen minutes after the massage, the peak concentration of 100 ng linalool/ml

plasma was reached. A biological half-life of 14 min was determined (Jäger et al., 1992; Belsito et al., 2008).

A series of *in vitro* human skin penetration studies were conducted RIFM, 2006c,d,e, 2007c,d,e with 4% linalool under in-use (unoccluded) and occluded conditions in diethyl phthalate (DEP), dipropylene glycol (DPG), ethanol/water, petrolatum, ethanol/DEP or ethanol/DPG vehicles. Twelve active dosed diffusion cells were prepared from seven donors for each application condition (unoccluded, occluded, and an unoccluded control cell). Epidermal membranes were used, and their integrity was assessed by measuring the permeation rate of tritiated water over a period of 1 h. Permeation of linalool from a 5 μl/cm^2 dose was then measured at 12 time-points over 24 h. Occluded conditions reduced the loss of volatile application vehicles and test compounds but may have also increased skin hydration, factors which caused a significant increase in the permeation of linalool. Under unoccluded experimental conditions, there was a gradual but comprehensive evaporative loss. Total absorbed dose values from an unoccluded application ranged from 1.8% to 3.57% (DPG < ethanol/DPG < ethanol/DEP < DEP < petrolatum < ethanol/water). Total absorbed dose values from an occluded application ranged from 5.73% to 14.4% (DEP < ethanol/DEP < DPG < petrolatum < ethanol/DPG < ethanol/water).

A similar study was conducted with dihydromyrcenol, an *in vitro* human skin absorption study with both in-use (unoccluded) and occluded conditions. The absorption of each dihydromyrcenol component (A and B) was measured via GC–MS and used to calculate the total dihydromyrcenol absorption. Skin permeation and distribution was determined using epidermal membranes from cosmetic surgery donors. Skin membranes were mounted into Franz-type diffusion cells with the stratum corneum facing the donor chamber. The average area available for diffusion was 1.2 cm^2. Dihydromyrcenol was applied, at the maximum in-use concentration of 6%, in 70/30 (v/v) ethanol/water to the skin surface at a dose of 5 μl/cm^2. At 24 h, 3.85 ± 0.29 μg/cm^2 (unoccluded) and 15.0 ± 1.6 μg/cm^2 (occluded) (mean ± standard error, SE) of dihydromyrcenol had permeated, corresponding to 1.30 ± 0.10% (unoccluded) and 5.06 ± 0.53% (occluded) of the applied dose of 296.2 μg/cm^2. Levels of dihydromyrcenol in the epidermis (plus any remaining stratum corneum after tape stripping), filter paper membrane support and receptor fluid were combined (as per SCCFP guidelines) to result in a total absorbed dose value of 1.45 ± 0.10% (unoccluded) and 5.67 ± 0.58% (occluded). Differential absorption of the two components was observed, with greater levels of dihydromyrcenol A being absorbed under both unoccluded and occluded conditions. Overall recovery of dihydromyrcenol at 24 h was 2.36 ± 0.24% (unoccluded) and 22.5 ± 2.1% (occluded). Low recoveries were attributed due to rapid evaporative loss of dihydromyrcenol. Under occluded conditions dihydromyrcenol may have undergone evaporation from the skin surface and subsequent loss through donor chamber sealing grease (RIFM, 2007g,h).

In human skin,*in vitro* penetration into all skin layers was demonstrated for citronellol and linalool after 1 h of exposure. Total penetration amounts of linalool and citronellol were 827 and 954 μg/cm^2, respectively. Elimination from the skin was observed only for *citronellol* while the total skin content of *linalool* did not change, although diffusion from the stratum corneum into the epidermis/dermis occurred (Cal and Sznitowska, 2003; Belsito et al., 2008).

2.1.2. Animal studies

Undiluted *farnesol* applied *in vitro* at 20% and 50% on pig skin stayed in the lipids of stratum corneum, and diluted *farnesol* in DMSO penetrated the epidermis and dermis of pigs (Bobin et al., 1997; Belsito et al., 2008).

2.2. Oral route of exposure

When tritium labeled phytol was given to rats, the highest specific activity was found in the liver. The total activity remaining in the body was of the same order of magnitude as the levels of phytol metabolites, phytanic and phytenic acid, in the liver, as determined by gas chromatography. When phytol was fed in the diet, both metabolites were found in the liver (Bernhard et al., 1967). In rats, 72 h after a single oral dose of 500 mg ^{14}C-labelled linalool/kg body weight, about 55% of the dose was excreted in the urine, 15% in the feces, and 23% as $^{14}CO_2$ in the expired air. Only 3–4% residual activity was found in tissues (Parke et al., 1974; Belsito et al., 2008).

2.3. Respiratory route of exposure

For the compounds under review, no data on inhalation uptake were found. In studies with non-cyclic terpene alcohols, uptake via inhalation in mice was demonstrated (Belsito et al., 2008).

After a 1 h inhalation exposure of mice to 5 mg/l linalool, serum levels were 7–9 ng/ml; they increased to 12 ng/ml linalool after addition of beta-glucuronidase to the blood assay (Jirovetz et al., 1991; Buchbauer et al., 1991; Belsito et al., 2008).

After a 1 h inhalation exposure to an atmosphere generated from 20–50 mg of essential oils or the pure materials (no data on air concentrations provided), the amounts detected in the plasma of mice at the end of the exposure period were 1.70 ng geraniol/ml, 2.90 ng citronellol/ml, 4.22 ng linalool/ml and 5.70 ng nerol/ml. Farnesol was not detected (Buchbauer et al., 1993; Belsito et al., 2008).

3. Metabolism

There are only limited data on metabolism of the alcohols under study. Data on terpene alcohols are available and applicable to these alcohols (Belsito et al., 2008).

The main metabolism routes identified for the terpene alcohols include conjugation with glucuronic acid and oxidation of the primary alcohol group via the aldehyde to the acid and eventually to carbon dioxide. Alcohols with alkyl or alkenyl substituents may be oxidized at the allylic position to yield polar diol metabolites. Hydrogenation of the double bonds has also been demonstrated. Due to the structural similarities, similar metabolism pathways are expected for the alcohols under review.

3.1. Conjugation

Glucuronic acid conjugation and excretion is the primary route of metabolism of linalool, citronellol, nerol, and geraniol which are substrates of UDPGTs (UDP-glucuronosyltransferases). They show typical phenobarbital-like P450 induction behavior in Wistar rat liver (Boutin et al., 1985; Belsito et al., 2008).

3.2. Oxidation of the carbon chain

2-Methyl-3-buten-2-ol, a member of the group of tertiary allylic branched chain alcohols, induced cytochrome P450 3 A in mice after application of 1% or 2% via the drinking water for 3 days. It did not induce CYP450 2E and moderately induced CYP450 1 A (Mannering and Shoeman, 1996).

Oxidation of the carbon chain, i.e. omega-hydroxylation or methyl side-chain oxidation was demonstrated for geraniol and linalool in rats. It is mediated by cytochrome P450 mainly in the liver but was also shown with rat lung and kidney microsomes for citronellol, geraniol, linalool and nerol. Further metabolism of

the diol metabolites of geraniol and linalool to aldehydes by alcohol dehydrogenase (ADH) is inhibited due to the bulky neighboring alkyl substituents and the substrate specificity of the enzyme (Chadha and Madyastha, 1982, 1984; Parke et al., 1974; JECFA, 1999; Eder et al., 1982a; Belsito et al., 2008).

3.3. Oxidation of the alcohol group

Primary alcohols: The oxidation of primary and primary allylic alcohols by alcohol dehydrogenase was investigated. Allylic alcohols were better substrates for human liver alcohol dehydrogenase than the corresponding saturated alcohols. A K_m value of 0.0045 mM was measured *in vitro* for 3-methyl-2-buten-1-ol. The reactivity of allylic alcohols increased with chain length (C3–C6 investigated) (Pietruszko et al., 1973).

Further oxidation of the aldehydes produces acids. The oxidation of the primary allylic alcohol phytol to the corresponding acids, phytanic acid (with reduced double bond; hexadecanoic acid, 3,7,11,15-tetramethyl-) and phytenic acid (2-hexadecenoic acid, 3,7,11,15-tetramethyl-), was shown in rats (Bernhard et al., 1967).

Especially short chained alcohols (e.g., 3-methyl-2-buten-1-ol) are primarily oxidized to the corresponding carboxylic acid that may enter the beta-oxidation pathway yielding shorter chain carboxylic acids that are subsequently metabolized to CO_2 via the tricarboxylic acid pathway (JECFA, 2004).

Secondary alcohols: Secondary alcohols are expected to be excreted via conjugation or oxidation to ketones, which cannot be further oxidized. Additionally, they can be excreted unchanged or undergo hydroxylation of the carbon chain, which in turn may give rise to a metabolite that can be excreted. Generally all the metabolites show a low reactivity.

Tertiary alcohols: Tertiary alcohols cannot be oxidized. They are expected to be excreted via conjugation, to be excreted unchanged, or to undergo hydroxylation of the carbon chain, which in turn may give rise to a metabolite that can be excreted.

3.4. Hydrogenation of double bonds

After a single oral dose of linalool to rats, reduced 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; Belsito et al., 2008).

All of these reactions can occur to a varying degree, and they generally lead to polar metabolites. These metabolites can then be excreted by the kidneys or with the feces. As examples, the metabolisms of geraniol, a primary allylic alcohol, and linalool, a tertiary alcohol, are shown in Figs. 1 and 2:

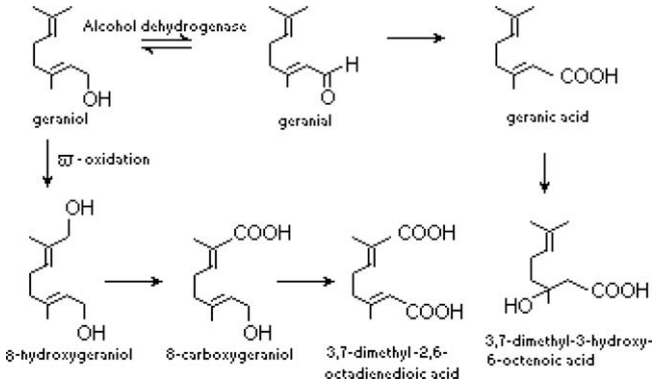


Fig. 1. Metabolism of geraniol in rats (Belsito et al., 2008).

4. Toxicological studies

4.1. Acute toxicity

The dermal LD_{50} values in rats, rabbits and guinea pigs are greater than 2000 mg/kg body weight and even greater than 5000 mg/kg body weight in some cases, indicating that these compounds are of low acute toxicity or are practically non-toxic via the dermal route (Table 2a).

The oral LD_{50} values in rats and mice are greater than 2000 mg/kg body weight except for 3-methyl-2-buten-1-ol and 2-methyl-3-buten-2-ol which show LD_{50} values in the range of 800–2300 mg/kg body weight (Table 2b).

The most reported clinical sign was lethargy after oral or dermal application, diarrhea and gastrointestinal tract irritation after oral application, and irritation of the skin after dermal application. Acute toxicity data obtained from studies with other than oral or dermal exposure are summarized in Table 2c.

4.2. Repeated dose toxicity

There is little information available on toxicity after repeated dermal application for the alcohols included in this summary (see Table 3). Only linalool was tested in a repeated dose dermal toxicity study (RIFM, 1980b).

Several of the alcohols under study were tested for toxicity after repeated oral application with histopathological evaluation. Ninety-day studies were conducted with isophytol, 3-methyl-2-buten-1-ol and dihydromyrcenol. Twenty-eight-day studies with 2-methyl-3-buten-2-ol and isophytol and a one-generation study with isophytol (see Section 4.5 and Table 5) were performed. Furthermore, linalool was tested in a 28-day study (Belsito et al., 2008), which is also included in this evaluation to increase the database. Only studies with histopathological examination were included. The results of these studies are summarized in Table 3.

4.2.1. Dermal studies

4.2.1.1. Primary and secondary alcohols. No studies are available for the members of these subgroups.

4.2.1.2. Tertiary alcohols. SD rats (20/sex/dose) were dosed dermally by open application with 0, 250, 1000 or 4000 mg/kg body weight/day of linalool for 13 weeks (RIFM, 1980b; Belsito et al., 2008). In order to minimize dermal irritation, the application sites were regularly changed. Slight erythema during the first three study weeks and slightly decreased activity were the only effects noted at the lowest dose level of 250 mg/kg body weight/day. One thousand mg/kg body weight/day caused slight erythema during the first six study weeks and a reduction in body weight in females. At 4000 mg/kg body weight/day, nine females and two males died. The food consumption in males was reduced early in the study, and a reduced body weight was found. Sporadic and transient lethargy was observed at the two lowest dose levels. Extreme lethargy was observed at the highest dose level. Liver weights were increased in both sexes; while kidney weight was elevated in females only. Slight erythema and slight to moderate epithelial hyperplasia were noted. No pathological findings were reported from hematology, clinical chemistry or urinalysis. The histopathological examination of skin, adrenals, brain, heart, kidneys, liver, thyroids, mesenteric lymph node, spinal cord, testes, ovaries, spleen, urinary bladder, sternal bone marrow, pituitaries and sciatic nerve did not show adverse effects. The no observed adverse effect level (NOAEL) was 250 mg/kg body weight/day;

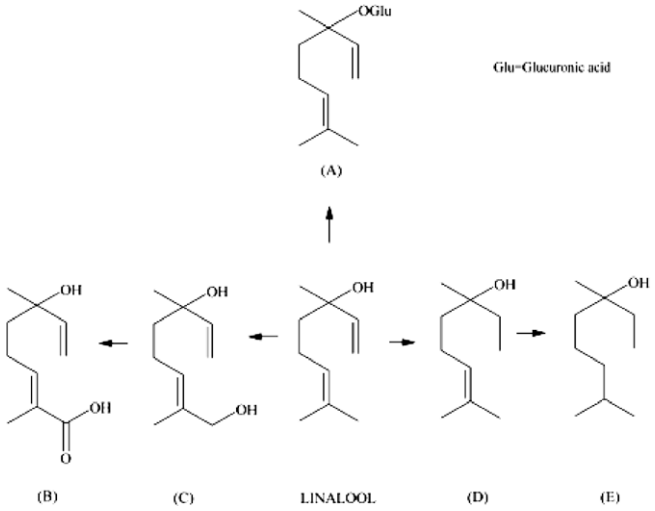


Fig. 2. Metabolism of linalool in rats (Belsito et al., 2008).

the lowest observed adverse effect level (LOAEL) was 1000 mg/kg body weight/day (based on body weight reduction in females).

4.2.2. Oral studies

4.2.2.1. Primary alcohols. No studies are available for members of this subgroup. Also, in the RIFM group summary of terpene alcohols (Belsito et al., 2008), no information on histopathological changes of primary non-cyclic terpene alcohols after repeated oral administration is contained.

4.2.2.2. Primary allylic alcohols. In a 90-day study according to OECD test guideline 408, 3-methyl-2-buten-1-ol was administered in the drinking water in concentrations of 0, 200, 1000 or 5000 ppm (14.4 and 21.0 mg/kg body weight/day, 65.4 and 82.1 mg/kg body weight/day or 243.8 and 307.2 mg/kg body weight/day for males and females). In the mid dose groups, feed and water consumption in males and females was reduced. In males, the mean absolute liver weights (but not the relative liver weights) were significantly decreased (high dose: −14.9%, mid dose: −7.9%) when compared to controls. At the high dose, in males and females, the urine volume was decreased with increased specific gravity, related to reduced water consumption. In males and females of the 5000 ppm group (243.8 and 307.2 mg/kg body weight/day), body weight and body weight gain were significantly reduced. The reduced absolute liver weight in high dose males can be explained by the reduced body weight, as the relative liver weight was not reduced. The NOAEL was assessed to be 1000 ppm (65.4 and 82.1 mg/kg body weight/day) based on significant decrease of body weight as a consequence of reduced food and water consumption at 5000 ppm (243.8 and 307.2 mg/kg body weight/day) (RIFM, 2002c).

4.2.2.3. Secondary and secondary allylic alcohols. No studies are available for members of these subgroups.

4.2.2.4. Tertiary alcohols. An oral 28-day study according to OECD test guideline 407 was conducted with 2-methyl-3-buten-2-ol (Roche, 1994 as cited in OECD/SIDS, 2005b). Ten to fourteen Wistar rats per sex and dose group were exposed to 0, 50, 200 or 600 mg/kg body weight/day by gavage. No toxicologically relevant changes were noted in the low dose group. In mid dose (200 mg/kg body weight/day) female rats, minimally increased (not stated whether relative or absolute) liver weights and hypertrophy of hepatocytes were observed. In males, minimally increased (not stated whether relative or absolute) kidney weights and a slight to moderate accumulation of renal hyaline droplets were noted. At 600 mg/kg body weight/day, two animals died spontaneously and without a known cause. The LOEL was reported as 200 mg/kg body weight/day based on increased liver weight and hypertrophy of hepatocytes (probably enzyme induction). The NOEL of this study was 50 mg/kg body weight/day.

Isophytol was tested in a 28-day repeated oral dose test according to OECD test guideline 407 in male and female Sprague–Dawley rats with an additional 14-day treatment-free observation

Table 2a
Acute dermal toxicity studies.

Material	Species	No. animals/dose	LD_{50} (mg/kg body weight)[a]	References[c]
Subgroup: primary				
2-Isopropenyl-5-methyl-4-hexene-1-ol[b]	Guinea pig	10	>5000	RIFM (1982a)
Subgroup: primary allylic				
2-Isopropyl-5-methyl-2-hexene-1-ol[b]	Rabbit	8	>5000	RIFM (1973a)
3-Methyl-2-buten-1-ol	Rabbit	4	3900 (95% C.I. 2500–6000)	RIFM (1977a)
	Rat	6 (3/sex)	>4000	RIFM (1979i)
Phytol	Rabbit	10	>5000	RIFM (1977a)
Subgroup: secondary				
Methylheptenol	Rabbit	10	>5000	RIFM (1976a)
7-Nonen-2-ol,4,8-dimethyl-	Rabbit	10	>2000	RIFM (1979d)
Subgroup: tertiary				
7-Octen-2-ol, 2-methyl-6-methylene-, dihydro derivative	Rabbit	10	>5000	RIFM (1973a)
2,6-Dimethyl-2-hepten-6-ol[b]	Rabbit	10	>5000	RIFM (1974a)
3,7-Dimethyl-1,6-nonandien-3-ol	Rabbit	10	>5000	RIFM (1975a)
Dihydromyrcenol	Rabbit	10	>5000	RIFM (1977a)
Isophytol	Rabbit	10	>5000	RIFM (1982a)
2-Methyl-3-buten-2-ol	Rabbit	Not reported	>2000	RIFM (1972e)
3-Methyl-1-octen-3-ol[b]	Rabbit	10	>5000	RIFM (1978a)
3-Methyl-1-octyn-3-ol[b]	Rabbit	4 (2/sex)	5600 (95% C.I. 4000–8000)	RIFM (1979a)
Nerolidol (isomer unspecified)[d]	Rabbit	10	>5000	RIFM (1973b)
3,7,9-Trimethyl-1,6-dicadien-3-ol[b]	Rabbit	10	>5000	RIFM (1977a)

[a] Units have been converted to make easier comparisons; original units are in the fragrance material reviews.
[b] No relevant use was reported, therefore the available data are mentioned only in the table but not in the text.
[c] Not all of the original reports in the OECD/SIDS assessment were made available to RIFM.
[d] Materials have been previously reviewed by in RIFM's safety assessment of terpene alcohols (Belsito et al., 2008).

Table 2b
Acute oral toxicity studies.

Material	Species	No. animals/dose	LD_{50} (mg/kg body weight)[a]	References[c]
Subgroup: primary				
2-Isopropenyl-5-methyl-4-hexene-1-ol[b]	Mouse	10 (males)	>5000	RIFM (1982a)
Subgroup: primary allylic				
2-Isopropyl-5-methyl-2-hexene-1-ol[b]	Rat	10	>5000	RIFM (1973a)
3-Methyl-2-buten-1-ol	Rat	10	810 (95% C.I. 550–1180)	RIFM (1977a)
	Rat	20 (10/sex)	1591	RIFM (1970e)
				RIFM (2003a)
Phytol	Rat	10	>5000	RIFM (1977a)
	Rat	Not reported	>10,000 (50% in olive oil)	RIFM (1978b)
Subgroup: secondary				
7-Nonen-2-ol,4,8-dimethyl-	Rat	10	>5000	RIFM (1979c)
	Rat	10	>2000	RIFM (2004a)
Methylheptenol	Rat	10	>5000	RIFM (1976a)
	Mouse	5	3903 ± 297	RIFM (1967a)
Subgroup: secondary allylic				
4-Methyl-3-decen-5-ol	Mouse	10	>8000	RIFM (1980a)
Subgroup: tertiary				
7-Octen-2-ol, 2-methyl-6-methylene-, dihydro derivative	Rat	10	3600 (95% C.I. 3000–4200)	RIFM (1973a)
	Rat	10 (5/sex)	4150 (95% C.I. 2990–6060)	RIFM (1977b)
2,6-Dimethyl-2-hepten-6-ol[b]	Rat	10	>5000	RIFM (1974a)
3,7-Dimethyl-1,6-nonadien-3-ol	Rat	10	5000	RIFM (1975a)
	Mouse	5	5283 ± 383	RIFM (1967a)
Dihydromyrcenol	Rat	10	4100 (95% C.I. 3500–4800)	RIFM (1977a)
Isophytol	Rat	10	>5000	RIFM (1982a)
	Rat	Not reported	5400	RIFM (1969)
				RIFM (1970a)
	Rat	5 or 10	>8000	Bächtold (1973) as cited in OECD/SIDS (2006)
	Mouse	5 or 10	>8000	Bächtold (1980) as cited in OECD/SIDS (2006)
Isophytol (crude)	Rat	5 or 10	>12,000	Bächtold (1980) as cited in OECD/SIDS (2006)
	Mouse	5 or 10	>8000	Bächtold (1980) as cited in OECD/SIDS (2006)
2-Methyl-3-buten-2-ol	Rat	Not reported	1800	RIFM (1991)
	Rat	Not reported	2280	Roche (1990) as cited in OECD/SIDS (2005b)
3-Methyl-1-octen-3-ol[b]	Rat	10	1800 (95% C.I. 1300–2500)	RIFM (1978a)
3-Methyl-1-octyn-3-ol[b]	Rat	5 (male)	860 (95% C.I. 610–1200)	RIFM (1979a)
Nerolidol (isomer unspecified)[d]	Rat	10	>5000	RIFM (1973b)
	Mouse	5 (male)	9976 ± 350	RIFM (1967a)
3,7,9-Trimethyl-1,6-dicadien-3-ol[b]	Rat	10	>5000	RIFM (1977a)
	Mouse	5 (male)	5892 ± 555	RIFM (1967a)

[a] Units have been converted to make easier comparisons; original units are in the fragrance material reviews.
[b] No relevant use was reported, therefore the available data are mentioned only in the table but not in the text.
[c] Not all of the original reports in the OECD/SIDS assessment were made available to RIFM.
[d] Materials have been previously reviewed by in RIFM's safety assessment of terpene alcohols (Belsito et al., 2008).

period for half of the control and high dose animals (Strobel and Lambert, 1998, as cited in OECD/SIDS, 2006). In control and high dose groups, 12 animals per sex were exposed, and the remaining two groups used six per sex. Doses administered were 0, 250, 500 or 1000 mg/kg body weight/day per gavage. No obvious treatment-related abnormalities were observed at necropsy or during histopathological examination. Hunched posture, weight loss and pallor, increased body weight in males, a number of clinical chemistry changes in males and females, increased liver weights in both sexes, and increased kidney and spleen weights in females were associated with the 1000 mg/kg body weight/day dosage group. The majority of clinical findings, although statistically different from the vehicle control group, were within the ranges of historical background data quoted for control animals. After a 14-day treatment-free period, the majority of changes were no longer apparent. The NOAEL was 500 mg/kg body weight/day while the LOAEL, based on minor and reversible changes, was set at 1000 mg/kg body weight/day.

Coriander oil containing 72.9% linalool was tested in a 28-day study on rats. The oil was administered by gavage to male and female rats at dose levels of 160, 400 or 1000 mg/kg body weight/day (117, 290, and 729 mg *linalool*/kg body weight/day) (RIFM, 1990; Belsito et al., 2008). Absolute liver weights were increased in mid and high dose animals. In the high dose group, degenerative lesions were found in the renal cortex of males, and hepatocellular cytoplasmic vacuolization was seen in females. Based on these effects, the NOAEL was 160 mg/kg body weight/day (117 mg linalool/kg body weight/day).

Dihydromyrcenol was tested in a 90-day toxicity study in rats according to OECD test guideline 408 (RIFM, 2007a,b,c,d,e,f,g,h). The test substance was administered by gavage to male and female rats at dose levels of 0, 10, 50, 500 or 1000 mg/kg body weight/day in corn oil, with 10 animals per sex and group. Incidents of increased salivation were evident in all dose groups, indicative of local irritation but not of a systemic effect. No toxicologically relevant changes were noted in females of the low dose group. In males of all dose groups, a greater incidence and severity of basophilic tubules or globular accumulations of eosinophilic material consistent with an accumulation of α_{2u}-globulin within the proximal tubular epithelium were observed. Males treated with doses of 50 mg/kg body weight/day and higher showed reduced platelet counts and elevated plasma urea and creatinine levels. Absolute and relative liver weights were elevated in males as well. Animals of the two higher dose groups revealed reduced body weight gain and feed consumption, increased water consumption, elevated cholesterol levels and increased relative and absolute kidney weights. Animals of either sex treated with 500 and 1000 mg/kg body weight showed statistically significant increases in liver

Table 2c
Acute miscellaneous toxicity studies.

Material	Dosing route	Species	No. animals/dose	LD_{50}	References[b]
Subgroup: primary allylic					
3-Methyl-2-buten-1-ol	Inhalation, exposure to a saturated vapor (20 °C) for 3 h and 8 h	Rat	3 h: 12 (6/sex) 8 h: 6 (3/sex)	LC_{50} extrapolated to 4 h according to Haber's rule: > 7.7 mg/l (4 h) >16.8 mg/l (4 h) Reduced post observation time (7 days instead of 14 days)	RIFM (1970e, 2003e)
	i.p. injection (water emulsion in gum tragacanth)	Mouse	10 (5/sex)	413 mg/kg body weight	RIFM (2003b)
Subgroup: secondary allylic					
4-Methyl-3-decen-5-ol	i.p. injection (Gummi arabicum emulsion)	Mouse	10	1000–2000 mg/kg body weight (10/10 died at 2000 mg/kg body weight, No mortality at 1000 mg/kg body weight)	RIFM (1980a)
Subgroup: tertiary					
Isophytol	i.p. injection (1–30% water emulsion in gum tragacanth)	Mouse	Not reported	Approx. 0.2 ml/kg body weight	RIFM (1969, 1970a)
	Inhalation, exposure to isophytol-saturated air (20 °C and 100 °C) for 8 h	Rat	12	No deaths and no lesions at necropsy,	RIFM (1969, 1970a)
2-Methyl-3-buten-2-ol	4 h inhalation	Rat	5/sex	LC_{50} > 21.2 mg/l	RIFM (1989e)
	i.p. injection	Rat	Not reported	1315 mg/kg body weight	Wohlfahrt et al. (1993)
	i.p. injection	Mouse	Not reported (only males)	1117 mg/kg body weight	Wohlfahrt et al. (1993)
3-Methyl-1-octyn-3-ol[a]	1 h inhalation	Rat	10 (5/sex)	LC_{50} > 20 mg/l	RIFM (1979a)

[a] No relevant use was reported; therefore the available data are mentioned only in the table but not in the text.
[b] Not all of the original reports in the OECD/SIDS assessment were made available to RIFM.

weights, both absolute and relative to terminal body weights. Both sexes also had centrilobular hepatocyte enlargement, occasionally with associated centrilobular lipid-type vacuolation of hepatocytes.

Renal tubular necrosis was noted in males of the 500 and 1000 mg/kg body weight/day group. Also, reductions in haemoglobin, haematocrit, albumin/globulin ratio, and erythrocyte counts were found in females treated with 1000 mg/kg body weight/day, and the reductions on erythrocyte count extended into the females treated with 500 mg/kg body weight/day. In high dose animals, noisy respiration, increased salivation, hunched posture and tiptoe gait were observed throughout the treatment period. In males, higher grades of severity of adipose infiltration of the bone marrow were observed, which was interpreted by the authors as indication of hypoplasia. The α_{2u}-globulin nephropathy is a male rat-specific renal syndrome and has no relevance for humans. The authors concluded that the histopathologically identified kidney changes could be regarded as male rat-specific effects. The NOAEL was 10 mg/kg body weight/day in males because of elevated liver weight and elevated plasma levels of urea and creatinine at 50 mg/kg body weight/day. However, in female rats at this dose, no treatment-related changes were noted and a NOEL of 50 mg/kg body weight/day was established.

In a one-generation study according OECD test guideline 415 (Beekhuijzen, 2002, as cited in OECD/SIDS, 2006), female and male Wistar Crl: (WI) BR (outbred, SPF) rats were orally administered isophytol in vegetable oil per gavage at doses of 0, 250, 500 or 1000 mg/kg body weight/day. Exposure duration in males ranged from 91 to 134 days (average 98 days) while in females exposure ranged from 52 to 108 days (average 64 days). The following toxicologically relevant findings were noted for the parental animals: Dilated renal tubules and general mineralization were consistently observed in all treatment groups and in both males and females. In addition, in males of all treatment groups, a decrease in the incidence of hyaline droplets was found. In the two higher dose groups, absolute and relative kidney weights were significantly increased in females; in the kidneys of males and females basophilic aggregates and increased basophilic tubules were noted. In the high dose group a significant increase in the relative kidney weight was observed in males, however, body weight was depressed. In high dose females there was an increase in lethargy, hunched posture, piloerection, and body weight loss during lactation. The animals showed minimal to moderate periportal hepatocyte vacuolation. Based on the kidney effects, no NOAEL can be derived. The LOAEL is 250 mg/kg body weight/day.

No effects on kidneys were observed (Strobel and Lambert, 1998, as cited in OECD/SIDS, 2006) in the isophytol 28-day repeated dose toxicity test discussed above, which might be due to the shorter exposure time in comparison to the one-generation study or to differences in the strain of rat and diet.

4.2.3. Inhalation studies

No repeated-dose inhalation toxicity studies are available.

4.3. Genotoxicity

Genotoxicity testing with the alcohols under study has been performed mostly *in vitro*, with only a few substances (the primary allylic alcohol 3-methyl-2-buten-1-ol and the tertiary alcohols isophytol and 2-methyl-3-buten-2-ol) tested *in vivo*. To supplement the database, studies with the primary allylic alcohols, farnesol and geraniol, and the tertiary alcohol, linalool, which have already been assessed (Belsito et al., 2008), were used for the evaluation of the genotoxic potential of alcohols with unsaturated branched chain. The results of these tests are summarized in Tables 4a and 4b.

4.3.1. In vitro genotoxicity studies

The *in vitro* genotoxicity studies contained in Belsito et al., 2008 have been checked for whether the substances were tested up to cytotoxic levels to ensure the validity of negative test results.

In an assay for sister chromatid exchange, up to 150 μg linalool/ml gave negative results in Chinese Hamster Ovary (CHO) cells (Sasaki et al., 1989). A test for induction of unscheduled DNA synthesis with linalool was negative in rat primary hepatocytes in concentrations up to 43.6 μg/ml (Heck et al., 1989; RIFM, 1986a). The positive and equivocal results observed in two rec-assays with linalool "may have been caused by unspecific cytotoxicity, and are therefore of limited relevance for the evaluation of the genotoxicity of linalool" (Belsito et al., 2008). Citronellol was negative in a rec-assay (Belsito et al., 2008).

The primary alcohol, citronellol; the primary allylic alcohols, farnesol, geraniol, and 3-methyl-2-buten-1-ol; the secondary allylic alcohol, 4-methyl-3-decen-5-ol; and the tertiary alcohols, 3,7-dimethyl-1,6-nonadien-3-ol, isophytol, 2-methyl-3-buten-2-ol, dehydrolinalool and linalool were inactive in bacterial mutagenicity assays (Ames tests). *Linalool* was also inactive in mammalian cell systems (mouse lymphoma cells). The weak positive result with *linalool* in one mouse lymphoma assay (Heck et al., 1989) was probably associated with unphysiological changes in the culture medium, as a second test under normal osmolality and pH was negative (Belsito et al., 2008).

In a host-mediated assay the urine of rats given citronellol or linalool showed no mutagenic activity in *Salmonella typhimurium*strains TA98 and TA100 without S9 activation (Rockwell and Raw, 1979; Belsito et al., 2008).

The primary allylic alcohols, farnesol and geraniol, as well as the tertiary alcohol, linalool, did not induce chromosome aberrations *in vitro* when incubated with Chinese hamster ovary or Chinese hamster fibroblast cells (Ishidate et al., 1984; RIFM, 1983b; Rupa et al., 2003).

When geraniol was tested up to toxic levels (78.1–156.3 μg/ml) the results were inconclusive *in vitro* (Rupa et al., 2003). However, in a micronucleus test *in vivo* by the same authors, *geraniol* was not mutagenic (see *in vivo* genotoxicity studies below). Therefore, the inconsistency observed *in vitro* genotoxicity is not expressed *in vivo* and not of concern (Belsito et al., 2008).

4.3.2. In vivo genotoxicity studies

The primary allylic alcohols, farnesol, geraniol and 3-methyl-2-buten-1-ol; and the tertiary alcohols, isophytol, 2-methyl-3-buten-2-ol and linalool, were non-genotoxic in the mouse bone marrow micronucleus test (RIFM, 1992; RIFM, 2001b; Meerts, 2002 as cited in OECD/SIDS, 2006; RIFM, 2001; Rupa et al., 2003).

4.4. Carcinogenicity

No valid bioassays on carcinogenicity are available for the alcohols with unsaturated branched chain or for closely structurally related substances.

4.5. Reproductive and developmental toxicity

4.5.1. Fertility

4.5.1.1. Primary alcohols. No studies are available for the members this subgroup or for closely structurally related substances.

4.5.1.2. Primary allylic alcohols. Histopathological examinations of the reproduction organs of male and female rats in the 90-day repeated dose study with 3-methyl-2-buten-1-ol (RIFM, 2002c) administered by drinking water showed no adverse effects on males and females up to the highest concentration tested (243.8 and 307.2 mg/kg body weight/day). No treatment-related changes in sperm analysis were observed (see Table 3).

4.5.1.3. Secondary alcohols. No studies are available for the members of these subgroups.

4.5.1.4. Tertiary alcohols. No gross or histopathological effects on the primary reproduction organs (ovaries, uterus, testes and epididymis) were noted in rats after administration of coriander oil containing 72.9% of linalool for 28 days. The oil was given by gavage to male and female rats at dose levels of 160, 400 or 1000 mg/kg body weight/day (117, 292 or 729 mg *linalool*/kg body weight/day) (RIFM, 1989d; Belsito et al., 2008) (see Table 3).

Dihydromyrcenol was tested in a 90-day toxicity study in rats. The test substance was administered by gavage to male and female rats at dose levels of 0, 10, 50, 500, or 1000 mg/kg body weight/day. Histopathological examinations of the reproduction organs showed no adverse effects. No treatment-related effects on female estrous cycles or proportion of females with anomalous estrous cycles were observed. In males, sperm motility values, morphological assessments, or homogenization-resistant spermatid counts were unaffected (RIFM, 2007a) (see Table 3).

In a screening test for reproductive and developmental toxicity according to OECD test guideline 421 (draft), 2-methyl-3-buten-2-ol was administered to 10 male and 10 female Fü–Albino (RORO) rats per sex and group at doses of 0, 12.5, 50 or 200 mg/kg body weight/day (Roche, 1995b as cited in OECD/SIDS, 2005b). The test material was given by gavage once daily, starting 14 days premating. The exposure duration was 22 days and the duration of the study 54 days. At the high dose, parental effects reported include reduced body weight in males and a slight compound-related decrease of the food consumption of females. The parental NOAEL was 50 mg/kg body weight/day. The reproduction parameters were unaffected (mean number of: corpora lutea, implantations, pups per litter; resorption rates, mean gestation lengths, mean pup weights, pup sex ratios). Administration of 2-methyl-3-buten-1-ol at levels up to 200 mg/kg body weight/day was without effect on the general reproductive performance of the test animals.

In a one-generation study according to OECD test guideline 415, isophytol in doses of 0, 250, 500 or 1000 mg/kg body weight/day was administered by gavage to 24 male and 24 female rats per dose group (Beekhuijzen, 2002 as cited in OECD/SIDS, 2006). The parental effects were described above in Section 4.2.2. Reproductive parameters were affected in the highest dose group. Females showed a slightly increased mean pre-coital time and decreases in fertility index and conception rate. The numbers of dead pups at first litter check, postnatal losses and breeding losses were significantly increased, resulting in a decreased weaning index. In conclusion, 250 mg/kg body weight/day was the LOAEL for parental systemic toxicity based on effects in kidneys in males and females (dilated renal tubule, renal mineralization). Five hundred mg/kg body weight/day was the NOAEL for parental effects on reproduction based on slightly increased mean pre-coital time, decreased fertility index and conception rate in females.

The reproductive toxicity of linalool was investigated in four groups of 10 virgin Crl CD rats administered 0, 250, 500 or 1000 mg/kg body weight/day of an essential oil (coriander oil) containing 72.9% linalool by mass (182, 365 or 729 mg linalool/kg body weight/day) (RIFM, 1989d). The test material was given by gavage once daily; seven days prior to cohabitation; through cohabitation (maximum of seven days), gestation, and delivery; and for a 4-day post-parturition period. The duration of the study was 39 days. Maternal indices monitored included observation, body weights, feed consumption, duration of gestation, and reproductive parameters (mating and fertility index, gestation index, number of offspring per litter). In the dams, all dosages caused ex-

Table 3
Repeated dose toxicity studies.

Material	Method	Dose (mg/kg body weight/day)[a]	Species (no./dose group)	Results (mg/kg body weight/day)[a]	References[b]
Subgroup: primary allylic					
3-Methyl-2-buten-1-ol	Oral (drinking water), 14 days	0.25, 0.5, 0.75	rat (3/sex/dose)	No effects	RIFM (2003c)
	Oral (drinking water), 14 days	250, 500, 750, 1500	Rat (3/sex/dose)	Decreased food and water consumption at 250 mg/kg	
				Slight to moderate salivation at 500 and 750 mg/kg	RIFM (2003c)
				Significant decreases in food and water consumption at 1500 mg/kg (treatment stopped after day 5) NOAEL = 65.4 (m) or 82.1 (f) LOAEL = 243.8 (m) or 307.2 (f)	RIFM (2003d)
	Oral (drinking water), 90 days, OECD 408	m: 14.4, 65.4, 243.8 f: 21, 82.1, 307.2	Rat (Wistar) (10/sex/dose)	14.4 or 21: no effects	
				⩾65.4 or 82.1: food consumption decreased (f), water consumption decreased (m,f); abs. liver weight decreased (m) 243.8 or 307.2: food consumption decreased (m), body weight decreased (m,f), body weight gain decreased (m,f); urinary volume decreased (m,f), urine specific gravity increased (m,f)	RIFM (2002c)
Subgroup: tertiary					
2-Methyl-3-buten-2-ol	Oral (gavage) 28 day	30, 150, and 750	Rat (Wistar) (5/sex/dose)	NOAEL = 150	
				750: ataxia (m,f), decrease in chloride (m,f) triglycerides (m) and potassium (f), increase in cholesterol (m,f) and magnesium (m). No substance-related findings 30, or 150 NOEL = 50 NOAEL = 50 LOAEL = 200	RIFM (1994d)
	Oral (gavage), 28 days, OECD 407	0, 50, 200, 600 (vehicle not mentioned)	Rat (Wistar) (10–14/sex/dose)	⩾200: liver weight increased (f), hypertrophy of hepatocytes (1f); kidney weight increased (m), slight to moderate accumulation of renal hyaline droplets (m) 600: sedation, ataxia, uncoordinated gait during first days of application (m,f); salivation increased (m,f); 2 animals died (1m, 1f); liver weight increased (m), periacinar hypertrophy of hepatocytes (m,f), transaminases increased (m,f) NOEL females = 50 NOAEL males = 10	Roche (1994) as cited in OECD/SIDS (2005b)
Dihydromyrcenol	Oral (gavage), 90 days OECD 408	0 (corn oil), 10, 50, 500 or 1000	Rat (crl:CD (SD) IGS BR) (10/sex/dose)	⩾10: overall activity increased (f); plasma urea decreased (f), ; rel. and abs. adrenal weight increased (m), rel. and abs. thymus weight increased (m); incidence and/or severity of groups of basophilic tubules increased (m), accumulation of α_{2u}-globulin in renal proximal tubular epithelium (m) ⩾50: platelet count decreased (m); plasma urea increased (m), creatinine increased (m); rel. and abs. liver weight increased (m) ⩾500: body weight gain decreased, food consumption decreased (m, f), water consumption increased (m,f); cholesterol increased (m,f);, erythrocyte count decreased (f),, rel. and abs. kidney weight increased (m,f), rel. and abs. liver weight increased (f); centrilobular hepatocyte enlargement, occasionally with associated centrilobular lipid-type vacuolation of hepatocytes (2m,2f), tubular necrosis (m) 1000: last 20% of recorded mobile activity increased (m); increased salivation, noisy respiration, hunched posture, tiptoe gait (m,f);, haemoglobin, haematocrit decreased (f), higher grades of severity of adipose infiltration of the bone marrow increased (m);albumin/globulin ratio decreased (f); urine volume increased (m,f), specific gravity decreased (m,f); rel. and abs. adrenal weight increased (f); centrilobular hepatocyte enlargement, occasionally with associated centrilobular lipid-type vacuolation of hepatocytes (stat. sign.) (m,f) NOAEL = 500 LOAEL = 1000	RIFM (2007a)
Isophytol	Oral (gavage), 28 days plus 14 days post-treatment observation (control and high dose group) OECD 407	0 (maize/corn oil), 250, 500, 1000	Rat (Crl:CD (SD)BR (VAF plus) (6 or 12 (control, high dose) animals/sex/group)	⩾250: blood Ca increased (f) (reversible); abs. kidney weight increased (f), abs. spleen weight increased (m,f); terminal body weight increased (m)	

(*continued on next page*)

Table 3 (*continued*)

Material	Method	Dose (mg/kg body weight/day)[a]	Species (no./dose group)	Results (mg/kg body weight/day)[a]	References[b]
				⩾500: blood Ca increased (m), alanine aminotransferase increased (m) (both reversible); urine volume increased, specific gravity decreased (m)	Strobel and Lamber (1998) as cited in OECD/SIDS (2006)
				1000: fur-staining (f), hypoactivity, hunched posture, weight loss, pallor (in 1 f); alanine aminotransferase increased (f) (reversible); white blood cell counts increased (f), mean prothrombin time decreased (m) (both reversible); urine volume increased, specific gravity decreased (f) (no recovery); abs. and rel. liver weight increased (m,f) (reversible), rel. kidney weight increased (f), rel. spleen weight increased (f), rel. brain weight decreased (m,f) LOAEL = 250	
	Oral (gavage), one generation study, males average 98 day (91–134), females average 64 day (52-108), OECD 415	0 (maize/corn oil), 250, 500, 1000	Rat (Wistar, Crl:WI (BR) outbred, SPF) (24/sex/dose)	⩾ 250: dilated renal tubules (m,f), renal mineralization (m,f), renal hyaline droplets decreased (m)	
				⩾ 500: abs. kidneys weight increased (m,f), rel. kidney weight increased (f), incidence and severity of renal basophilic aggregates increased (m,f), incidence and severity of renal basophilic tubules increased (m,f)	Beekhuijzen (2002) as cited in OECD/SIDS (2006)
				1000: lethargy, hunched posture, piloerection (f); body weight, terminal body weight decreased (m), body weight loss during lactation (f), food consumption during lactation decreased (f); abs. and rel. prostate weight decreased, abs. seminal vesicles weight decreased, rel. kidneys weight increased (m), abs. and rel. uterus weight increased (f); periportal hepatocyte vacuolation decreased(f) NOAEL: 250	
Linalool[c]	dermal, open application, 13 weeks	0 (saline), 250, 1000 or 4000	SD rat (20/sex/dose)	⩾250: slightly decreased activity, slight erythema during the first 3 weeks	
				⩾1000: slight erythema during the first 6 weeks, body weight decreased (f) 4000: 9 females and 2 males died; lethargy in females; slight erythema; food consumption in males decreased early in study, body weight decreased (m); liver weight increased, kidney weight (f) increased, slight to moderate epithelial hyperplasia; histology, hematology, clinical chemistry and urinalysis findings normal NOAEL: 117	RIFM (1980b)
Linalool (72.9% in coriander oil)[c]	Oral (gavage), 28 day study	0 (vehicle), 160, 400 or 1000 mg coriander oil/kg body weight/day in 1% methylcellulose (117, 290, 729 mg linalool/kg body weight/day)	SD rat (10/sex/dose)	117 mg/kg body weight/day: no adverse effects	
				⩾290 mg/kg body weight/day: abs. and rel. kidney weight increased (m), abs. and rel. liver weight increased, total protein and serum albumin increased (m), histopathology: lesions in the nonglandular region of the stomach (f) 729 mg/kg body weight/day: abs. and rel. kidney weight increased (f), total protein and serum albumin increased (f), serum calcium increased (m), histopathology: degenerative lesions in renal cortex (m); hepatocellular vacuolization (f)	RIFM (1990) and Belsito et al. (2008)

NOEL: no observed effect level.
NOAEL: no observed adverse effect level.
LOAEL: lowest observed adverse effect level.
m: male, f: female.
rel: relative, abs.: absolute.

[a] Units have been converted to make easier comparisons; original units are in the fragrance material reviews.
[b] Not all of the original reports in the OECD/SIDS assessment were made available to RIFM.
[c] Materials have been previously reviewed by in RIFM's safety assessment of terpene alcohols (Belsito et al., 2008).

cess salivation, a sign of local irritation. At 729 mg/kg body weight/day, there were statistically significant decreases in gestation index, length of gestation, body weight during premating, feed consumption, and litter size. The NOAEL for systemic maternal toxicity and fertility was 365 mg/kg body weight/day based on decreased body weight and gestation index at 729 mg/kg body weight/day.

4.5.2. Developmental toxicity

4.5.2.1. Primary and primary allylic alcohols. The developmental toxicity of 3-methyl-2-buten-1-ol was investigated according to OECD test guideline 414. Time-mated female Wistar rats ($n = 25$) were dosed via gavage on gestational days 7–19 post coitum with an aqueous suspension of 3-methyl-2-buten-1-ol at 0, 50, 200 or 600 mg/kg body weight/day (RIFM, 2002d). In the high dose group, clinical signs including salivation, lacrimation, abdominal position and piloerection were observed throughout the treatment period. One dam in the high dose group died before scheduled sacrifice. It is likely that the death of this dam is substance related because high dose rats showed signs of maternal toxicity. However, no other clinical or necropsy findings were observed that would help explain this unscheduled death. Feed consumption, body weight, and body weight gain were statistically significantly reduced. No signs of substance-induced maternal toxicity occurred at the low and the mid dose levels. The maternal NOAEL was 200 mg/kg body weight/day based on clinical signs and effected body weights at the highest dose. At 600 mg/kg body weight/day, developmental toxicity was not observed.

4.5.2.2. Secondary alcohols. No studies are available for the members of these subgroups or for closely structurally related substances.

4.5.2.3. Tertiary alcohols. In a one-generation study according to OECD test guideline 415, 0, 250, 500 or 1000 mg of isophytol/kg body weight/day was administered by gavage to 24 male and 24 female rats per dose group (Beekhuijzen, 2002 as cited in OECD/SIDS, 2006; see above). A parental NOAEL was not obtained (see Section 4.5.1). In the highest dose group, the survival and general fitness of pups was reduced. Growth retardation, little or no milk uptake and mortality were observed. Mean body weights of both female and male pups of the high dose group were significantly decreased on days 4–7 of lactation in comparison with controls. The NOAEL for postnatal developmental toxicity was 500 mg/kg body weight/day.

In a screening test for reproduction and developmental toxicity according to OECD test guideline 421 (draft), 2-methyl-3-buten-2-ol was administered by gavage to 10 male and 10 female Fü–Albino (RORO) rats per sex and group at doses of 0, 12.5, 50 or 200 mg/kg body weight/day (Roche, 1995b as cited in OECD/SIDS, 2005b; see above). The pup viability index was reduced at the highest dose level. The NOAEL for developmental toxicity was 50 mg/kg body weight/day.

An essential oil (coriander oil) containing 72.9% linalool by mass was tested in a one-generation study in four groups of 10 virgin Crl CD rats. The estimated doses of linalool were 0, 250, 500 or 1000 mg/kg body weight/day (RIFM, 1989d). The authors concluded that there were no effects observed in the dams at 250 mg/kg body weight/day or in the offspring at the 250 and 500 mg/kg body weight/day levels of coriander oil. 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.

The developmental toxicity of linalool was investigated in Sprague–Dawley rats. Twenty-five presumed pregnant rats were dosed via gavage on gestational days 7–17 with linalool in corn oil at 0, 250, 500, or 1000 mg/kg body weight/day (Politano et al., 2008). There were no test substance-related clinical signs or gross lesions. Body weight gains were slightly but not significantly reduced (11%) in the 1000 mg/kg body weight/day group during the dosage period. During the post-dosage period, body weight gains in the 1000 mg/kg body weight/day group were increased over the vehicle control. Pregnancy occurred in 22, 23, 20, and 22 dams in the 0, 250, 500, or 1000 mg/kg body weight/day groups, respectively. No litter parameters were affected by doses of linalool as high as 1000 mg/kg body weight/day. No gross external, soft tissue, or skeletal fetal alterations were observed. The maternal NOAEL is 500 mg/kg body weight/day. No developmental toxicity was observed at the highest tested dose of 1000 mg/kg body weight/day.

Dihydromyrcenol was also tested for developmental toxicity in rats. One hundred pregnant Crl:CD(SD) rats (25/group) were orally administered via gavage 10 ml/kg of dihydromyrcenol at 0 (corn oil), 250, 500 or 1000 mg/kg/day on days 7–17 of gestation. Dams were observed for viability, clinical signs, abortions, premature deliveries, deaths, body weights, and feed consumption. On gestation day 21, all dams were Caesarean-sectioned and a gross necropsy was performed on the thoracic, abdominal and pelvic viscera. Uteri were examined for implantations, fetuses, and resorptions. Number of corpora lutea were recorded. Fetuses were weighed and examined for gender and gross external changes. One-half of the fetuses in each litter were examined for soft tissue alterations and the remaining for skeletal alterations. No deaths or treatment-related clinical signs were observed. The 1000 mg/kg body weight/day dosage group had maternal body weight losses in the first two days of dosing which persisted for the entire dosage period. These reductions were associated with significant reductions in feed consumption. Fetal body weights in the 1000 mg/kg body weight/day groups were reduced 3% compared to vehicle controls and were associated with retardation in the ossification of the metatarsal bones. These observations were within the historical range of the testing facility and are not considered toxicologically important. Fetal body weights in the 1000 mg/kg body weight/day group were reduced 3% compared to vehicle controls; the reduction in female fetuses was statistically significant. Although these observations were within the historical control values for the testing facility, the reduction correlated with a maternally toxic dosage in which reduced maternal body weight gains and feed consumption occurred at 1000 mg/kg/day early in the dosage period. A small but statistically significant reversible retardation in the ossification of the metatarsal bones in the hind paws was observed in the 1000 mg/kg/day dosage group. This is not considered to be of toxicological importance because the value is within the historical range of the testing facility and other ossification sites in the fetuses were not affected. An increase in supernumerary thoracic ribs and associated increases and decreases in thoracic and lumbar vertebrae, respectively, were also observed in fetuses from the 1000 mg/kg body weight/day group. This minor variation is reversible and often observed at maternally toxic doses. Due to maternal body weight and feed consumption effects as well as fetal body weight reductions and increases in reversible variations in skeletal ossification, the maternal and developmental NOELs of 500 mg/kg body weight/day and NOAELs of 1000 mg/kg bodyweight/day were established for dihydromyrcenol (Politano et al., 2009).

4.6. Skin irritation

4.6.1. Human studies

Nine alcohols with unsaturated branched chains and worldwide uses of >0.01 metric tons/year have been well studied for their potential to produce skin irritation in humans (see Table 6a).

Table 4a
Genotoxicity: *in vitro* studies.

Material	Test system		Concentrations	Results	References[a]
Subgroup: primary					
Citronellol[b]	Rec-assay	*Bacillus subtilis* strains H 17 (rec+) and M 45 (rec−)	17 μg/disc publication in Japanese, not clear whether tested up to cytotoxic concentrations	Not mutagenic	Oda et al. (1979)
	Ames assay with S9 activation	*Salmonella typhimurium* TA98, TA100	100 μl cytotoxicity: not reported	Not mutagenic	Rockwell and Raw (1979)
	Host mediated assay, with and without beta-glucuronidase	*Salmonella typhimurium* TA98, TA100	50–300 μl of 24 h direct urine sample or aqueous fractions of ether extracts from urine of two rats given 0.5 ml undiluted test material p.o.cytotoxicity: not reported	Not mutagenic	Rockwell and Raw (1979)
Subgroup: primary allylic					
Farnesol[b]	Ames assay with and without S9 activation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	Up to 5000 μg/plate not cytotoxic	Not mutagenic	RIFM (1989a)
	Ames assay with and without S9 activation	*Salmonella typhimurium, E. coli*	To the level of toxicity	Not mutagenic	Rupa et al. (2003)
	Chromosome aberration test with and without S9 activation	Chinese hamster ovary cells	To the level of toxicity	Not clastogenic	Rupa et al. (2003)
Geraniol[b]	Ames assay with and without S9 activation (liquid suspension test)	*Salmonella typhimurium* TA100	10–3000 μg per 2 ml incubation volume cytotoxicity: not reported	Not mutagenic	Eder et al. (1980, 1982a,b) and Lutz et al. (1980)
	Ames assay with and without S9 activation	*Salmonella typhimurium* TA92, TA94, TA98, TA100, TA1535, TA1537	Up to 500 μg/plate in DMSO (highest non-toxic dose)	Not mutagenic	Ishidate et al. (1984)
	Ames assay with and without S9 activation	*Salmonella typhimurium, E. coli*	To the level of toxicity	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 48h (highest non-toxic dose)	8.0% cells with polyploidy, structural aberrations (4%) not increased over control; judged as equivocal result with regard to polyploidy	Ishidate et al. (1984)
	Chromosome aberration test with and without S9 activation	Chinese hamster ovary cells (CHO)	To the level of toxicity	Inconclusive (increase in number of cells with structural aberrations in 1 of 2 experiments with metabolic activation	Rupa et al. (2003)
Phytol	Ames assay with and without S9 activation (plate incorporation test and pre-incubation test)	*Salmonella typhimurium* TA 100	0.5%, 1.0%, 2.5%, and 5.0%	Not mutagenic	Choi et al. (1993)
	Drosophila wing spot test	Transheterozygous larvae (*mwh+/+flrl*) *Drosophila melanogaster*	50, 10, or 200 μl/plate	Phytol did not induce any mutation including gene mutations, deletions, or mitotic recombinations	Choi et al. (1993)
3-Methyl-2-buten-1-ol	Ames assay with and without S9 activation (plate incorporation test and pre-incubation test) OECD 471	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	20–5000 μg/plate cytotoxicity: ⩾100 μg/plate (TA100)	Not mutagenic	RIFM (1989h)
	Modified Ames test (liquid suspension pre-incubation assay)	*Salmonella typhimurium* TA98, TA100	20–5000 μg/plate not cytotoxic	Not mutagenic	RIFM (1991c)

Subgroup: secondary					
7-Nonen-2-ol,4,8-dimethyl-	Ames assay with and without S9 activation (plate incorporation test and pre-incubation test)	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 *E. coli* WP2uvrA	Up to 313 μg/plate	Not mutagenic	RIFM (1979e)
Subgroup: secondary allylic					
4-Methyl-3-decen-5-ol	Ames assay with and without S9 activation (plate incorporation test and pre-incubation test)	*Salmonella typhimurium* TA98, TA100, TA102, TA1535, TA1537	Plate incorporation test: 1–1000 or 100–2000μl/plate (TA102/-S9) toxic ⩾33 μl/plate (−S9) or ⩾333 μl/plate (+S9) ⩾1000 μl/plate (TA102/−S9) pre-incubation test: 0.3–333 μl/plate cytotoxicity: ⩾33 μl/plate	Not mutagenic	RIFM (2002a)
Subgroup: tertiary					
Dehydrolinalool[b]	Ames assay with and without S9 activation (standard plate and preincubation assay)	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	20–5000 μg/plate (standard plate assay) to the level of toxicity 4–2500 μg/plate (preincubation assay) cytotoxicity: ⩾100–500 μg/plate	Not mutagenic	RIFM (1989b)
3,7-Dimethyl-1,6-nonadien-3-ol	Ames assay with and without S9 activation (plate incorporation test and pre-incubation test)	*Salmonella typhimurium* TA98, TA100, TA102, TA1535, TA1537	Plate incorporation test: 10–1000 μl/plate or 500–3000 μl/plate (+S9) cytotoxicity: 1000 μl/plate or ⩾2000 μl/plate (+S9) pre-incubation test: 3–1000 μl/plate toxic ⩾100 μl/plate	Not mutagenic	RIFM (2002b)
Isophytol	Ames assay with and without S9 activation	*Salmonella typhimurium* TA97, TA98, TA100, TA1535	Not reported cytotoxicity: not reported	Equivocal	Zeiger and Margolin (2000)
	Ames assay with and without S9 activation	*Salmonella typhimurium* TA97, TA98, TA100, TA102, TA104, TA1535	Up to 10,000 μg/plate 10,000 μg/plate were close to the toxic concentration	Not mutagenic	US National Toxicology Program (1993, 2000)
	Ames assay with and without S9 activation (plate incorporation test and pre-incubation test)	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	20–5000 μg/plate not cytotoxic	Not mutagenic	RIFM (1989g)
	Modified Ames test (liquid suspension pre-incubation assay)	*Salmonella typhimurium* TA98, TA100	20–5000 μg/plate not cytotoxic	Not mutagenic	RIFM (1991b)
Linalool[b]	Ames assay with and without S9 activation (liquid suspension test)	*Salmonella typhimurium* TA100	10–3000 μg per 2 ml incubation volume cytotoxicity: not reported	Not mutagenic	Eder et al. (1980, 1982a,b) and Lutz et al. (1980)
	Ames assay with and without S9 activation	*Salmonella typhimurium* TA92, TA94, TA98, TA100, TA1535, TA1537	Up to 1000 μg/plate in DMSO (highest non-toxic dose)	Not mutagenic	Ishidate et al. (1984)
	Ames assay with S9 activation	*Salmonella typhimurium* TA98, TA100	100 μl (87,000 μg) cytotoxicity: not reported	Not mutagenic	Rockwell and Raw (1979)
	Ames assay with and without S9 activation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538	5–10,000 μg/plate cytotoxicity: 10,000 μg/plate	Not mutagenic	RIFM (1983a)
	Mutation assay	*E. coli* WP2*uvrA*	125–1000 μg/plate to the level of toxicity	Not mutagenic	Yoo (1986)

(*continued on next page*)

Table 4a (*continued*)

Material	Test system		Concentrations	Results	References[a]
	Host mediated assay, with and without beta-glucuronidase	*Salmonella 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 publication in Japanese, not clear whether tested to cytotoxic concentrations	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 nl/ml (3.4–261 μg/ml highly toxic ⩾ 200 nl/ml (174 μg/ml) (−S9) resp. 300 nl/ml (261 μg/ml) (+S9)	Not genotoxic in one experiment and weakly positive in the other	RIFM (1982b) 35826 and Heck et al. (1989)
	Mammalian cell mutation with and without S9 activation	Mouse lymphoma L5178Y TK+/−	12.5–274 μg/ml highly toxic ⩾200 μg/ml	Not genotoxic	RIFM (1994a)
	Chromosome aberration test with and without S9 activation	Chinese hamster lung fibroblasts (CHL)	Up to 0.25 mg/ml in DMSO for 48h (highest non-toxic dose)	Not genotoxic	Ishidate et al. (1984)
	Chromosomal aberration test with and without S9 activation	Chinese hamster ovary cells	16.7–500 μg/ml toxic ⩾350 μg/ml	Not genotoxic	RIFM (1983b)
	Sister chromatid exchange	Chinese hamster ovary cells	5–150 μg/ml not toxic	Not genotoxic	Sasaki et al. (1989)
	Unscheduled DNA synthesis	primary rat hepatocytes	0.5–43.6 μg/ml cytotoxic ⩾0.1 μl/ml (87 μg/ml)	Not genotoxic	RIFM (1986a) and Heck et al. (1989)
2-Methyl-3-buten-2-ol	Ames assay with and without S9 activation (plate incorporation test and pre-incubation test)	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	20–5000 μg/plate cytotoxicity: not reported	Not mutagenic	RIFM (1989f)

[a] Not all of the original reports in the OECD/SIDS assessment were made available to RIFM.
[b] Materials have been previously reviewed by in RIFM's safety assessment of terpene alcohols (Belsito et al., 2008).

Table 4b
Mutagenicity and genotoxicity: *in vivo* studies.

Material	Test system	Species	Dose or concentration	Results	References[b]
Subgroup: primary allylic					
Farnesol[a]	Bone marrow micronucleus assay	Mouse	To the level of toxicity	Not genotoxic	Rupa et al. (2003)
Geraniol[a]	Bone marrow micronucleus assay	Mouse	To the level of toxicity	Not genotoxic	Rupa et al. (2003)
3-Methyl-2-buten-1-ol	Bone marrow micronucleus assay sampling time: 24 h after last dosing	NMRI mouse (five males per dose)	0, 125, 250, 500 mg/kg body weight in olive oil by two i.p. injections at a 24 h interval positive control: cyclophosphamid, vincristine	Not genotoxic; PCE/NCE reduced at ⩾250 mg/kg body weight 500 mg/kg body weight led to evident signs of toxicity	RIFM (2001b)
Subgroup: tertiary					
Isophytol	Bone marrow micronucleus assay; sampling times: 24, 48 h after dosing OECD 474	NMRI BR mouse (5 males per group)	0, 2000 mg/kg body weight in maize/corn oil by single gavage positive control cyclophosphamid	Not genotoxic; PCE/NCE not affected	Meerts (2002) as cited in OECD/SIDS (2006)
Linalool[a]	Bone marrow micronucleus assay	Mouse	500, 1000, 1500 mg/kg body weight by single gavage	Not genotoxic	RIFM (2001)
2-Methyl-3-buten-2-ol	Bone marrow micronucleus assay	NMRI mouse (male and female), n not reported	0, 500, 1000, 1500 mg/kg body weight in water by single gavage positive control: cyclophosphamid, vincristine	Not genotoxic; PCE/NCE not affected	RIFM (1992)

[a] Materials have been previously reviewed by in RIFM's safety assessment of terpene alcohols (Belsito et al., 2008).
[b] Not all of the original reports in the OECD/SIDS assessment were made available to RIFM.

No irritation was observed in predictive tests (e.g. in pre-tests for maximization studies with single occlusive applications for 48 h) with the highest concentrations tested: 30% 3,7-dimethyl-1,6-nonadien-3-ol (RIFM, 1975b), 10% 3-methyl-2-buten-1-ol (RIFM, 1977c), 10% phytol (RIFM, 1977d), 10% isophytol (RIFM, 1982a), 4% nerolidol (RIFM, 1973c), 4% 7-octen-2-ol, 2-methyl-6-methylene-, dihydro derivative (RIFM, 1973c), 4% dihydromyrcenol (RIFM, 1977d), 2% methylheptenol (RIFM, 1976b).

Neat 7-octen-2-ol, 2-methyl-6-methylene-, dihydro derivative led to moderate skin reactions in two out of 99 volunteers during the induction phase of a human repeat insult patch test (HRIPT) (RIFM, 2006b). No irritation was observed with up to 20% 7-octen-2-ol, 2-methyl-6-methylene-, dihydro derivative during the induction phase of two other HRIPTs (RIFM, 1973c, 1995). The repeated application of 10% 4-methyl-3-decen-5-ol during the induction phase of an HRIPT yielded little or no irritation (RIFM, 1981b). A moderate skin reaction appeared in only 1 of 41 subjects under repeated application of 7.5% dihydromyrcenol (RIFM, 1977d).

Further details on studies of dermal irritation in humans are provided in Table 6a.

4.6.2. Animal studies

Ten of the alcohols under review with worldwide uses of >0.01 metric tons/year have been tested in animal models of skin irritation using rabbits or guinea pigs (see Table 6b).

If applied undiluted, phytol, methylheptenol, 3,7-dimethyl-1,6-nonandien-3-ol, 2-methyl-3-buten-2-ol and nerolidol produced no irritation to moderate irritation in almost all studies with rabbits or guinea pigs regardless of the method used with the exception of undiluted 3-methyl-2-buten-1-ol, which was corrosive after 1h occlusive application (RIFM, 1979j) and undiluted isophytol, which produced severe irritation after 1 min application (RIFM, 1970a). Tests performed in accordance with current test guidelines (4 h, semi-occlusive) with 4-methyl-3-decen-1-ol, 7-octen-2-ol, 2-methyl-6-methylene-, dihydro derivative and dihydromyrcenol showed slight to moderate irritation.

No effects or only slight effects were observed in rabbits or guinea pigs with diluted compounds: 50% dihydromyrcenol and 5% methylheptenol, slight reactions; 5% nerolidol, very slight reaction. Moderate skin effects were observed in rabbits with 5% 3,7-dimethyl-1,6-nonandien-3-ol after a 24 h application.

Further details on studies of dermal irritation in animals are provided in Table 6b.

4.7. Mucous membrane irritation

No human studies on mucous membrane irritation are available.

The potential to induce eye irritation has been studied in animals for 10 alcohols under review with worldwide uses of >0.01 metric tons/year (see Table 7).

Some alcohols, phytol (RIFM, 1978b), isophytol (RIFM, 1970a), nerolidol (RIFM, 1968), and methylheptenol (RIFM, 1968), elicited no irritation or only slight eye irritation in rabbits when tested undiluted. 2-Methyl-3-buten-2-ol was irritating to the rabbit eye after 8 h but eventually returning to normal when tested undiluted (no further information available; RIFM, 1972e).

Undiluted 7-octen-2-ol, 2-methyl-6-methylene-, dihydro derivative (RIFM, 1980d), 3,7-dimethyl-1,6-nonadien-3-ol (RIFM, 1968), dihydromyrcenol (RIFM, 1977e) and 4-methyl-3-decen-5-ol showed moderate irritation. The effects noted were reversible after up to 10 days. Thirty percent and 10% 4-methyl-3-decen-5-ol were only slightly irritating and without corneal effects. Moderate conjunctival irritation with corneal involvement was reported for undiluted 3-methyl-2-buten-1-ol. The effects did not clear completely after

Table 5
Reproductive and developmental toxicity studies.

Material	Method	Concentration(s)/dose (mg/kg body weight/day)[a]	Species	Results (mg/kg body weight/day)[a]	References[b]
Subgroup: primary allylic					
3-Methyl-2-buten-1-ol	Pre-test for maternal toxicity 10 pregnant females/dose via gavage on days 6–19 p.c.	100, 300, or 1000 as an aqueous suspension	Rats (Wistar)	100: no effects 300: transient salivation 1000: three dams died prematurely and remaining seven were sacrificed early. Clinical observations included unsteady gait, abdominal position, salivation, ataxia, tremor, urine smeared fur, piloerection, fluid filled stomach, and ulceration. Reduction (~35%) in food consumption	RIFM (2003h)
	OECD TG 414 25 pregnant females/dose were dosed via gavage on gestational days 6–19 p.c.	0, 50, 200, 600 as aqueous suspension (0.5% carboxymethylcellulose CB 30,000 in doubly distilled water)	Rat (Wistar)	NOAEL maternal = 200 NOAEL developmental = 600 *Maternal:* 600: salivation, lacrimation, abdominal position, piloerection; 1 died; mean food consumption, mean body weight, mean body weight gain decreased, corrected body weight gain, mean carcass weight decreased *Offspring:* No effects	RIFM (2002d)
Subgroup: tertiary					
Isophytol	OECD TG 415, one-generation study 24 male and female rats were dosed via gavage exposure duration: males: 10 weeks prior to mating till termination (mean: 98) females: 2 weeks prior to mating till termination (mean: 64 day)	0 (vehicle), 250, 500 or 1000 in maize/corn oil	Rat (Wistar)	LOAEL parental toxicity = 250 NOAEL fertility: 500 NOAEL developmental toxicity = 500 *Maternal:* ⩾250: dilated renal tubules (m,f), renal mineralization (m, f), renal hyaline droplets decreased (m) ⩾500: abs. kidneys weight increased (m,f), rel. kidney weight increased (f), incidence and severity of renal basophilic aggregates increased (m,f), incidence and severity of renal basophilic tubules increased (m,f) 1000: lethargy, hunched posture, piloerection (f); body weight, terminal body weight decreased (m), body weight loss during lactation (f), food consumption during lactation decreased (f); abs. and rel. prostate weight decreased, abs. seminal vesicles weight decreased, rel. kidneys weight increased (m), abs. and rel. uterus weight increased (f); periportal hepatocyte vacuolation decreased (f) pre-coital time increased, fertility index decreased, conception rate decreased *Offspring:* 1000: survival decreased, general fitness decreased, mean body weights during lactation period (m,f) decreased	Beekhuijzen (2002) as cited in OECD/SIDS (2006)
Dihydromyrcenol	OECD and ICH Harmonized Tripartite Guideline Stages C + D 100 (25/group) female rats were dosed via gavage on GD 7–17 p.c.	10 ml/kg of 0, 250, 500 or 1000 in maize/corn oil	Crl:CD (SD) rats	NOAEL maternal 500 mg/kg body weight/day NOAEL developmental 500 mg/kg body weight/day *Maternal*: Absolute and relative feed consumption values decreased *Offspring:* Statistically significant reduction in fetal bodyweights at 1000 mg/kg body weight/day (but within historical controls of facility). Skeletal variations were limited reversible changes at 1000 mg/kg body weight/day	RIFM (2007d)

Linalool (72.9% in coriander oil)[c]	Coriander oil, dissolved in corn oil was administered daily 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 (182, 365, 729 mg linalool/kg body weight/day)	Rat	NOAEL maternal and fertility = 365 mg linalool/kg body weight/day NOAEL developmental: 365 mg linalool/kg body weight/day *Maternal* 365: salivation, statistically non significant: food consumption decreased, body weight decreased, gestation index decreased, length of gestation decreased 729: salivation, urine-stained abdominal fur, ataxia and/or decreased motor function, statistically significant: average maternal body weight gain during the premating period decreased, litter size decreased, gestation index decreased, length of gestation decreased *Offspring* 729: a 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 (1989d) and Belsito et al. (2008)
Linalool[c]	25 presumed pregnant rats were daily dosed via gavage on gestational days 7–17	0 (vehicle), 250, 500 or 1000 in corn oil	Crl:CD® (SD) IGS BR VAF/PLUS® rats	NOAEL maternal = 500 LOAEL maternal = 1000 (reduction in body weight gain, reduced feed consumption) NOAEL developmental toxicity = 1000 *Maternal* Pregnancy occurred in 22, 23, 20, and 22 dams in the 0, 250, 500, or 1000 respectively. There were no test substance-related clinical signs or gross lesions. 1000: body weight gains reduced (11%) during the dosage period (increased during post-dosage period). Absolute and relative feed consumption values significantly reduced (7%) for the dosage period. *Offspring* No litter parameters affected. No gross external, soft tissue, or skeletal fetal alterations.	Politano et al. (2008)
2-Methyl-3-buten-2-ol	OECD TG 421 (screening test) male and female rats (10/sex/group) were dosed via gavage premating exposure period (both sexes): 2 weeks exposure period: 22 days	0 (vehicle), 12.5, 50 or 200	Rat (Fü-Albino (RORO))	NOAEL parental and offspring: 50 mg/kg body weight/day *Parental:* 200 mg/kg body weight/day: body weights (m) decreased; food consumption during lactation period (f) decreased pasty feces (m,f) *Offspring* 200 mg/kg body weight/day: pup viability index decreased	Roche (1995b) as cited in OECD/SIDS (2005b)

p.c. = post coitum.

[a] Units have been converted to make easier comparisons; original units are in the fragrance material reviews.

[b] Not all of the original reports in the OECD/SIDS assessment were made available to RIFM.

[c] Materials have been previously reviewed by in RIFM's safety assessment of terpene alcohols (Belsito et al., 2008).

eight days. The authors concluded that the substance has a risk of serious damage to the eyes (RIFM, 1970e).

4.8. Skin sensitization

4.8.1. Human studies

Nine of the alcohols under review with worldwide uses of >0.01 metric tons/year have been evaluated for their potential to induce sensitization in humans (see Tables 8a and 8b).

In the subgroup of primary allylic alcohols, no evidence of sensitizing effects in a maximization test with volunteers was observed with 3-methyl-2-buten-1-ol (10%, RIFM, 1977c). Phytol was considered to be a marginal sensitizer when 1 in 25 volunteers showed a positive reaction (10%, RIFM, 1977d).

Methylheptenol (2%, RIFM, 1976b) from the subgroup of secondary alcohols, 4-methyl-3-decen-5-ol (10%, RIFM, 1981b) from the subgroup of secondary allylic alcohols, and 7-octen-2-ol, 2-methyl-6-methylene-, dihydro derivative (neat or 20%, RIFM, 1995, 2006b), 3,7-dimethyl-1,6-nonadien-3-ol (30%, RIFM, 1975b), dihydromyrcenol (7.5%, RIFM, 1972c), isophytol (10%, RIFM, 1981a) and nerolidol (4%, RIFM, 1973c) from the subgroup of tertiary alcohols did not induce positive reactions in maximization tests or repeated insult patch tests.

From the previously reviewed terpene alcohol groups (Belsito et al., 2008), sensitization reactions were observed in human predictive tests with geraniol (6% in petrolatum), farnesol (undiluted) and rhodinol (3,7-dimethyl-7-octen-1-ol; 5% in petrolatum). Restrictions for use apply to farnesol, geraniol (considered weak sensitizers), rhodinol, and citronellol (considered extremely week sensitizers) (IFRA, 2006, 2007b,c; Api et al., 2006).

4.8.1.1. Elicitation studies. In Belsito et al. (2008), the diagnostic patch test data was summarized for several materials in this group. Positive reactions in the diagnostic patch tests on dermatitis patients were reported for geraniol, nerol, nerolidol, citronellol, and in very few cases for linalool and rhodinol.

Benke and Larsen (1984) studied the dose response relationships of geraniol in product use by testing 12 pre-sensitized subjects. Patch test thresholds were initially determined using 48 h patches of 0.5–5% in petrolatum. Four patients reacted to geraniol at concentrations greater than 2.5%, and no reactions were seen in control subjects. Eight to 10 weeks after threshold levels had been determined, 48 h patch tests were conducted on the same 12 patients with a mixture of hydroxycitronellal, geraniol, and 3 and 4-(4-hydroxy-4-methylpentyl)-. Individual materials were not tested alone, and the dose was not reported. One patient who previously reacted to geraniol also reacted to a mixture of hydroxycitronellal and geraniol as well as a mixture of all three. Three patients who had not previously reacted to geraniol reacted to a mixture of geraniol and hydroxycitronellal. One patient who had not previously reacted to geraniol reacted to a mixture of geraniol and hydroxycitronellal, as well as to a mixture of all three. The 12 dermatitis patients determined from confirmed sensitivity in 48 h closed patch tests were then supplied with shampoos containing the fragrance mixture with overall concentrations of 0.03%, 0.09%, 0.3%, 0.9%, 3%, 9% or 15%. Reactions were reported in two dermatitis patients and one control patient with the shampoo containing 5% of each material (the highest dose, an overall concentration of 15%).

Johansen et al. (1998) investigated the ability of deodorants, which had previously caused axillary dermatitis in fragrance mix sensitive eczema patients, to provoke reactions on repeated open application tests (ROATs) to the upper arm and in the axillae. Trials of 20 deodorants were tested among 14 patients where two applications were made per day in the axilla and simultaneously on a 25 cm^2 area of the upper arm. Geraniol was present in 15 of the deodorants analyzed. Nine of the deodorants containing geraniol (mean concentration of 0.023%) resulted in use test positive reactions and five deodorants (mean concentration of 0.018%) were negative in the use test. In general the mean concentration of fragrance mix constituents was higher in deodorants causing a positive use test.

A ROAT was conducted with farnesol in a patient who reacted positively to fragrance mix II (which contains farnesol). The patient reacted to 2.8% farnesol on day 8 (Frosch et al., 2005).

4.8.2. Animal studies

Information on the individual animal studies is provided in Table 8c. In comparison to humans, sensitization in animals has been less studied. Only tertiary alcohols were tested.

7-Octen-2-ol, 2-methyl-6-methylene-, dihydro derivative (RIFM, 1994b,c, 1996), dihydromyrcenol (RIFM, 2007b) and isophytol (RIFM, 1970a) were negative in guinea pig sensitization tests.

Weak reactions were found in guinea pig tests with nerolidol. Nerolidol was weakly positive in two adjuvant tests with challenge concentrations of 3% and 10% (Hausen et al., 1995). An open epicutaneous test (OET) (Klecak, 1979, 1985) and a Draize sensitization test (Sharp, 1978) were negative. To evaluate cross-sensitization, guinea pigs induced with farnesyl acetate were cross-challenged with nerolidol and no cross-reactions were observed (RIFM, 1977f).

Certain oxidation products of alcohols (hydroperoxides) may give rise to skin sensitization, as was shown for linalool (Belsito et al., 2008). There is an IFRA standard on linalool which limits the peroxide level to 20 mmol/l in the raw material (IFRA, 2004). Oxidation has to be avoided and it has to be ensured that only pure materials are used in fragrances.

4.9. Phototoxicity and photoallergenicity

Limited data were available with regard to the phototoxicity and photoallergenicity of alcohols with unsaturated chains (see Table 9). From human or animal studies, reliable data were available on the phototoxicity of the secondary allylic alcohol, 4-methyl-3-decen-5-ol, and the tertiary alcohols, 7-octen-2-ol, 2-methyl-6-methylene-, dihydro derivative and dihydromyrcenol. 4-Methyl-3-decen-5-ol was the only compound tested for its photoallergenic potential.

No phototoxic reactions were seen in groups of 10 human volunteers exposed to 1–8% 7-octen-2-ol, 2-methyl-6-methylene-, dihydro derivative and 12% dihydromyrcenol, followed by irradiation with UVA (RIFM, 1981c).

Only one reliable phototoxicity animal study was performed. In guinea pigs, 10% 4-methyl-3-decen-5-ol in ethanol elicited no reactions (RIFM, 1980g). Isophytol was tested in a non-valid study with guinea pigs (RIFM, 1999). The study was performed without control animals. No conclusion regarding phototoxicity potential can be made because all the test doses were irritating without UV irradiation.

Results obtained in non-validated *in vitro* yeast assays with 7-octen-2-ol, 2-methyl-6-methylene-, dihydro derivative and dihydromyrcenol are not considered to be reliable or relevant (Bagley et al., 1988; RIFM, 1980i; Tenenbaum et al., 1984).

There are no studies investigating the photoallergic potential in humans.

Only 4-methyl-3-decen-5-ol was tested for its photoallergenicity in a reliable test with guinea pigs (RIFM, 1989c). No photoallergenicity was observed in guinea pigs induced with 10% in petrolatum and 10 J/cm^2 UVA (after injection of FCA before the first induction) then challenged three weeks after initiation of induction with up to 30% (in acetone:ethanol 1:1) and irradiation.

Table 6a
Skin irritation studies in humans.

Material	Method	Concentration	Subjects	Results	References
Subgroup: primary					
2-Isopropenyl-5-methyl-4-hexene-1-ol[a]	48 h, occlusive (pre-test for a maximization study)	5% in petrolatum	26 volunteers	No irritation	RIFM (1981a)
Subgroup: primary allylic					
2-Isopropenyl-5-methyl-2-hexene-1-ol[a]	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	5 male volunteers	No irritation	RIFM (1972a)
	Induction phase of HRIPT	vehicle and concentration not reported	16 female volunteers	Little or no irritation	RIFM (1972b)
3-Methyl-2-buten-1-ol	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	26 healthy volunteers	No irritation	RIFM (1977c)
Phytol	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	25 healthy volunteers	No irritation	RIFM (1977d)
(Z)-2-Penten-1-ol	Induction phase of HRIPT	0.25% in alcohol SDA 40	38 healthy volunteers	No irritation	RIFM (1971)
Subgroup: secondary					
5,9-Dimethyl-8-decen-3-ol[a]	Induction phase of HRIPT (semi-occlusive)	1% in ethanol	39 healthy volunteers	No irritation	RIFM (1965)
Methylheptenol	48 h, occlusive (pre-test for a maximization study)	2% in petrolatum	25 healthy volunteers	No irritation	RIFM (1976b)
7-Nonen-2-ol,4,8-dimethyl-	Induction phase of HRIPT (semi-occlusive)	20% in white petrolatum	50 healthy volunteers	No irritation	RIFM (1979e)
Subgroup: secondary allylic					
4-Methyl-3-decen-5-ol	Induction phase of HRIPT (occlusive)	10% in dimethyl phthalate	50 healthy volunteers	No irritation	RIFM (1981b)
6,10-Dimethylundeca-1,5,9-trien-4-ol[a]	Induction phase of HRIPT (occlusive)	0.5% in Alcohol SDA 39 C	38 volunteers	No irritation	RIFM (1973d)
Subgroup: tertiary					
7-Octen-2-ol, 2-methyl-6-methylene-, dihydro derivative	Induction phase of HRIPT	5% (vehicle not provided)	42 healthy volunteers	No irritation	RIFM (1964b)
	Induction phase of HRIPT	20% in diethyl phthalate (DEP)	109 healthy volunteers	No irritation	RIFM (1995)
	Induction phase of HRIPT	20% in 1:3 diethyl phthalate:Ethanol (DEP:EtOH)	99 healthy volunteers	Barely perceptible to mild irritation with equivalent or less irritation produced by saline, 2/99 barely perceptible to moderate and marked erythema	RIFM (2006b)
	48 h, occlusive (pre-test for a maximization study)	4% in petrolatum	5 healthy volunteers	No irritation	RIFM (1973c)
2,6-Dimethyl-2-hepten-6-ol[a]	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	5 healthy volunteers	No irritation	RIFM (1974b)
3,7-Dimethyl-1,6-nonadien-3-ol	48 h, occlusive (pre-test for a maximization study)	30% in petrolatum	25 healthy volunteers	No irritation	RIFM (1975b)
Dihydromyrcenol	48 h, occlusive (pre-test for a maximization study)	4% in petrolatum	25 healthy volunteers	No irritation	RIFM (1977d)
	Induction phase of HRIPT	7.5% in alcohol SDA 39 C	41 healthy volunteers	Moderate irritation in 1/41	RIFM (1972c)
Isophytol	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	27 healthy volunteers	No irritation	RIFM (1981a)
3-Methyl-1-octen-3-ol[a]	48 h, occlusive (pre-test for a maximization study)	10% in petrolatum	25 healthy volunteers	No irritation	RIFM (1978c)
3-Methyl-1-octyn-3-ol[a]	48 h, occlusive (pre-test for a maximization study)	2% in petrolatum	25 healthy volunteers	No irritation	RIFM (1979b)
Nerolidol (mixed isomers)[b]	48 h, occlusive (pre-test for a maximization study)	4% in petrolatum	5 healthy volunteers	No irritation	RIFM (1973c)
3,7,9-Trimethyl-1,6-decadien-3-ol[a]	48 h, occlusive (pre-test for a maximization study)	20% in petrolatum	26 healthy volunteers	No irritation	RIFM (1977c)

[a] No relevant use was reported, therefore the available data are mentioned only in the table but not in the text.
[b] Materials have been previously areviewed by in RIFM's safety assessment of terpene alcohols (Belsito et al., 2008).

UV spectra have been obtained for 13 materialsa (6-ethyl-3-methyloct-6-en-1-ol; (Z)-2-penten-1-ol; methylheptenol; 4-methyl-3-decen-5-ol; 7-octen-2-ol, 2-methyl-6-methylene-, dihydro derivative; 3,7-dimethyl-1,6-nonadien-3-ol; dihydromyrcenol; isophytol; 2-methyl-3-buten-2-ol; (E)-nerolidol; nerolidol (isomer unspecified); 3-methyl-2-buten-1-ol; (2E,6Z)-nona-2,6-dien-1-ol). In general, they did not absorb UVB light (290-320 nm). They all absorbed UV light peaking in the UVC range (<290 nm; peaking in the range of 200–220 nm) (see Table 10). Based on the UV spectra and review of phototoxic/photoallergy data, the materials in this group would not be expected to elicit phototoxicity or photoallergy under the current conditions of use as fragrance ingredients.

4.10. Miscellaneous studies

4.10.1. Hepatotoxicity

In isolated perfused livers of rats, 65.1 mmol 3-methyl-2-buten-1-ol/l (5600 mg/l) was cytotoxic as evidenced by the release of liver enzymes into the perfusate. In comparison to C3 and C4-alcohols tested, the cytotoxicity was not influenced by saturation or

Table 6b
Skin irritation studies in animals.

Material	Method	Concentration	Species	Results	References[b])
Subgroup: primary					
2-Isopropenyl-5-methyl-4-hexene-1-ol[a]	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Guinea pig (n = 10)	Slight to absent skin reactions	RIFM (1982a)
Subgroup: primary allylic					
2-Isopropyl-5-methyl-2-hexene-1-ol[a]	24 h, occlusive, 0.5 ml as a single application on intact and abraded skin, readings: 24 h, 72 h	n.f.i	Rabbit (n = 6)	Not irritating (Primary Irritation Index: 1.5)	RIFM (1972d)
3-Methyl-2-buten-1-ol	1, 5, 15 min and 20 h, occlusive, 0.5 ml, single application on intact skin, observation: 24 h, 8 days	Undiluted	Rabbit (n = 8, 2 per exposure time)	Corrosive: 1 and 5 min: slight erythema (at 24 h), slight scaling (at 8 days) 15 min: moderate erythema, slight edema (at 24 h), moderate scaling (at 8 days) 20 h: moderate erythema, slight edema, necrosis (at 24 h), necrosis (at 8 days)	RIFM (1970a, 2003g)
	24 h, occlusive, 0.5 ml as a single application on intact and abraded skin	Undiluted	Rabbit (n = 6)	Extremely irritating	RIFM (1979j)
	4 h, occlusive, 0.5 ml as a single application	Undiluted	Rabbit (n = 4)	Corrosive (Primary Irritation Index: 6.13, calculation not done in the original report, done by OECD)	SCAT (1992) as cited in OECD/SIDS (2005a)
	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit (n = 4)	Moderate to severe erythema mild to severe edema	RIFM (1977a)
	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rat (n = 6)	Slight local skin irritation	RIFM (1979j)
	1 h, occlusive, 0.5 ml as a single application	Undiluted	Rabbit (n = 4)	Corrosive in 2 out of 4 animals after 1 h of occlusive exposure	
Phytol	4h, semi-occlusive, 0.5 ml as a single application	undiluted	rabbit (n = 10)	Mild to moderate erythema and edema	RIFM (1977a)
	1, 5 and 120 min, no information if semi-occlusive, single application on intact skin	n.f.i	Rabbit (n = 2)	1 min: mild erythema (1/2) 5 min: mild erythema (2/2), at 8 days questionable erythema; questionable (1/2) to mild edema (1/2), reversible at 8 days 120 min: mild erythema (2/2), persisted until 8 days, questionable or mild edema, reversible at 8 days moderately irritating	RIFM (1978b)
	2 h, single application on intact and abraded skin, readings at 24 h, 72 h, 8 days, according to Federal Register 38, No 187, §1500.41, 27.09.1973	n.f.i	Rabbit (n = 6)	Moderately irritating (Primary irritation index: 5.0), effects persisted until 8 days	RIFM (1978b)
(Z)-2-penten-1-ol	24 h, occlusive, 0.5 ml as a single application on intact and abraded skin	0.25% in alcohol SDA 40	Rabbit (n = 3)	Erythema and Eschar formation was observed on the abraded skin at 24 h. Produced a primary irritation index of 1	RIFM (1970b)
Subgroup: secondary					
Methylheptenol	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit (n = 10)	Moderate to marked erythema slight to moderate edema	RIFM (1967b, 1976d)
	24 h, occlusive, single application on intact and abraded skin,, readings at patch removal and at 48 h	Undiluted and 5% in diethylphthalate	Rabbit (n = 3)	100%: Very slight erythema (3/3, at 24 h), very slight (1/3) to well-defined (2/3) erythema (at 48 h), without edema 5%: very slight erythema (at 24 h), reversible at 48 h	RIFM (1968)
7-Nonen-2-ol,4,8-dimethyl-	24 h, single application on intact and abraded skin, readings at 24 h, and 72 h	Undiluted	Rabbit (n = 10)	Very slight to well-defined erythema very slight to slight edema at 24 h	RIFM (1979a)
	24 h, single application on intact and abraded skin, readings at 24 h, and 72 h	Undiluted	Rabbit (n = 6)	Very slight to well-defined erythema which increased from 24 to 72 h very slight to slight edema	RIFM (1979f)
	48 h, occlusive, 0.3 ml as a single application	1%, 10%, or 100% in petrolatum	Guinea pig (3/dose)	1% mild irritation 10% moderate irritation 100% severe irritation	RIFM (2004a)
	Cumulative open application of 0.3 ml once daily for two weeks	10% or 100%	Guinea pig (3/dose)	10% weak irritation 100% severe irritation (discontinued)	RIFM (2004a)
	Maximization (Induction: six intradermal injections and an occluded 48 h patch)	0.05% in 1:3 dipropylene glycol:aqueous propylene glycol 10% in dipropylene glycol	Guinea pig (n = 10)	Irritation reactions were observed with intradermal injections of Freund's complete adjuvant alone and mixed in solution.	RIFM (1976c)

Subgroup: secondary allylic					
4-Methyl-3-decen-5-ol	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit ($n = 3$)	Slightly irritating (mean score for erythema 1.33 and for edema 0.56), effects reversible (erythema by 7 days, edema by 4 days, scaling by 21 days)	RIFM (2000)
	48 h, 0.1 ml as a dermal application	10% in acetone/ethanol (1:1)	Guinea pig ($n = 8$)	At 4 h slight irritation observed in 2/8 reversible by 48 h	RIFM (1980g)
6,10-Dimethylundeca-1,5,9-trien-4-ol[a]	24 h, occlusive, 0.5 ml as a dermal application	0.5% in alcohol SDA 39 C	Rabbit ($n = 3$)	No irritation observed to the intact and abraded skin	RIFM (1973f)
Subgroup: tertiary					
7-Octen-2-ol, 2-methyl-6-methylene-, dihydro derivative	Buehler (pre-test), 6 h, occluded 0.4 ml as 3 applications	5, 12.5, 25,50, 100%	Guinea pig ($n = 2$)	No irritation reactions were observed	RIFM (1994c)
	24 h, occluded, 5 g/kg as a single application	Undiluted	Rabbit ($n = 10$)	Slight (6/10) to moderate (1/10) erythema and Slight (5/10) to moderate (1/10) edema	RIFM (1973a)
	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit ($n = 3$)	Irritating (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 ($n = 4$)	Slightly irritating (mean score for erythema 1.5 and for edema 0.5)	RIFM (1985)
2,6-Dimethyl-2-hepten-6-ol[a]	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit ($n = 10$)	Marked redness in 10, moderate edema in 7 and marked edema in 3	RIFM (1974a)
3,7-Dimethyl-1,6-nonandien-3-ol	24 h, no information if semi-occlusive, 0.5 ml, single application on intact and abraded skin, observations 24 and 72 h	Undiluted and 5% in DEP	Rabbit ($n = 3$)	Undiluted: well-defined erythema, still present at study end as slight erythema, 5% in DEP: very slight (2/3) to well-defined erythema (1/3) cleared by 72 h	RIFM (1968)
	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit $n = 10$)	Slight to moderate erythema and edema	RIFM (1975a)
Dihydromyrcenol	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit ($n = 3$)	Irritating according to EEC classification (mean erythema score of 2.0 in 2 animals, 0.3 in one animal): very slight erythema (2/3), marked desquamation (3/3), very slight edema (1/3) at 160 h	RIFM (1984a)
	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit ($n = 4$)	Irritating (mean score for erythema 2.0 and for edema 1.6), at 168 h very slight (1/4) to well-defined	RIFM (1985)
	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit ($n = 10$)	Moderate to sever erythema and edema	RIFM (1977a)
	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted and 50% in DEP	Rabbit ($n = 4$)	Undiluted: irritating (mean score for erythema 2.0 and for edema 1.9) 50%: non-irritating (mean score for erythema 1.8 and for edema 1.7)	RIFM (1986b)
Isophytol	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit ($n = 10$)	moderate to severe erythema and edema	RIFM (1982c)
	single application (n.f.i.) back: 1, 5, 15 min and 20 h ear: 20 (observation after 24 h and 8 day)	Undiluted	Rabbit (number not reported)	Back: all durations: very severe erythema (at 24 h), severe flaking (at day 8) 20 h: additional severe edema (at 24 h), severe flaking and severe erythema (at day 8) ear: 20 h: very severe at 8 day: severe flaking	RIFM (1969, 1970a)
	phototoxicity study: occlusive without UV irradiation, duration of application not reported, invalid study, observations at 24 and 48 h	5, 10%, 30% and 50% in acetone, no control	Guinea pig (Hartley; female) (5)	5%, 10%, 30%, 50%: dose dependently irritating (with and without UV irradiation), PII (irradiated and non-irradiated): 0.4, 0.9, 1.6, 1.8 (5%, 10%, 30%, 50%)	RIFM (1999)
3-Methyl-1-octen-3-ol[a]	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit ($n = 10$)	Slight redness in 2/10 animals, moderate redness in 1/10 animals and severe redness in 7/10 animals. Moderate edema in 10/10 animals. Limited mobility due to eschar formation	RIFM (1978a)

(*continued on next page*)

Table 6b (*continued*)

Material	Method	Concentration	Species	Results	References[b]
3-Methyl-1-octyn-3-ol[a]	24 h, occlusive, 0.5 g, single application on intact and abraded skin, readings at patch removal and at 72 h	n.f.i	Rabbit ($n = 6$)	No irritation (Primary irritation score: 1.09)	RIFM (1979a)
Nerolidol (isomer unspecified)[c]	24 h, no information if semi-occlusive, 0.5 ml, single application on intact and abraded skin, readings at 24 and 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 (1968)
3,7,9-Trimethyl-1,6-dicadien-3-ol[a]	24 h, occlusive, 0.5 ml, single application on intact and abraded skin, readings at 24 and 48 h	undiluted and 5% in DEP	Rabbit ($n = 3$)	Undiluted: very slight to well-defined erythema, still present as very slight at study end 5% in DEP: very slight to well-defined erythema, cleared by 72 h	RIFM (1968)
	4 h, semi-occlusive, 0.5 ml as a single application	Undiluted	Rabbit ($n = 10$)	Moderate redness in 10, mild edema in 3 and moderate edema in 7. Skin hairless at exposure site in 6 at necropsy	RIFM (1977a)

DEP = diethylphthalate.
n.f.i. = no further information.
[a] No relevant use was reported, therefore the available data are mentioned only in the table but not in the text.
[b] Not all of the original reports in the OECD/SIDS assessment were made available to RIFM.
[c] Materials have been previously reviewed by in RIFM's safety assessment of terpene alcohols (Belsito et al., 2008).

branching of the carbon chain. Unsaturated alcohols in general decreased the content of reduced glutathione and ATP in the liver to a greater extent than saturated alcohols. However, this was not the case for 3-methyl-2-buten-1-ol. Lipid peroxidation was observed with unsaturated alcohols including 3-methyl-2-buten-1-ol. The mechanism(s) of hepatic injury by unsaturated alcohols may include oxidation to a reactive metabolite (allylic aldehyde) which depresses the glutathione content (Strubelt et al., 1999).

4.10.2. Effects on nervous system

2-Methyl-3-buten-2-ol seems to contribute to the sedative action of hops. Administration of 206.5 mg 2-methyl-3-buten-2-ol/kg body weight i.p. to Wistar rats caused a decline of motility by 50% within two minutes. A maximum response was reached within 2 h (Wohlfahrt et al., 1993).

Neurophysiological stimulation of jasmine absolute oil and certain identified components thereof, e.g. phytol and isophytol, was tested in a mouse model (Tsuchiya et al., 1992). Mice were anaesthetised using sodium pentobarbital i.p. and exposed to atmospheric concentrations of jasmine absolute or its components. Jasmine absolute and phytol significantly reduced the pentobarbital sleep time; whereas isophytol had no effect on sleeping time.

Nerolidol and phytol had sedative (50 and 100 mg/kg body weight, respectively.) and spasmolytic effects (EC_{50} 1.5 and 20 μg/ml, respectively) in mice (Binet et al., 1972).

5. Summary

The compounds assessed in this group summary are structurally related and have similar metabolism and toxicity profiles.

5.1. Exposure summary

Calculated maximum daily systemic exposures for 15 of the compounds under review when applied dermally were estimated to range from 0.0003 to 0.33 mg/kg body weight/day for the individual substances in users with high consumption of cosmetic products containing these materials (see Table 1). The highest maximum skin level concentration for the alcohols in fine fragrances has been reported to be 6.8% for dihydromyrcenol. Data on inhalation exposure during use of the substances are lacking.

5.2. Toxicokinetics summary

Although data on pharmacokinetics are scarce, the alcohols under review are expected to be taken up via the skin and the lung as demonstrated by structurally related terpene alcohols. Uptake via the oral route was demonstrated for *phytol* and *linalool* as well as for other materials by toxicity after acute oral application in animal experiments (see Section 4.2). Quantitative data on uptake and elimination are lacking for the compounds under review. For *linalool* a rapid uptake and elimination from blood was shown in a volunteer after application to the skin. Urine followed by expired air and feces are the main excretion pathways for *linalool* in rats.

5.3. Metabolism summary

Data on metabolism for the compounds under review are available only for phytol.

Data from structurally similar non-cyclic terpene alcohols that contain all key structural elements (a hydroxy group, methyl substituents, and double bonds including allylic alcohols) and potential sites of metabolism as the members of this group demonstrate that the major pathways of metabolism and fate are:

Table 7
Mucous membrane irritation studies in rabbits.

Material	Method	Results	References[b]
Subgroup: primary allylic			
2-Isopropyl-5-methyl-2-hexene-1-ol[a]	0.1 ml, used as received (n.f.i.), observations at 24, 48, 72 h, 6 animals	Slight to moderate conjunctivitis in 4/6 (24 h), reversible	RIFM (1972d)
3-Methyl-2-buten-1-ol	0.1 ml, undiluted, observations at 24, 48, 72 h, 3 animals	Highly irritating (Irritation score (24, 48 and 78 h): 28.7, max. score = 110): slight to moderate corneal opacity, moderate conjunctival redness and chemosis, not completely reversible within 8 days	RIFM (1979k)
	0.05 ml, undiluted, 2 animals	Irritating: slight corneal opacity, moderate redness and edema, reversible after 8 days except a slight conjunctival redness	RIFM (1970e, 2003f)
Phytol	*n* = 6, according to Federal Register 38, No. 187, §1500.42, 27019 (27.9.73)	Slight to moderate conjunctival erythema and slight secretion, primary irritation index: 3.2 authors: not irritating	RIFM (1978b)
(Z)-2-penten-1-ol	0.1 ml, 0.25% in alcohol SDA 40, 3 animals	Produced a moderate irritation involving the conjunctivae of the treated eyes eyes returned to normal by 7th day	RIFM (1970c)
Subgroup: secondary			
5,9-Dimethyl-8-decen-3-ol[a]	0.1 ml, 5%, observations at 24, 48, 72, 96 h, 7 day, 3 animals	No corneal or iris effects, mild vessel injection (1/3) or more diffuse redness (2/3) of palpebral conjunctivae, with slight (2/3) or obvious chemosis (1/3) and very slight (2/3) to slight discharge (1/3), all effects cleared by the 7th day	RIFM (1964a)
Methylheptenol	0.1 ml, undiluted and 5% in diethylphthalate, observations immediately and at 1, 2, 4, 24 and 48 h, 3 animals	100%: very slight corneal opacity (3/3, tested with fluorescein at 48 h), very slight erythema in 3/3 (4 h), 2/3 (24 h), 1/3 (48 h), very slight chemosis (2/3), cleared by 24 h, discharge: well-defined in 3/3 (4 h), very slight in 1/3 (24 h, 48 h) 5%: very slight erythema at instillation, normalized after 1 h, very slight discharge in 1/3 (1 and 2 h), normalized by 4 h	RIFM (1968)
7-Nonen-2-ol,4,8-dimethyl-	0.1 ml, undiluted, observations up to 3 days, 6 animals	Irritation observed. Corneal and conjunctival irritation persisted until day 3	RIFM (1979g,h)
Subgroup: secondary allylic			
4-Methyl-3-decen-5-ol	0.1 ml, undiluted, 30% and 10% in diethylphthalate observations immediately and at 1, 24, 48, 72 h, 7 and 14 days, 3 animals	100%: moderate redness, very slight edema, accompanied by corneal opacity, all effects cleared by the 7th day 30% and 10%: slight erythema without cornea effects, cleared after 4 days and 72 h resp.	RIFM (1980c)
6,10-Dimethylundeca-1,5,9-trien-4-ol[a]	0.1 ml, 0.5% in alcohol SDA 39 C, 3 animals	Mild conjunctival irritation which lasted seven days in one animal with that animal showing corneal involvement	RIFM (1973e)
	0.1 ml, 0.5% in alcohol SDA 39 C, 3 animals	Conjunctival irritation which did not clear on the 10th day of observation with corneal involvement	RIFM (1975c)
	0.1 ml, 0.1% in alcohol SDA 39 C, 3 animals	Conjuctival irritation which cleared on the 10th day of observation with corneal involvement clearing on the 4th day	RIFM (1975d)
Subgroup: tertiary			
7-Octen-2-ol, 2-methyl-6-methylene-, dihydro derivative	0.1 ml, undiluted, 6 animals	Conjunctival irritation and corneal opacity was observed in all rabbits. All eyes had normalized by day 10	RIFM (1980d)
	0.1 ml, 7% in propylene glycol, 6 animals	Conjunctival irritation (6/6), corneal opacity (3/6); vascularization on day 7 in one rabbit. All eyes had normalized by day 7	RIFM (1980e)
	0.1 ml, 5% (vehicle not provided), 3 animals	Mild vessel injection of palpebral conjunctivae was observed. The treated eyes were normal on the third day	RIFM (1980f)
3,7-Dimethyl-1,6-nonadien-3-ol	0.1 ml, undiluted and 5% in diethylphthalate, observations immediately and at 1, 2, 4, 24, 48 and 72 h, 3 animals	100%: very slight to well-defined erythema, still present at 72 h, very slight to well-defined chemosis, cleared by 72 h, very slight cornea opacity (3/3), still present at 72 h, discharge: well-defined to moderate till 4 h, at 72 h very slight discharge still present in 1/3 5%: very slight erythema at instillation, normalized by 1 h, very slight discharge in 2/3 (1 and 2 h), normalized by 4 h	RIFM (1968)
Dihydromyrcenol	0.1 ml, 7.5% in alcohol SDA 39 C, 3 animals	Conjunctival irritation (moderate redness, slight to moderate edema and slight to severe discharge), with corneal involvement, effects still present after 7 days. Effects in control rabbits (0.1 ml alcohol SDA 39 C) more severe	RIFM (1977e)
	0.1 ml, undiluted, 6 animals	Irritating: conjunctival irritation (6/6), iris involvement (4/6) and opacity (2/6) was observed, all eyes had normalized by day 7 (Draize scores of 16.9, 9.0 and 8.4 at days 1, 2, and 3)	RIFM (1984b)
Isophytol	0.05 ml, undiluted, (n.f.i.)	Slight redness by 1 h and 24 h, slight corneal clouding by 24 h; cleared after 8 days	RIFM (1969, 1970a)
2-Methyl-3-buten-2-ol	"internal method BASF", rabbit (n.f.i.)	irritating (n.f.i.)	RIFM (1972e)
3-Methyl-1-octyn-3-ol[a]	0.1 g, undiluted, observations at 1 h and 1, 2, 3, 5, 7 and 14 days, 6 animals 0.1 g, undiluted, washout after 5 sec, observations at 1 h and 1, 2, 3, 5, 7 days, 3 animals	Conjunctival erythema, chemosis and discharge and opacity was observed in all rabbits. In 2/6 effects still present after 14 days conjunctival erthema, chemosis and discharge and opacity were observed in all rabbits, chemosis (3/3) and discharge (1/3) still present after 7 days	RIFM (1979a)
Nerolidol (isomer unspecified)[c]	0.1 ml undiluted and 5% in DEP, 3 animals	Undiluted: very slight redness, cleared by 2 h 5%: no effects	RIFM (1968)
3,7,9-Trimethyl-1,6-dicadien-3-ol[a]	0.1 ml undiluted and 5% in DEP, 3 animals	Undiluted: very slight to well-defined redness and chemosis, very slight to moderate discharge, redness and discharge still present at the end of study (72 h) 5%: very slight redness at instillation, very slight discharge till 2 h	RIFM (1968)

DEP = diethylphthalate
n.f.i.: no further information
[a] No relevant use was reported, therefore the available data are mentioned only in the table but not in the text.
[b] Not all of the original reports in the OECD/SIDS assessment were made available to RIFM.
[c] Materials have been previously reviewed by in RIFM's safety assessment of terpene alcohols (Belsito et al., 2008).

Table 8a
Skin sensitization studies in humans.

Material	Method	Concentration(s)	Subjects	Results	References
Subgroup: primary					
2-Isopropenyl-5-methyl-4-hexene-1-ol[a]	Maximization test	5% in petrolatum	26 volunteers	No sensitization reactions	RIFM (1981a)
Subgroup: primary allylic					
2-Isopropenyl-5-methyl-2-hexene-1-ol[a]	Maximization test	10% in petrolatum	25 male volunteers	No sensitization reactions	RIFM (1972a)
	HRIPT	concentration and vehicle not reported	16 female volunteers	No sensitization reactions	RIFM (1972b)
3-Methyl-2-buten-1-ol	Maximization test	10% in petrolatum	26 volunteers	No sensitization reactions	RIFM (1977c)
Phytol	Maximization test	10% in petrolatum	25 volunteers	1 positive reaction	RIFM (1977d)
(Z)-2-Penten-1-ol	HRIPT	0.25% in alcohol SDA 40	38 healthy volunteers	No sensitization reactions	RIFM (1971)
Subgroup: secondary					
5,9-Dimethyl-8-decen-3-ol[a]	HRIPT	1% in ethanol	39 volunteers	No sensitization reactions	RIFM (1965)
Methylheptenol	Maximization test	2% in petrolatum	25 volunteers	No sensitization reactions	RIFM (1976b)
7-Nonen-2-ol,4,8-dimethyl-	HRIPT	20% in white petrolatum	50 healthy volunteers	No sensitization reactions	RIFM (1979e)
Subgroup: secondary allylic					
4-Methyl-3-decen-5-ol	HRIPT (occlusive)	10% in dimethyl phthalate	50 volunteers	No sensitization reactions	RIFM (1981b)
6,10-Dimethylundeca-1,5,9-trien-4-ol[a]	HRIPT	0.5% in alcohol SDA 39 C	38 volunteers	No sensitization reactions	RIFM (1973d)
Subgroup: tertiary					
7-Octen-2-ol, 2-methyl-6-methylene-, dihydro derivative	Maximization test	4% in petrolatum	25 volunteers	No sensitization reactions	RIFM (1973c)
	HRIPT	5% in ethanol	42 volunteers	No sensitization reactions	RIFM (1964b)
	HRIPT	20% in diethyl phthalate	109 volunteers	No sensitization reactions	RIFM (1995)
	HRIPT	20% in 1:3 EtOH:DEP	99 volunteers	No sensitization reactions	RIFM (2006b)
2,6-Dimethyl-2-hepten-6-ol[a]	Maximization test	10% in petrolatum	25 volunteers	No sensitization reactions	RIFM (1974b)
3,7-Dimethyl-1,6-nonadien-3-ol	Maximization test	30% in petrolatum	25 volunteers	No sensitization reactions	RIFM (1975b)
Dihydromyrcenol	Maximization test	4%, vehicle not mentioned	25 volunteers	No sensitization reactions	RIFM (1977d)
	HRIPT	7.5% in alcohol SDA 39 C	41 volunteers	No sensitization reactions	RIFM (1972c)
Isophytol	Maximization test	10% in petrolatum	27 volunteers	No sensitization reactions	RIFM (1981a)
3-Methyl-1-octen-3-ol[a]	Maximization test	10% in petrolatum	25 volunteers	No sensitization reactions	RIFM (1979b)
	Maximization test	10% in petrolatum	25 volunteers	2 positive reactions at induction (mild to moderate reaction), 1 positive reaction at challenge (moderate)	RIFM (1978c)
3-Methyl-1-octyn-3-ol[a]	Maximization test	2% in petrolatum	25 volunteers	No sensitization reactions	RIFM (1979b)
Nerolidol (isomers unspecified)[b]	Maximization test	4% in petrolatum	25 volunteers	No sensitization reactions	RIFM (1973c)
3,7,9-Trimethyl-1,6-decadien-3-ol[a]	Maximization test	20% in petrolatum	26 volunteers	No sensitization reactions	RIFM (1977c)

HRIPT: human repeat insult patch test.
[a] No relevant use was reported, therefore the available data are mentioned only in the table but not in the text.
[b] Materials have been previously reviewed by in RIFM's safety assessment of terpene alcohols (Belsito et al., 2008).

Table 8b
Elicitation studies in humans.

Material	Method	Concentration(s)	Subjects	Results	References
Subgroup: tertiary					
Nerolidol (isomers unspecified)[a]	Patch test	1% in petrolatum	2273 dermatosis patients were tested with balsam of Peru, 445 reacted, 102 of these were tested with nerolidol (constituent of balsam of Peru)	Three positive reactions	Hausen (2001)
Geraniol[a]	48 h Patch test	0.5–5% in petrolatum	1 male and 11 female patients with a history of dermatitis	Two reactions at 2.5% or greater 2 reactions at 4% or greater	Benke and Larsen (1984)
Geraniol[a]	48 h Patch test	No dose reported in mixture of geraniol, hydroxycitronellal, or 3 and 4-(4-Hydroxy-4-methylpentyl)-	1 male and 11 female patients with a history of dermatitis	Two patients who previously reacted to geraniol did not react to any of the mixtures One patient who previously reacted to geraniol reacted to mixtures of geraniol with hyroxycitronellal as well as a mixture of geraniol, hydroxycitronellal, and 3 and 4-(4-Hydroxy-4-methylpentyl)- Three patients who had not previously reacted to geraniol reacted to a mixture of geraniol and hydroxycitronellal One patient who had not previously reacted to geraniol reacted to a mixture of all three materials	Benke and Larsen
Geraniol[a]	Use test with shampoos	Overall concentrations of 0.03%, 0.09%, 0.3%, 0.9%, 0.3%, 3%, 9% and 15% in geraniol, hydroxycitronellal, and 3 and 4-(4-Hydroxy-4-methylpentyl)- mixture (1:1:1)	1 male and 11 female patients with a history of dermatitis	One patient reacted with visible skin reaction to 15% mixture Second patient reported burning sensation to 15% mixture Two control subjects reported stinging sensation to 15% mixture	Benke and Larsen (1984)

[a] Materials have been previously reviewed by in RIFM's safety assessment of terpene alcohols (Belsito et al., 2008).

- conjugation of the alcohol group with glucuronic acid,
- oxidation of the alcohol group,
- carbon chain oxidation yielding polar metabolites which may be conjugated and excreted – or further oxidation to an aldehyde, a carboxylic acid, and to CO_2,
- hydrogenation of the double bonds,
- excretion of the unchanged parent compound.

The same metabolism pathways are expected for the members of this group of alcohols due to the structural similarity.

These metabolism pathways are common for primary and secondary and except for oxidation for tertiary alcohols. In most cases, metabolism yields innocuous metabolites that are excreted in the urine and feces. Some substances of this assessment, however, may generate alpha, beta-unsaturated compounds or be oxidized to hydroperoxides which can undergo nucleophilic and electrophilic addition reactions with biological material (Belsito et al., 2008). The respective parent compounds, for which no data on toxicity after repeated application exist, are 2-isopropyl-5-methyl-2-hexene-1-ol, 2-methyl-2-buten1-ol, phytol, 3,7,11,15-tetramethyl-2-hexadecen1-ol, 6,10-dimethylundeca-1,5,9-trien-4-ol, 4-methyl-3-decen-5-ol and 2,2,8-trimethylnonen-3-ol.

5.4. Acute toxicity summary

LD_{50} values indicate a low oral and dermal toxicity. Most dermal (rabbit, rat, guinea pig) and oral (mouse, rat) LD_{50} values exceed 2000 mg/kg body weight with the majority of values being greater than 5000 mg/kg body weight. 3-Methyl-2-buten-1-ol and 2-methyl-3-buten-2-ol show LD_{50} values in the range of 800–2300 mg/kg body weight.

Clinical signs after dermal application were lethargy and irritation of the skin. After oral administration, lethargy and diarrhea were observed.

5.5. Repeated dose toxicity summary

The database on repeated dose toxicity for the members of this group is limited. Therefore, studies with linalool, a terpene alcohol with unsaturated branched chain, were included (Belsito et al., 2008). The repeated dermal exposure to SD rats with linalool for 13 weeks induced only a slight lethargy in two of the lower dose levels, and a reduction in female body weight. The NOAEL was 250 mg/kg body weight/day and the LOAEL was 1000 mg/kg body weight/day.

The target organs of the tested alcohols after repeated oral application are kidneys and liver. Some alcohols have the potential to induce α_{2u}-nephropathy in male rats. This is a male rat-specific effect and has no relevance for humans. In rats, NOELs and NOAELs ranged from 10 (dihydromyrcenol) to 65 mg/kg body weight/day (3-methyl-2-buten-1-ol) in oral 90-day studies. Higher doses increased liver weight (probably due to enzyme induction) without histopathological alterations or induced kidney effects (dilated renal tubules and general mineralization of basophilic tubules) in females and males. The NOAEL for dihydromyrcenol is 50 mg/kg body weight/day whereas the primary allylic alcohol, 3-methyl-2-buten-1-ol, which would be expected to yield a reactive aldehyde intermediate, was 65 mg/kg body weight/day. From the few studies available, no consistent differences in toxicity between the subgroups are seen.

5.6. Genotoxicity summary

The five tested primary allylic, secondary allylic and tertiary alcohols (3-methyl-2-buten-1-ol, 4-methyl-3-decen-5-ol, 3,7-dimethyl-1,6-nonadien-3-ol, isophytol and 2-methyl-3-buten-2-ol) along with the five terpene alcohols (citronellol, dehydrolinalool,

Table 8c
Skin sensitization studies in animals.

Material	Method	Concentration(s)	Subjects	Results	References[a]
Subgroup: secondary					
7-Nonen-2-ol,4,8-dimethyl-	Maximization test	Induction: 10% i.d. injections & 100% dermal application challenge: 100% dermal application	Guinea pig	No sensitization	RIFM (1976c)
	Maximization test	Induction: 30% i.d. injections & 100% dermal application challenge: 0.1%, 1%, 3%, 5%, or 30% dermal application	Guinea pig	No sensitization	RIFM (2004a)
Subgroup: secondary allylic					
4-Methyl-3-decen-5-ol	Photoallergy test (Controls)	Induction (topical): 10% challenge (topical) 30%, 10%, 3%, 1% vehicle: acetone/ethanol (1:1)	Guinea pig, injected with FCA	No sensitization	RIFM (1989c)
Subgroup: tertiary					
7-Octen-2-ol, 2-methyl-6-methylene-, dihydro derivative	Local Lymph Node assay	1%, 10% and 30% (w/v) in acetone	CBA mice	No sensitization	RIFM (1996)
	Maximization test	Induction with 5% in oleum arachidis (intradermal) and undiluted (percutaneous), challenge: undiluted	Guinea pig (20 in test group, 10 in control group)	No sensitization	RIFM (1994b)
	Buehler test	Induction with closed patch topical application of undiluted material for 6 h once a week for three weeks; challenge: undiluted	Guinea pig (20 in test group, 10 in control group)	No sensitization	RIFM (1994c)
Dihydromyrcenol	Local Lymph Node assay	0.5%, 1%, 2.5%, 10%, 25% (w/v) in ethanol/diethylphthalate (1:3)	CBA female mice	No sensitization (EC3 value not determined, estimated to be >25%)	RIFM (2007b)
Isophytol	Maximization test	Induction with 1% in light paraffin (intradermal) and 50% (percutaneous) in ethanol, challenge: 25% in ethanol, re-challenge: 12.5% in ethanol	Guinea pig (20 in test group, 10 in control group)	Challenge: 15/20 of test group and 6/10 of control group showed skin reactions (discrete or patchy erythema to moderate and confluent erythema) = irritating concentration re-challenge: 7/20 and 2/10 resp. showed skin reactions effects observed were interpreted as signs of irritation	Csato and Chubb (1996) as cited in OECD/SIDS (2006)
	Skin painting test, open epicutaneous	Induction: 10% in acetone (1/10) or 1% (9/10) challenge: 0.5% in acetone (control group: 0.5% (3/6) or 1% (3/6)	Guinea pig (10 in test group, 6 in control group)	questionable erythema in 5/10 test animals and 2/3 control animals (1%), no erythema in control group (0.5%); effects were interpreted as signs of irritation	RIFM (1970a,d)
Nerolidol (isomers unspecified)[b]	Modified FCA method	Challenge: 3%	Guinea pig (10)	Weak sensitizing capacity (mean response 0.28)	Hausen et al. (1992)
	Modified FCA method	Challenge: 10%	Guinea pig (number not reported)	Weak sensitizing capacity (mean response 0.28)	Hausen et al. (1995)
	Modified Draize method	Induction: 1%, challenge: 1% and 20%	Guinea pig (10)	No sensitization	Sharp (1978)
	OET	Challenge: 4%	Guinea pig	No sensitization	Klecak (1979, 1985)
	Intradermal injection test	Induction: 0.25% or 25% farnesyl acetate cross-challenge: 0.2% nerolidol	Guinea pig (10 in test group, 6 in control group)	No cross-sensitization	RIFM (1977f)

FCA: Freund's complete adjuvant.
OET: open epicutaneous test.
n.i.: no information.
[a] Not all of the original reports in the OECD/SIDS assessment were made available to RIFM.
[b] Materials have been previously reviewed by in RIFM's safety assessment of terpene alcohols (Belsito et al., 2008).

farnesol, geraniol and linalool) were inactive in bacterial tests. Linalool was inactive in mammalian cell systems (mouse lymphoma cells). Farnesol, geraniol and linalool showed no clastogenic activity in Chinese hamster ovary or Chinese hamster fibroblast cells. Linalool did not induce unscheduled DNA synthesis in fibroblasts or sister chromatid exchange in CHO cells. All six alcohols that were tested in the *in vivo* mouse micronucleus test were not genotoxic.

Overall, the alcohols tested were not genotoxic *in vitro* and *in vivo*.

5.7. Carcinogenicity summary

No valid bioassays on carcinogenicity are available for the alcohols with unsaturated branched chains or closely structurally related substances.

5.8. Reproductive and developmental toxicity summary

Reproductive and developmental toxicity data are limited to studies with primary allylic and tertiary alcohols in rats.

5.8.1. Fertility

Histopathological examinations of the reproductive organs of male and female rats in 90-day studies showed no adverse effects up to 243.8 and 307.2 mg/kg body weight/day 3-methyl-2-buten-1-ol and 1000 mg/kg body weight/day dihydromyrcenol , the highest dose tested. No effects on male or female fertility were noted for linalool in coriander oil at 365 mg/kg body weight/day, for linalool alone at 500–1000 mg/kg, for 2-methyl-3-buten-2-ol at 200 mg/kg body weight/day, or for isophytol (female fertility only) at 500 mg/kg body weight/day.

Table 9
Phototoxicity and photoallergenicity.

Material	Method	Concentration	Species	Results	References
Subgroup: secondary					
7-Nonen-2-ol,4,8-dimethyl-	As part of an HRIPT 20 volunteers were treated with a nine semi-occlusive patches over a three week period. Sites were irradiated (365 nm) for 15 min at a distance of 15 in.	0.2 g of 20% in white petrolatum	human	Not phototoxic not photoallergic	RIFM (1979e)
	Open applicationto two sites on the dorsal skin with a 0.02 ml on 1.5 cm × 1.5 cm area. Then subsequently irradiated with 320–400 nm of UV light from a distance of 10 cm for 60 min.	3%, 10%, or 30% in ethanol	guinea pig	Weak phototoxic reactions at 30% only	RIFM (2004a)
Subgroup: secondary allylic					
4-Methyl-3-decen-5-ol	8 animals per group; patch applied 48 h; 4 h after removal of patches left flank of two groups of experimental animals was radiated: Group A: with UVA (320–400 nm), 30 min Group B: with UVB (280-370 nm), 15 min Group C (control): no radiation Group D (control): not pretreated, radiated from both light sources; observations 4, 24 and 48 h after radiation	10% in ethanol	Guinea pig	Not phototoxic	RIFM (1980g)
	Photoallergy test induction: FCA injection followed by topical administration of test substance, 30 min later irradiation with UVA (320–400 nm, 10 J/cm^2) and UVB (280-320 nm, 1.8 J/cm^2), induction repeated on days 3, 5, 8, 10 without FCA injection challenge: three weeks after initiation of induction ± UVA irradiation	induction (topical): 10% + UVA + UVB challenge (topical) 30%, 10%, 3%, 1% ± UVA; vehicle: acetone/ethanol (1:1)	Guinea pig, injected with FCA	No photoallergenicity	RIFM (1989c)
Subgroup: tertiary					
7-Octen-2-ol, 2-methyl-6-methylene-, dihydro derivative	semi-occlusive patch for 24 h, followed by irradiation for 12 min (150 W, 290–400 nm, covered by a UVB filter to block transmission of 290–320 nm), readings at 24 and 48 h, 10 healthy adults	1%	Human	Not phototoxic	RIFM (1981c)
	In vitro	5%, 10%	*S. cerevisiae*	Not phototoxic	Bagley et al. (1988) and Tenenbaum et al. (1984)
	In vitro	0.1%, 1%, 10%	*S. cerevisiae*	0.1%: not phototoxic 1%, 10%: phototoxic	RIFM (1980i)
Dihydromyrcenol	Semi-occlusive patch for 24 h, followed by irradiation for 12 min (150 W, 290–400 nm, covered by a UVB filter to block transmission of 290–320 nm), readings at 24 and 48 h, 10 healthy adults	12%	Human	Not phototoxic	RIFM (1981c)
	In vitro	0.1%, 1%, 10%	*S. cerevisiae*	0.1%, 1%: not phototoxic 10%: phototoxic	RIFM (1980h)
Isophytol	Five animals, UV irradiation at 320–400 nm for 70 min; observations at 24 and 48 h	5%, 10%, 30% and 50% in acetone, no control	Guinea pig (Hartley; female)	Not phototoxic	RIFM (1999)

[a]Materials have been previously reviewed by in RIFM's Safety Assessment of Terpene Alcohols (Belsito et al., 2008).
FCA: Freund's complete adjuvant.

5.8.2. Developmental toxicity

3-Methyl-2-buten-1-ol showed no developmental effects in rats exposed at doses up to the maternally toxic dose of 600 mg/kg body weight/day. In a one-generation study with isophytol, growth retardation and reduced survival occurred at 1000 mg/kg body weight/day, and a NOAEL of 500 mg/kg body weight/day was derived. A LOAEL for maternal toxicity of isophytol was set at 250 mg/kg body weight/day. The NOAEL for linalool (72.9% in coriander oil) in a one-generation study is 183 mg/kg body weight/day for maternal and 365 mg/kg body weight/day for developmental. In a developmental toxicity study, the highest tested maternally toxic dose of linalool, 1000 mg/kg body weight/day, showed no developmental toxicity. In an OECD TG 421 test with 2-methyl-3-buten-2-ol, the NOAEL was 50 mg/kg body weight/day, a dose which was maternally non-toxic. The next higher dose of 200 mg/kg body weight/day reduced the viability of the pups.

No specific teratogenic effect was observed in any study.

5.8.3. Estrogenic activity

Nerolidol showed no ability to bind to the rat uterine estrogen receptor (Blair et al., 2000).

In the RIFM group summary of terpene alcohols (Belsito et al., 2008), a study to investigate the potential estrogenic activity of a number of essential oil constituents is described. Estrogenic activity was detected for high concentrations of geraniol in a bioassay using recombinant yeast cells expressing the human estrogen receptor. Geraniol and nerol did not show estrogenic or anti-estrogenic activity in the human cell line Ishikawa Var 1 and no androgenic or anti-androgenic activity in yeast. In ovariectomized mice, geraniol did not induce estrogenic responses.

5.9. Skin irritation summary

The potential for skin irritation of most of the alcohols assessed in this report has been well characterized in humans and in experimental animals.

Table 10
Summary of UV spectra data.

Material	UV spectra range of absorption (nm)
6-Ethyl-3-methyloct-6-en-1-ol	Peaked at 210–215
3-Methyl-2-buten-1-ol	Peaked at 200–205
(Z)-2-Penten-1-ol	Peaked at 210–215
(2E,6Z)-Nona-2,6-dien-1-ol	Peaked at 200–210
Methylheptenol	Peaked at 200–210
4-Methyl-3-decen-5-ol	Peaked at 200–210
7-Octen-2-ol, 2-methyl-6-methylene-, dihydro derivative	Peaked at 200–210
3,7-Dimethyl-1,6-nonadien-3-ol	Peaked at 200–210
Dihydromyrcenol	Peaked at 200–210
Isophytol	Peaked at 200–205
2-Methyl-3-buten-2-ol	Peaked at 200–205
(E)-Nerolidol	Peaked at 200–210
Nerolidol (isomer unspecified)	Peaked at 200–220

Phytol, methylheptenol, 3,7-dimethyl-1,6-nonandien-3-ol, 2-methyl-3-buten-2-ol, and nerolidol, when tested undiluted in rabbits, induced no irritation to moderate skin irritation with the exception of 3-methyl-2-buten-1-ol, which was corrosive, and isophytol, which produced severe irritation. When tested in humans, no evidence of irritation at concentrations of 2–30% for 3,7-dimethyl-1,6-nonadien-3-ol, 7-octen-2-ol, 2-methyl-6-methylene-, dihydro derivative, dihydromyrcenol, isophytol, 3-methyl-2-buten-1-ol, 4-methyl-3-decen-5-ol, methylheptenol, nerolidol and phytol was noted. It can be concluded that at current concentrations of use (Table 1), the alcohols under review are not irritating to the skin. For dihydromyrcenol a maximum skin level of 6.8%, which is slightly above the human NOAEL for irritation, was reported.

5.10. Mucous membrane summary

Undiluted phytol, isophytol, nerolidol and methylheptenol showed no irritation or only slight eye irritation in rabbits. Moderate eye irritation was noted for undiluted 2-methyl-3-buten-2-ol, 7-octen-2-ol, 2-methyl-6-methylene-, dihydro derivative, 3,7-dimethyl-1,6-nonadien-3-ol, dihydromyrcenol and 4-methyl-3-decen-5-ol. Undiluted 3-methyl-2-buten-1-ol was highly irritating.

5.11. Skin sensitization summary

The sensitization potential for nine of the alcohols with worldwide uses of >0.01 metric tons/year has been well characterized in humans. Supporting data from animal experiments exist for four of these nine alcohols. IFRA Standards (IFRA, 2006, 2007b,c) restricting the use of geraniol, dl-citronellol, rhodinol (3,7-dimethyl-7-octen-1-ol) and farnesol are based on the dermal sensitization QRA approach (Api et al., 2006).

No sensitizing potential has been demonstrated in human tests in concentrations from 4 to 100% of the following alcohols: 3-methyl-2-buten-1-ol, methylheptenol, 4-methyl-3-decen-5-ol, 7-octen-2-ol, 2-methyl-6-methylene-, dihydro derivative, 3,7-dimethyl-1,6-nonadien-3-ol, dihydromyrcenol, isophytol, and nerolidol. For phytol, a sensitization potential cannot be excluded due to one human reaction at 10% in petrolatum.

In animal experiments no sensitization potential for 7-octen-2-ol, 2-methyl-6-methylene-, dihydro derivative, dihydromyrcenol, isophytol and nerolidol was demonstrated.

Oxidation products of alcohols (hydroperoxides) may give rise to skin sensitization, as was shown for *linalool* (Belsito et al., 2008). There is an IFRA standard on linalool which limits the peroxide level to 20 mmol/l in the raw material (IFRA, 2004). Oxidation has to be avoided and it has to be ensured that only pure materials are used in fragrances.

5.12. Phototoxicity and photoallergenicity summary

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

6. Conclusion

Because there is insufficient information for many of the 40 compounds under review, the database is supplemented with studies from previously assessed materials that share similar structural features and metabolic patterns. It is expected that these would share similar systemic toxicity profiles.

The RIFM Expert Panel is of the opinion that there are *no safety concerns* regarding the branched chain unsaturated alcohols under the present declared levels of use and exposure. These materials have not been evaluated at levels other than reported in this group summary. Use of these materials at higher maximum dermal levels or higher systemic exposure levels requires re-evaluation by the panel. This opinion was based on the following reasons:

- No evidence or only minimal evidence of skin irritation in humans was associated with current levels of use at 2–30% for individual compounds considered. Therefore, due to the structural similarities, the compounds in the present assessment not tested for skin irritation in humans are expected to be of no concern provided concentrations in end products are in the range of 2–10%.
- Sensitizing hydroperoxides may be formed by contact with air. It should be ensured that oxidation reactions are prevented in the end product. There is an IFRA standard on linalool which limits the peroxide level to 20 mmol/l in the raw material (IFRA, 2004b). The use of these materials under the declared levels of use and exposure will not induce sensitization. For those individuals who are already sensitized, there is a possibility that an elicitation reaction may occur. The relationship between the no effect level for induction and the no effect level for elicitation is not known for this group of materials.
- Available data for eight of the substances show that there is no sensitization potential. However, for phytol, a single positive reaction in a human maximization test has been detected, which indicates weak sensitization potential. There are IFRA Standards (IFRA, 2006, 2007b,c) restricting the use of geraniol, citronellol, rhodinol (3,7-dimethyl-7-octen-1-ol) and farnesol. They are based on the dermal sensitization QRA approach (Api et al., 2006).
- From the limited data available there is no indication for a relevant phototoxic activity of this group of materials.
- The compounds have a low order of acute toxicity.
- The branched chain, unsaturated alcohols tested were of low systemic toxicity after repeated application. Changes indicative of enzyme induction in the liver (liver enlargement) and α_{2u}-nephropathy in male rats have been observed at doses from $\geqslant$200 mg/kg body weight/day. From the subacute and subchronic oral studies available, no consistent differences in toxicity between the subgroups are seen. The NOAEL for dihydromyrcenol (from the least reactive tertiary alcohols) is 50 mg/kg body weight/day whereas the primary allylic alcohol, 3-methyl-2-buten-1-ol, which would be expected to yield a reactive aldehyde intermediate (and thus display greater toxicity), was 65 mg/kg body weight/day. The database does not allow a definite conclusion that the toxicity after dermal application is lower than after oral application by gavage (oral bolus dose vs.

slow uptake via the skin). However, linalool had a higher systemic NOAEL of 250 mg/kg body weight/day in a subchronic dermal study compared to the lowest oral NOAEL of 50 mg/kg body weight/day (dihydromyrcenol).Compared to the conservative estimated daily uptake of about 0.49 mg/kg body weight/day of 7-octen-2-ol, 2-methyl-6-methylene-, dihydro derivative (100% dermal resorption assumed), the margin of safety for this compound is 100 (100% oral resorption is assumed on the basis of a study with linalool and is also used in Belsito et al., 2008). For the other compounds with estimated daily doses (Table 1), the margin of safety is between 150 and 160,000. There is an adequate margin of safety for the alcohols under review when used in consumer products at the current concentrations.

- The three group members tested, 3-methyl-2-buten-1-ol, isophytol and 2-methyl-3-buten-2-ol, and the non-cyclic terpene alcohol, linalool, did not show specific adverse effects in relation to fertility and developmental toxicity. For dihydromyrcenol, no effects on the reproductive organs, sperm parameters and estrous cycle in rats were noted.
- Apart from the double bonds, especially those in conjugation with primary and secondary alcohol groups, the substances of this group evaluation do not posses further reactive structures that may give rise to genotoxic potential. Available *in vitro* and *in vivo* studies from five compounds of this group or the structurally related non-cyclic terpene materials do not show genotoxic potential. Therefore, the remaining compounds are not expected to be genotoxic.
- Valid data on carcinogenicity of the compounds or for closely structurally related substances are not available, but in view of the negative mutagenicity tests so far obtained, they are not of primary concern.

Conflict of interest statement

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

References

Api, A.M., Basketter, D.A., Cadby, P.A., Cano, M.-F., Ellis, G., Gerberick, G.F., Griem, P., McNamee, P.M., Ryan, C.A., Safford, B., 2006. Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. The Toxicologist 90 (1), 465.

Bagley, D.M., Blankson, J., Kong, B.M., DeSalva, S.J., 1988. Optimization and evaluation of an *in vitro* yeast assay to predict phototoxicity. Journal of Toxicology, Cutaneous and Ocular Toxicology 7 (4), 295–307.

Behan, J.M., MacMaster, A.P., Perring, K.D., Tuck, K.M., 1996. Insight into how skin changes perfume. International Journal of Cosmetic Science 18 (5), 237–246.

Belsito, D., Bickers, D., Bruze, M., Greim, H., Hanifin, J.H., Rogers, A.E., Saurat, J.H., Sipes, I.G., Calow, P., Tagami, H., 2008. A toxicologic and dermatologic assessment of cyclic and non cyclic terpene alcohols when used as fragrance ingredients. Food and Chemical Toxicology 46 (11S), 1–71.

Bernhard, V.K., Maier, R., Ritzel, G., 1967. Effect of phytol on liver lipids. Hoppe–Seyler's Zeitschrift fur Physiologische Chemie 348 (7), 759–764.

Binet, L., Binet, P., Miocque, M., Roux, M., Bernier, A., 1972. Investigation on the pharmacodynamic properties (sedative action and spasmolytic action) of some aliphatic terpene alcohols. Annales Pharmaceutiques Francaises 30, 611–616.

Bobin, M.F., Durand, F., Pelletier, J., Martini, M.C., 1997. Dosage of farnesol in the skin. In: International Symposium on Flavors and Sensory Related Aspects. Rivista Italiana Eppos.

Boutin, J.A., Thomassin, J., Siest, G., Cartier, A., 1985. Heterogeneity of hepatic microsomal UDP–glucuronosyltransferase activities. Conjugations of phenolic and monoterpenoid aglycons in control and induced rats and guinea pigs. Biochemical Pharmacology 34, 2235–2249.

Buchbauer, G., Jirovet, L., Jäger, W., Dietrich, H., Plank, C., Karamat, E., 1991. Aromatherapy: evidence for sedative effects of the essential oil of lavender after inhalation. Zeitschrift fur Naturforschung C Biosciences 46, 1067–1072.

Buchbauer, G., Jirovetz, L., Jäger, W., Plank, C., Dietrich, H., 1993. Fragrance compounds and essential oils with sedative effects upon inhalation. Journal of Pharmaceutical Science 82 (6), 660–664.

Cadby, P., Troy, W.R., Vey, M.G.H., 2002. Consumer exposure to fragrance ingredients: providing estimates for safety evaluation. Regulatory Toxicology and Pharmacology 36, 246–252.

Cal, K., Sznitowska, M., 2003. Cutaneous absorption and elimination of three acyclic terpenes – *in vitro* studies. Journal of Controlled Release 93, 369–376.

Chadha, A., Madyastha, K.M., 1982. Omega-hydroxylation of acyclic monoterpene alcohols by rat lung microsomes. Biochemical and Biophysical Research Communications 108, 1271–1277.

Chadha, A., Madyastha, K.M., 1984. Metabolism of geraniol and linalool in the rat and effects on liver and lung microsomal enzymes. Xenobiotica 14, 365–374.

Choi, Y.-H., Ahn, S.-J., Park, K.-Y., Yoo, M.-A., Lee, W.-H., 1993. Effects of phytol on the mutagenicity of UV and EMS in salmonella and drosophila mutation assaying systems. Environmental Mutagens and Carcinogens 13 (2), 92–100.

Eder, E., Neudecker, T., Lutz, D., Henschler, D., 1980. Mutagenic potential of allyl and allylic compounds. Structure–activity relationship as determined by alkylating and direct *in vitro* mutagenic properties. Biochemical Pharmacology 29, 993–998.

Eder, E., Henschler, D., Neudecker, T., 1982a. Mutagenic properties of allylic and alpha-beta unsaturated compounds: considerations of alkylating mechanisms. Xenobiotica 12, 831–848.

Eder, E., Neudecker, T., Lutz, D., Henschler, D., 1982b. Correlation of alkylating and mutagenic activities of allyl and allylic compounds: standard alkylation test vs. kinetic investigation. Chemico-Biological Interactions 38, 303–315.

Food and Drug Administration (FDA), 2007. Everything added to food in the United States. <http://www.cfsan.fda.gov/~dms/eafus.html>.

Ford, R.A., Domeyer, B., Easterday, O., Maier, K., Middleton, J., 2000. Criteria for development of a database for safety evaluation of fragrance ingredients. Regulatory Toxicology and Pharmacology 31, 166–181.

Frosch, P.J., Rastogi, S.C., Pirker, C., Brinkmeier, T., Andersen, K.E., Bruze, M., Svedman, C., Goossens, A., White, I.R., Uter, W., Arnau, E.G., Lepoittevin, J.P., Johansen, J.D., Menne, T., 2005. Patch testing with a new fragrance mix – reactivity to the individual constituents and chemical detection.

Hausen, B.M., 2001. Contact allergy to balsam of Peru. II. Patch test results in 102 patients with selected balsam of Peru. American Journal of Contact Dermatitis 12 (2), 93–102.

Hausen, B.M., Evers, P., Stuwe, H.T., Konig, W.A., Wollenerber, E., 1992. Propolis allergy (IV). Studies with further sensitizers from propolis and constituents common to propolis, poplar buds and balsam of Peru. Contact Dermatitis 26 (1), 34–44.

Hausen, B.M., Simatupang, T., Bruhn, G., Evers, P., Koening, W.A., 1995. Identification of new allergenic constituents and proof of evidence for coniferyl benzoate in Balsam of Peru. American Journal of Contact Dermatitis 6 (4), 199–208.

Heck, J.D., Vollmuth, T.A., Cifone, M.A., Jagannath, D.R., Myhr, B., Curren, R.D., 1989. An evaluation of food flavoring ingredients in a genetic toxicity screening battery. The Toxicologist 9 (1), 257.

International Fragrance Association (IFRA), 2004. Volume of Use Survey, February 2007.

International Fragrance Association (IFRA), 2004b. Code of Practice. Standard on Linalool, April 2004.

International Fragrance Association (IFRA), 2006. Code of Practice. Standard on Farnesol, May 2007.

International Fragrance Association (IFRA), 2007a. Use Level Survey, August 2004.

International Fragrance Association (IFRA), 2007b. Code of Practice. Standard on Geraniol, May 2007.

International Fragrance Association (IFRA), 2007c. Code of Practice. Standard on Citronellol and Rhodinol, May 2007.

Ishidate Jr., M., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., Matsuoka, A., 1984. Primary mutagenicity screening of food additives currently used in Japan. Food and Chemical Toxicology 22 (8), 623–636.

Jäger, W., Buchbauer, G., Jirovetz, L., Fritzer, M., 1992. Percutaneous absorption of lavender oil from a massage oil. Journal of the Society of Cosmetic Chemists 43, 49–54.

Joint Expert Committee on Food Additives (JECFA), 1998. Safety evaluation of certain food additives. Prepared by the joint FAO/WHO Expert Committee on Food Additives. WHO Food Additives Series, vol. 40. World Health Organization, Geneva, 2004.

Joint Expert Committee on Food Additives (JECFA), 1999. Safety evaluation of certain food additives. Prepared by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). WHO Food Additives Series, vol. 42. IPCS, WHO, Geneva.

Joint Expert Committee on Food Additives (JECFA), 2004. Aliphatic branched-chain saturated and unsaturated alcohols, aldehydes, acids, and related esters. In: Who Food Additives Series, vol. 52. WHO, Geneva.

Jirovetz, L., Jäger, W., Buchbauer, G., Nikiforov, A., Raverdino, V., 1991. Investigations of animal blood samples after fragrance drug inhalation by gas chromatography/mass spectrometry with chemical ionization and selected ion monitoring. Biological Mass Spectrometry 20, 801–803.

Johansen, J.D., Rastogi, S.C., Bruze, M., Andersen, K.E., Frosch, P., Dreier, B., Lepoittevin, J.P., White, I., Menne, T., 1998. Deodorants: a clinical provocation study in fragrance-sensitive individuals. Contact Dermatitis 39 (4), 161–165.

Klecak, G., 1979. The open epicutaneous test (OET), a predictive test procedure in the guinea pig for estimation of allergenic properties of simple chemical compounds, their mixtures and of finished cosmetic preparations. International Federation Societies Cosmetic Chemists.

Klecak, G., 1985. The Freund's complete adjuvant test and the open epicutaneous test. Current Problems in Dermatology 14, 152–171.
Kuroda, K., Tanaka, S., Yu, Y.S., Ishibashi, T., 1984. Rec-assay of food additives. Nippon Kosnu Eisei Zasshi 31, 277–281 (In Japanese).
Lutz, D., Neudecker, T., Eder, E., 1980. Mutagenic effects of allylic alcohols and their corresponding aldehydes. Archives of Pharmacology 311 (Suppl.), R25. Abstract 97.
Mannering, G.J., Shoeman, J.A., 1996. Murine cytochrome P4503A is induced by 2-methyl-3-buten-2-ol, 3-methyl-1-pentyn-3-ol(meparfynol), and tert-amyl alcohol. Xenobiotica 26 (5), 487–493.
McGinty, D., Letizia, C.S., Api, A.M., submitted for publication. Fragrance material review on 2-methyl-3-buten-2-ol. Food and Chemical Toxicology.
Oda, Y., Hamano, Y., Inoue, K., Yamamoto, H., Niihara, T., Kunita, N., 1979. Mutagenicity of food flavors in bacteria. Shokuhin Eisei Hen (9), 177–181 (in Japanese).
OECD and Screening Information Datasets (SIDS), 2005a. High production volume chemicals 3-methylbut-2-en-1-ol (Cas No: 556-82-1). Processed by United Nations Environmental Program, (UNEP) Chemicals. <http://www.chem.unep.ch/irptc/sids/OECDSIDS/indexcasnumb.htm> (not all of the original reports were made available to RIFM).
OECD and Screening Information Datasets (SIDS), 2005b. High production volume chemicals 2-methy-3-buten-2-ol (Cas No: 115-18-4). Processed by United Nations Environmental Program, (UNEP) Chemicals. <http://www.chem.unep.ch/irptc/sids/OECDSIDS/indexcasnumb.htm> (not all of the original reports were made available to RIFM).
OECD and Screening Information Datasets (SIDS), 2006. High production volume chemicals isophytol (CAS No: 505-32-8). Processed by United Nations Environmental Program, (UNEP) Chemicals. <http://www.chem.unep.ch/irptc/sids/OECDSIDS/indexcasnumb.htm> (not all of the original reports were made available to RIFM).
Parke, D.V., Rahman, K.H.M.Q., Walker, R., 1974. Effect of linalool on hepatic drug-metabolizing enzymes in the rat. Biochemical Society Transactions 2, 615–618.
Parke, D.V., Rahman, K.H.M.Q., Walker, R., 1974a. The absorption, distribution and excretion of linalool in the rat. Biochemical Society Transactions 2, 612–615.
Pietruszko, R., Crawford, K., Lester, D., 1973. Comparison of substrate specificity of alcohol dehydrogenases from human liver, horse liver, and yeast towards saturated and 2-enoic alcohols and aldehydes. Archives of Biochemistry and Biophysics 159, 50–60.
Politano, V.T., Lewis, E.M., Hoberman, A.M., Christian, M.S., Diener, R.M., Api, A.M., 2008. Evaluation of the developmental toxicity of linalool in rats. International Journal of Toxicology 27 (2), 183–188.
Politano, V.T., Lewis, E.M., Hoberman, A.M., Christian, M.S., Diener, R.M., Api, A.M., 2009. Evaluation of the developmental toxicity of dyhydromyrcenol in rats. International Journal of Toxicology 28 (2), 80–87.
Research Institute for Fragrance Materials, Inc. (RIFM), 1964a. Irritant effects on the rabbit eye. Unpublished report from IFF, Inc., Report number 50817, 14 January. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1964b. Repeated insult patch test with dihydromyrcenol. Unpublished report from IFF, Inc., Report number 47074, 28 April. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1965. Repeated insult patch test. Unpublished report from IFF, Inc., Report number 50816, 1 October. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1967a. Acute toxicity, eye and skin irritation tests on aromatic compounds. Unpublished report from Hoffmann–LaRoche, Report number 30642, 20 September. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1967b. Acute toxicity, eye and skin irritation test of fragrance materials. Unpublished report from Hoffmann–LaRoche, 20 September. Report number 30645. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1968. Acute toxicity, eye and skin irritation tests on aromatic compounds. Unpublished report from Hoffmann–LaRoche, Report number 30645, 20 August. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1969. Acute toxicity studies on isophytol. Unpublished report from BASF. Report number 55376, 23 June. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1970a. Acute toxicity studies on isophytol. Unpublished report from BASF AG. Report number 4449, 23 June. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1970b. Skin irritation study with (Z)-2-penten-1-ol (cis-2-pentenol) in rabbits. Unpublished report from International Flavors and Fragrances. Report number 54718, 20 November. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1970c. Eye irritation study with (Z)-2-penten-1-ol (cis-2-pentenol) in rabbits. Unpublished report from International Flavors and Fragrances. Report number 54717, 16 November. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1970d. Report on the examination of isophytol for any skin sensitizing effect. Unpublished report from BASF, 17 August. Report number 55382. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1970e. Analytical toxicology of 3-methyl-2-buten-1-ol. Unpublished report from BASF. Report number 55393, 20 June. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1971. Repeated insult patch test with (Z)-2-penten-1-ol (cis-2-pentenol) humans. Unpublished report from International Flavors and Fragrances. Report number 54716, 23 October. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1972a. The contact-sensitization potential of fragrance materials by maximization testing in humans. RIFM report number 1804, February–November. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1972b. Repeated insult patch test. Unpublished report from Fritzsche Dodge & Olcott Inc., Report number 14605, 1 August. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1972c. Repeated insult patch test with dimyrcetol. Unpublished report from International Flavors and Fragrances. Report number 50437, 6 July. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1972d. Primary skin and acute eye irritation studies on a series of six samples. Unpublished report from Fritzsche Dodge & Olcott Inc. Report number 14607, 18 April. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1972e. Trade toxicology of 2-methyl-3-buten-2-ol. Unpublished report from BASF. Report number 55332, 13 October. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1973a. Acute toxicity studies on rats and rabbits. RIFM report number 2021, February to November. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1973b. Acute oral and dermal toxicity studies. RIFM report number 2033, March 5. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1973c. Report on human maximization studies. RIFM report number 1802, February–December. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1973d. Repeated insult patch test of 6,10-dimethylundeca-1,5,9-trien-4-ol. Unpublished report from International Flavors and Fragrances. Report number 53319, October 26. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1973e. Eye irritation with 6,10-dimethylundeca-1,5,9-trien-4-ol in rabbits. Unpublished report from International Flavors and Fragrances. Report number 53320, 17 July. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1973f. Dermal irritation with 6,10-dimethylundeca-1,5,9-trien-4-ol in rabbits. Unpublished report from International Flavors and Fragrances. Report number 53323, 10 July. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1974a. Acute oral and dermal toxicity studies. RIFM report number 1778, August 23. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1974b. Report on human maximization studies. RIFM report number 1779, June to November. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1975a. Acute toxicity studies on rats, rabbits and guinea pigs. RIFM report number 2020, April 09. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1975b. Report on human maximization studies. RIFM report number 1798, June 03. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1975c. Eye irritation with 6,10-dimethylundeca-1,5,9-trien-4-ol in rabbits. Unpublished report from International Flavors and Fragrances. Report number 53321, 13 May. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1975d. Eye irritation with 6,10-dimethylundeca-1,5,9-trien-4-ol in rabbits. Unpublished report from International Flavors and Fragrances. Report number 53322, 13 May. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1976a. Acute toxicity studies on rats, rabbits and guinea pigs. RIFM report number 2019, January to September. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1976b. Report on human maximization studies. RIFM report number 1797, February to December. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1976c. Screening test for delayed contact hypersensitivity with 7-nonen-2-ol, 4,8-dimethyl- in the albino guinea pig. Unpublished report from Firmenich Incorporated, 28 July. Report number 38741. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1976d. Acute toxicity studies in rats, mice, rabbits and guinea pigs. RIFM report number 2019, September 07. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1977a. Acute toxicity study in rats, rabbits and guinea pigs. RIFM report number 1695, January–October. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1977b. Determination of the acute oral toxicity of dihydromyrcenol in rats. Unpublished report from Quest International. Report number 45928. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1977c. Report on human maximization studies. RIFM report number 1691, February to October. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 1977d. Report on human maximization studies. RIFM report number 1702, February to November. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1977e. Rabbit eye irritation study with dimyrcetol. Unpublished report from International Flavors and Fragrances, February. Report number 50434. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1977f. Guinea pig skin sensitization test with farnesyl acetate. Unpublished report from Quest International, Report number 46005, March 29. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1978a. Acute toxicity studies in rats, mice, rabbits, and guinea pigs. RIFM report number 1699, October 4. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1978b. Acute toxicity studies on phytol. Unpublished report from BASF, 20 July. Report number 4455. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1978c. Report on human maximization studies. RIFM report number 1787, February to December. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1979a. Toxicity studies on methyl octynol. Unpublished Report from Air Products & Chemicals, Inc. Report number 13486, 2 February. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1979b. Report on human maximization studies. RIFM report number 1697, April to November. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1979c. Acute oral toxicity of 7-nonen-2-ol, 4,8-dimethyl- in rats. Unpublished report from Firmenich Incorporated, Report number 38735. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1979d. Acute dermal toxicity of 7-nonen-2-ol, 4,8-dimethyl- in rabbits. Unpublished report from Firmenich Incorporated, 18 September. Report number 38736. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1979e. Human repeated insult patch test of 7-nonen-2-ol, 4,8-dimethyl. Unpublished report from Firmenich Incorporated, 19 September. Report number 38740. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1979f. Primary dermal irritation of 7-nonen-2-ol, 4,8-dimethyl- in rabbits. Unpublished report from Firmenich Incorporated, 26 July. Report number 38737. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1979g. Eye irritation study of 7-nonen-2-ol, 4,8-dimethyl- in rabbits. Unpublished report from Firmenich Incorporated, 18 December. Report number 38738. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1979h. Eye irritation study of 7-nonen-2-ol, 4,8-dimethyl- in rabbits. Unpublished report from Firmenich Incorporated, 13 August. Report number 38739. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1979i. Report on the test of the acute dermal toxicity of 3-methyl-2-buten-1-ol in the rat. Unpublished report from BASF. Report number 55385, 23 April. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1979j. Report on the corrosive effect of 3-methyl-2-buten-1-ol in rabbits. Unpublished report from BASF. Report number 55395, 23 April. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1979k. Report on the primary eye irritant effect of 3-methyl-2-buten-1-ol in rabbits. Unpublished report from BASF. Report number 55399, 23 April. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1980a. Acute toxicity studies with 4-methyl-3-decen-5-ol. Unpublished report from Givaudan, 19 November. Report number 49101. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1980b. A 90-day subacute dermal toxicity study with Linalool in rats. RIFM report number 4001, April 04. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1980c. Irritation test with 4-methyl-3-decen-5-ol on the rabbit eye. Unpublished report from Givaudan, 24 June. Report number 49103. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1980d. Primary ocular irritation study of fragrance materials in rabbits. Unpublished report from International Flavors and Fragrances. Report number 47078, 12 June. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1980e. Primary ocular irritation study of dihydromyrcenol in rabbits. Unpublished report from International Flavors and Fragrances. Report number 47079, 11 November. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1980f. Eye irritation study of dihydromyrcenol in rabbits. Unpublished report from International Flavors and Fragrances. Report number 47080, November 11. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1980g. Determination of phototoxicity in guinea pigs with 4-methyl-3-decen-5-ol. Unpublished report from Givaudan. Report number 49102, 29 November. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1980h. Phototoxicity study of dimyrcetol. Unpublished report from International Flavors and Fragrance. Report number 50436. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1980i. *In vitro* phototoxicity assay. Unpublished Report from IFF. RIFM report number 47076, 6 August. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1981a. Report on human maximization studies. RIFM report number 1792. March to November. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1981b. Repeated insult patch test with 4-methyl-3-decen-5-ol. Unpublished report from Givaudan, Report number 49104, 28 April. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1981c. Phototoxicity testing of fragrance materials. Unpublished report from IFF Incorporated, RIFM report number 47075, 9 March. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1982a. Acute toxicity studies. Unpublished report from RIFM, RIFM report number 1689, February–September 1982. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1982b. Mutagenicity evaluation of linalool in the mouse lymphoma forward mutation assay. Report from Lorillard Tobacco Company, 31 August, cited in Heck et al. (1989). Report number 35826. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1982c. Acute toxicity studies. RIFM report number 1689, February 22. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1983a. Mutagenicity evaluation of linalool in the Ames Salmonella/microsome plate test. Unpublished report from Lorillard Tobacco Company, 20 July. Report number 35823. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1983b. Mutagenicity evaluation of linalool in an *in vitro* cytogenetic assay measuring chromosome aberration frequencies in Chinese hamster ovary (CHO) cells. Unpublished report from Lorillard Tobacco Company, Report number 35824, 7 October. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1984a. Primary irritation test in rabbits. RIFM report number 1795, June 01. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1984b. Acute eye irritation test of dimyrcetol in rabbits. Unpublished report from International Flavors and Fragrances, Report number 50435, April. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1985. Acute dermal irritation study in rabbits. RIFM report number 3099, June 01. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1986a. Unscheduled DNA synthesis in rat primary hepatocytes. Report from Lorillard Tobacco Company, 5 May, cited in Heck et al. (1989). Report number 35825. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1986b. Acute dermal irritation study in rabbits. RIFM report number 5664, June 01. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1989a. Report on the mutagenicity testing with farnesol. Unpublished report from Dragoco Gerberding and Co. GmbH. Report number 37820. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1989b. Report on the study of dehydrolinalool in the Ames test (Standard plate test and preincubation test with Salmonella typhimurium). Unpublished report from BASF. Report number 26074, 14 March. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1989c. Determination of photoallergenicity in albino guinea pigs with 4-methyl-3-decen-5-ol. Unpublished report from Givaudan, 27 November. Report number 49105. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1989d. Reproductive and developmental toxicity screening test of Coriander Oil administered orally via gavage to Crl: Cd(tm) (sd) br female rats. Unpublished report from Lorillard Tobacco Company, 12 April. Report number 36124. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1989e. Study on the acute inhalation toxicity of 2-methyl-3-buten-2-ol as a vapor in rats. Unpublished report from BASF. Report number 55325. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1989f. Report on the study of 2-methyl-3-buten-2-ol in the Ames test. Unpublished report from BASF. Report number 55328. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1989g. Report on the study of isophytol in the AMES test with Salmonella typhimurium. Unpublished report from BASF, 15 February. Report number 55368. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1989h. Report on the study of 3-methylbuten-2-o1-1 in the Ames test with Salmonella typhimurium. Unpublished report from BASF. Report number 55387, 24 February. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1990. A 28-day oral toxicity study of Coriander oil in rats. Unpublished report from Lorillard Tobacco Company, 25 January. Report number 36125. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1991. Report on the maximization test for the sensitizing potential of 2-methyl-3-buten-2-ol in guinea pigs. Unpublished report from BASF. Report number 55335. RIFM, Woodcliff Lake, NJ, USA.
Research Institute for Fragrance Materials, Inc. (RIFM), 1991b. Report on the study of isophytol in the liquid suspension assay modified Salmonella/Mammalian-Microsome mutagenicity test. Unpublished report from BASF, 15 October. Report number 55369. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 1991c. Report on the study of 3-methylbuten-2-ol-1 in the liquid suspension assay modified Salmonella/mammalian-microsome mutagenicity test. Unpublished report from BASF. Report number 55388, 19 September. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 1992. Cytogenetic study 2-methyl-3-buten-2-ol in mice. Unpublished report from BASF. Report number 55334. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 1994a. Mutagenicity test on linalool in the L5178YTK mouse lymphoma forward mutation assay with a confirmatory assay. Unpublished report from Lorillard Tobacco Company, 3 March. Report number 35827. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 1994b. Test for delayed contact hypersensitivity of dihydromyrcenol using the guinea pig maximization test. Unpublished report from Haarmann & Reimer GmbH. Report number 24241, 29 July. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 1994c. The Buehler test on dihydromyrcenol. Unpublished report from Haarmann & Reimer GmbH. Report number 24242, 30 September. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 1994d. Repeated dose oral toxicity study with 2-methyl-3-buten-2-ol in Wistar rats. Unpublished report from BASF. Report number 55324. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 1995. Repeated insult patch test on dihydromyrcenol on human subjects. RIFM report number 25722, June 21. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 1996. Local lymph node assay of dihydromyrcenol. Unpublished report from Haarmann & Reimer GmbH. Report number 35547. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 1999. Toxicology studies of isophytol in the guinea pig. Unpublished report from Takasago International Corporation, Report number 35058. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2000. 4-Methyl-3-decen-5-ol: primary skin irritation study in rabbits (4 h semi-occlusive application). Unpublished report from Givaudan Vernier SA. Report number 41335, 2 November. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2001a. Micronucleus test in bone marrow cells of the mouse with linalool. Unpublished report from Hoffmann–LaRoche. Report number 38577, 18 November. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2001b. Cytogenetic study in vivo with 3-methyl-2-buten-1-ol in the mouse micronucleus test after two intraperitoneal administrations. Unpublished report from BASF. Report number 55397, 14 May. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2002a. Evaluation of the mutagenic activity of 4-methyl-3-decen-5-ol in the *Salmonella typhimurium* reverse mutation assay. Unpublished report from Givaudan Vernier SA. RIFM report number 42179, 11 November. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2002b. Evaluation of the mutagenic activity of 3,7-dimethyl-1,6-nonadien-3-ol in the *Salmonella typhimurium* reverse mutation assay. Unpublished report from Givaudan. Report number 43045, 31 October. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2002c. 3-Methyl-2-buten-1-ol (Prenol): subchronic toxicity study in Wistar rats administered in drinking water for 3 months. Unpublished report from BASF. Report number 55401, 11 April RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2002d. 3-Methyl-2-buten-1-ol (Prenol) – Prenatal developmental toxicity study in Wistar rats by oral administration (gavage). Unpublished report from BASF. Report number 55398, 27 March. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2003a. Translation: details on an acute oral toxicity study in the rat with 3-methyl-2-buten-1-ol. Unpublished report from BASF. Report number 55408, 8 January. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2003b. Translation: details on an acute intraperitoneal toxicity study in the mouse with 3-methyl-2-buten-1-ol. Unpublished report from BASF. Report number 55406, 8 January. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2003c. 3-Methyl-2-buten-1-ol (Prenol): Test study in Wistar rats administered in the drinking water and by gavage for 2 weeks. Unpublished report from BASF. Report number 55403, 24 January. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2003d. 3-Methyl-2-buten-1-ol (Prenol): palatability study in Wistar rats administered in drinking water for 2 weeks. Unpublished report from BASF. Report number 55404, 24 January. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2003e. Translation: details on an inhalation risk test in the rat with 3-methyl-2-buten-1-ol. Unpublished report from BASF. Report number 55407, 8 January. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2003f. Translation: details on an eye irritation / corrosion study in rabbits with 3-methyl-2-buten-1-ol. Unpublished report from BASF. Report number 55409, 8 January. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2003g. Details on a skin irritation/corrosion study in rabbits with 3-methyl-2-buten-1-ol. Unpublished report from BASF. Report number 55405, 8 January. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2003h. 3-Methyl-2-buten-1-ol (Prenol): maternal toxicity study in Wistar rats by oral administration (gavage). Unpublished report from BASF. Report number 55402, 23 January. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2004a. Toxicity studies with 7-nonen-2-ol, 4,8-dimethyl- in guinea pigs and rats. Unpublished report from Takasago International Corporation, 29 July. Report number 46339. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2006b. Repeated insult patch test (modified Draize procedure). RIFM report number 45702, February 01. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2006c. *In vitro* human skin penetration of fragrance material linalool under both in-use and occluded conditions from an ethanol/water vehicle. In: Draft. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2006d. *In vitro* human skin penetration of fragrance material linalool under both in-use and occluded conditions from a dipropylene glycol (DPG) vehicle. In: Draft. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2006e. *In vitro* human skin penetration of fragrance material linalool under both in-use and occluded conditions from a diethyl phthalate (DEP) vehicle. In: Draft. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2007a. Dimyrcetol: ninety day repeated dose oral (gavage) toxicity study in the rat. RIFM report number 52794, April 24. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2007b. Local Lymph Node Assay. RIFM report number 52911, May 21. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2007c. *In vitro* human skin penetration of fragrance material linalool under both in-use and occluded conditions from an ethanol/dipropylene glycol vehicle. In: Draft. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2007d. *In vitro* human skin penetration of fragrance material linalool under both in-use and occluded conditions from an ethanol/diethyl phthalate vehicle. In: Draft. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2007e. *In vitro* human skin penetration of fragrance material linalool under both in-use and occluded conditions from a petrolatum vehicle. In: Draft. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2007f. Dimyrcetol: ninety day repeated dose oral (Gavage) toxicity study in the rat. RIFM report number 52794, April 27. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2007g. In vitro human skin penetration of fragrance material dimyrcetol under occluded conditions from a 70% ethanol vehicle. In: Draft. RIFM, Woodcliff Lake, NJ, USA.

Research Institute for Fragrance Materials, Inc. (RIFM), 2007h. In vitro human skin penetration of fragrance material Dimyrcetol under in-use (unoccluded) conditions from a 70% ethanol vehicle. In: Draft. RIFM, Woodcliff Lake, NJ, USA.

Rockwell, P., Raw, I., 1979. A mutagenic screening of various herbs, spices and food additives. Nutrition and Cancer 1 (4), 10–15.

Rupa, D.S., Riccio, E.S., Rausch, L.L., Shimon, J.A., Kapetanovic, I.M., Mortelmans, K.E., 2003. Genetic toxicology testing of cancer chemopreventive agents. Environmental and Molecular Mutagenesis 41 (3), 201.

Sasaki, Y.F., Imanishi, H., Ohta, T., Yasuhiko, S., 1989. Modifying effects of components of plant essence on the induction of sister chromatid exchanges in cultured Chinese hamster ovary cells. Mutatation Research 226, 103–110.

Sharp, D.W., 1978. The sensitization potential of some perfume ingredients tested using a modified Draize procedure. Toxicology 9 (3), 261–271.

Strubelt, O., Deters, M., Pentz, R., Siegers, C.-P., Younes, M., 1999. The toxic and metabolic effects of 23 aliphatic alcohols in the isolated perfused rat liver. Toxicological Sciences 49, 133–142.

Tenenbaum, S., Dinardo, J., Morris, W.E., Wolf, B.A., Schnetzinger, R.W., 1984. A quantitative *in vitro* assay for the evaluation of phototoxic potential of topically applied materials. Cell Biology and Toxicology 1 (1), 1–9.

Tsuchiya, T., Tanida, M., Uenoyama, S., Nakayama, Y., 1992. Effects of olfactory stimulation with jasmine and its component chemicals on the duration of pentobarbital-induced sleep in mice. Life Sciences 50 (15), 1097–1102.

US National Toxicology Program, 1993. NTP unpublished results. NTP Test Results Report. Results, status and publication information on all NTP chemicals produced from NTP Chemtrack system. Electronic publication <http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=salmonella.salmonellaData&study_no=A37965&cas_no=505%2D32%2D8& endpointlist=SA>.

US National Toxicology Program, 2000. NTP unpublished results. NTP Test Results Report. Results, status and publication information on all NTP chemicals produced from NTP Chemtrack system. Electronic publication <http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=salmonella.salmonellaData&study_no=A23522&cas_no=505%2D32%2D8&endpointlist=SA>.

Wohlfahrt, R., Hansel, R., Schmidt, H., 1993. Pharmacology of 2-methyl-3-buten-2-ol. Planta Medica 48, 120–123.

Yoo, Y.S., 1986. Mutagenic and antimutagenic activities of flavoring agents used in foodstuffs. Osaka City Medical Journal 34 (3–4), 267–288 (in Japanese).

Zeiger, E., Margolin, B.H., 2000. The proportions of mutagens among chemicals in commerce. Regulatory Toxicology and Pharmacology 32 (2), 219–225.