INTERNATIONAL FRAGRANCE ASSOCIATION

IFRA Standards

INTERNATIONAL FRAGRANCE ASSOCIATION

Index of IFRA Standards – 46th Amendment

The IFRA recommendations are grouped into three categories as follows:

P (prohibited)	The material should not be used as a fragrance ingredient.
R (restricted)	The use of the material should be limited quantitatively.
S (specified)	The material should only be used if it meets certain purity criteria or if it used in conjunction with other materials.

7 NEW Standards (are indicated in yellow)

	Substance	CAS	Last Amended	Standard
1.	Acetyl ethyl tetramethyl tetralin (AETT, Versalide)	88-29-9	11.77 (05.06) [1]	**P**
2.	5-Acetyl-1,1,2,3,3,6-hexamethyl indan (AHMI, Phantolid)	15323-35-0	10.87 (04.05)	**R**
3.	Acetyl isovaleryl (5-Methyl-2,3-hexanedione)	13706-86-0	02.80 (05.06)	**P**
4.	Alantroot oil (Elecampane oil)	97676-35-2	06.75 (05.06)	**P**
5.	Allyl Esters	N/A	02.77 (07.09)	**S**
6.	Allyl heptine carbonate	73157-43-4	05.07 (07.08)	**P**
7.	Allyl isothiocyanate	57-06-7	(07.08)	**P**
8.	Allyl phenoxyacetate	7493-74-5	07.09	**R-S**

[1] The dates in brackets indicate a modification of the Standard that did NOT affect the IFRA recommendations (for instance, an update of the references or a reformatting of the Standard). The dates without brackets refer to a change that affected the IFRA recommendations.

IFRA Operations
Avenue des Arts, 6
1210 Brussels, Belgium
Tel: +32-2 214 20 60
Fax: +32-2 214 20 69
www.ifraorg.org

	Substance	CAS	Last Amended	Standard
9.	Angelica root oil	8015-64-3	10.78 (04.05)	**R**
10.	alpha-Amyl cinnamic alcohol	101-85-9	05.07	**R**
11.	alpha-Amyl cinnamic aldehyde	122-40-7	05.07	**R**
12.	Amylcyclopentenone	25564-22-1	05.07 (07.08)	**P**
13.	Anisyl alcohol	105-13-5	05.07	**R**
14.	Anisylidene acetone (4-(p-methoxyphenyl)-3-butene-2-one)	943-88-4	11.74 (05.06)	**P**
15.	cis-and trans-Asarone ((E)-and(Z)-2,4,5-Trimethoxypropen-1-yl benzene)	2883-98-9 5273-86-9	12.91	**P-R**
16.	Benzaldehyde	100-52-7	07.09	**R**
17.	Benzene	71-43-2	04.04	**P**
18.	Benzyl alcohol	100-51-6	05.07	**R**
19.	Benzyl Benzoate	120-51-4	05.07	**R**
20.	Benzyl cinnamate	103-41-3	05.07	**R**
21.	Benzyl cyanide	140-29-4	04.04	**P**
22.	Benzylidene acetone (4-Phenyl-3-buten-2-one)	122-57-6	06.74 (05.06)	**P**
23.	Benzyl salicylate	118-58-1	05.07	**R**
24.	Bergamot oil expressed	8007-75-8	06.92	**R**
25.	Birch wood pyrolysate	8001-88-5 84012-15-7 85940-29-0 68917-50-0	04.04	**S-P**
26.	Bitter orange peel oil expressed	68916-04-1 72968-50-4	07.02	**R**
27.	Boldo oil	8022-81-9	07.09	**P**

	Substance	CAS	Last Amended	Standard
28.	3-Bromo-1,7,7-trimethylbicyclo[2.2.1]heptane-2-one	76-29-9	(07.08)	**P**
29.	Bromostyrene	103-64-0	(07.08)	**P**
30.	alpha-Butylcinnamaldehyde	7492-44-6	06.11	**R**
31.	p-tert-Butyl-dihydrocinnamaldehyde (Bourgeonal)	18127-01-0	07.08	**R**
32.	p-tert-Butyl-alpha-methylhydrocinnamic aldehyde (BMHCA)	80-54-6	07.08	**R**
33.	p-tert-Butylphenol	98-54-4	06.75 (05.06)	**P**
34.	Cade oil (Juniperus oxycedrus L.)	8013-10-3 90046-02-9	04.04	**S-P**
35.	Carvone; d-Carvone; l-Carvone	99-49-0 2244-16-8 6485-40-1	07.08	**R**
36.	Carvone oxide	33204-74-9	04.04	**P**
37.	Chenopodium oil	8006-99-3	(07.08)	**P**
38.	Cinnamic alcohol	104-54-1	07.08	**R**
39.	Cinnamic aldehyde	104-55-2	07.08	**R**
40.	Cinnamic aldehyde dimethyl acetal	4364-06-1	07.09	**R**
41.	Cinnamylidene acetone	4173-44-8	(07.08)	**P**
42.	Cinnamyl nitrile	1885-38-7 4360-47-8	07.08	**R**
43.	Citral	5392-40-5 141-27-5 106-26-3	05.06	**R**
44.	Citronellol	106-22-9 1117-61-9 26489-01-0 6812-78-8 141-25-3 68916-43-8 7540-51-4	05.07	**R**

	Substance	CAS	Last Amended	Standard
45.	Citrus oils and other furocoumarins containing essential oils		12.96	**R**
46.	Colophony	8050-09-7	12.92 (05.06)	**P**
47.	Costus root oil, absolute and concrete	8023-88-9	05.98 (05.06)	**P**
48.	Coumarin	91-64-5	07.08	**R**
49.	Cumin oil	8014-13-9	06.86 (04.05)	**R**
50.	Cyclamen alcohol (3-(4-Isopropylphenyl)-2-methylpropanol)	4756-19-8	10.78 (02.80)	**P-S**
51.	2,4-Decadienal	2363-88-4	07.09	**P**
52.	Dibenzyl ether	103-50-4	07.09	**R**
53.	1,3-Dibromo-2-methoxy-4-nitro-5-(1,1-dimethylethyl)-6-methyl-benzene (Musk alpha)	63697-53-0	(07.08)	**P**
54.	1,3-Dibromo-2-methoxy-4-methyl-5-nitrobenzene (Musk KS)	62265-99-0	(07.08)	**P**
55.	2,2-Dichloro-1-methylcyclopropylbenzene	3591-42-2	(07.08)	**P**
56.	Diethyl maleate	141-05-9	06.75 (05.06)	**P**
57.	Dihydrocoumarin (Melilotine)	119-84-6	10.74 (05.06)	**P**
58.	2,4-Dihydroxy-3-methylbenzaldehyde	6248-20-0	04.89 (05.06)	**P**
59.	Dimethylcyclohex-3-ene-1-carbaldehyde (mixed isomers)	68737-61-1 68039-49-6 68039-48-5 27939-60-2 67801-65-4	06.10	**R**
60.	1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one	56973-85-4	07.09	**R**
61.	4,6-Dimethyl-8-tert-butylcoumarin (Butolia)	17874-34-9	06.81 (05.06)	**P**

	Substance	CAS	Last Amended	Standard
62.	3,7-Dimethyl-2-octen-1-ol	40607-48-5	04.04	**P**
63.	2,2-Dimethyl-3-(3-tolyl)propan-1-ol (Majantol)	103694-68-4	06.10	**R-S**
64.	Dimethyl citraconate	617-54-9	10.76 (05.06)	**P**
65.	Diphenylamine	122-39-4	04.04	**P**
66.	Esters of 2-octynoic acid (Except Methyl heptine carbonate which is IFRA Restricted)	10484-32-9 10519-20-7	(07.08)	**P**
67.	Esters of 2-nonynoic acid, (Except Methyl octine carbonate)	10031-92-2	(07.08)	**P**
68.	Estragole (Methyl chavicol)	140-67-0	07.09	**R**
69.	2-Ethoxy-4-methylphenol	2563-07-7	07.08	**R**
70.	Ethyl acrylate	140-88-5	11.74 (05.06)	**P**
71.	Ethylene glycol monoethyl ether and its Acetate	110-80-5 111-15-9 (acetate)	04.04	**P**
72.	Ethylene glycol monomethyl Ether and its Acetate	109-86-4 110-49-6 (acetate)	04.04	**P**
73.	Eugenol	97-53-0	07.08	**R**
74.	Farnesol	4602-84-0	05.06	**R-S**
75.	Fig leaf absolute	68916-52-9	05.83 (05.06)	**P**
76.	Furfuryl alcohol	98-00-0	07.09	**P**
77.	Furfurylidene acetone	623-15-4	(07.08)	**P**
78.	Geraniol	106-24-1	05.07	**R**
79.	Geranyl nitrile	5146-66-7 5585-39-7 31983-27-4	11.06 (07.08)	**P**
80.	Grapefruit oil expressed	8016-20-4	06.92	**R**

	Substance	CAS	Last Amended	Standard
81.	2,4-Heptadienal	5910-85-0	07.09	**P**
82.	trans-2-Heptenal	18829-55-5	04.89 (05.06)	**P**
83.	2-Heptylidene cyclopentan-1-one	39189-74-7	06.11	**R**
84.	2,4-Hexadienal	80466-34-8	07.09	**P**
85.	Hexahydrocoumarin	700-82-3	02.80 (05.06)	**P**
86.	trans-2-Hexenal	6728-26-3	07.08	**R**
87.	trans-2-Hexenal diethyl acetal	67746-30-9	04.89 (05.06)	**P**
88.	trans-2-Hexenal dimethyl acetal	18318-83-7	04.89 (05.06)	**P**
89.	alpha-Hexyl cinnamic aldehyde	101-86-0	05.07	**R**
90.	alpha-Hexylidene cyclopentanone	17373-89-6	07.08	**R**
91.	Hexyl salicylate	6259-76-3	05.07	**R**
92.	Hydroabietyl alcohol, dihydroabietyl alcohol	13393-93-6 26266-77-3 1333-89-7	04.04	**P**
93.	Hydroquinone monoethyl ether (4-ethoxy-Phenol)	622-62-8	10.83 (05.06)	**P**
94.	Hydroquinone monomethyl ether (4-methoxy-Phenol)	150-76-5	10.83 (05.06)	**P**
95.	Hydroxycitronellal	107-75-5	07.08	**R**
96.	3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde (HMPCC)	31906-04-4 51414-25-6	07.09	**R**
97.	p-Isobutyl-α-methyl-hydrocinnamaldehyde	6658-48-6	07.09	**R**
98.	Isobutyl N-methylanthranilate	65505-24-0	07.09	**R**
99.	Isocyclocitral	1335-66-6 1423-46-7 67634-07-5	05.07	**R**

	Substance	CAS	Last Amended	Standard
100.	Isocyclogeraniol (2,4,6-Trimethyl-3-cyclohexene-1-methanol)	68527-77-5	07.08	**R**
101.	Isoeugenol	97-54-1	07.08	**R**
102.	Isophorone	78-59-1	(07.08)	**P**
103.	6-Isopropyl-2-decalol (Decatol)	34131-99-2	06.79 (05.06)	**P**
104.	Jasmine absolute (grandiflorum)	8022-96-6 8024-43-9 90045-94-6 84776-64-7	07.08	**R**
105.	Jasmine absolute (sambac)	91770-14-8	07.08	**R**
106.	Lemon oil cold pressed	8008-56-8	06.92	**R**
107.	Lime oil expressed	8008-26-2	06.92	**R**
108.	Limonene	138-86-3	12.95	**S**
109.	Linalool; d-Linalool; l-Linalool	78-70-6 126-90-9 126-91-0	04.04	**S**
110.	Massoia bark oil	85085-26-3	(07.08)	**P**
111.	Massoia lactone	54814-64-1	(07.08)	**P**
112.	Melissa oil (genuine Melissa officinalis L.)	8014-71-9 84082-61-1	07.09	**R**
113.	p-Mentha-1,8-dien-7-al (Perilla aldehyde)	2111-75-3	07.08	**R**
114.	Menthadiene-7-methyl formate (Isobergamate)	68683-20-5	07.08	**R**
115.	o-Methoxycinnamaldehyde	1504-74-1	06.11	**R**
116.	7-Methoxycoumarin	531-59-9	02.79 (07.08)	**P**
117.	Methoxy dicylopentadiene carboxaldehyde (Scentenal)	86803-90-9	07.08	**R**

	Substance	CAS	Last Amended	Standard
118.	4-Methoxy-α-methylbenzenepropanal	5462-06-6	07.09	**R**
119.	2-Methoxy-4-methylphenol (p-Creosol)	93-51-6	07.08	**R**
120.	alpha-Methyl anisylidene acetone (1-(4-Methoxyphenyl)-1-penten-3-one)	104-27-8	05.80 (05.06)	**P**
121.	alpha-Methyl-1,3-benzodioxole-5-propionaldehyde (MMDHCA)	1205-17-0	06.10	**R**
122.	alpha-Methyl cinnamic aldehyde	101-39-3	05.07	**R**
123.	6-Methylcoumarin (Toncarine)	92-48-8	05.80 (05.06)	**P**
124.	7-Methylcoumarin	2445-83-2	05.83 (05.06)	**P**
125.	Methyl crotonate	623-43-8	05.80 (05.06)	**P**
126.	4-Methyl-7-ethoxycoumarin (Maraniol)	87-05-8	06.79 (05.06)	**P**
127.	Methyl Eugenol	93-15-2	07.02	**R**
128.	6-Methyl-3,5-heptadiene-2-one (Methyl heptadienone)	1604-28-0	07.09	**R**
129.	Methyl heptine carbonate (MHC, Folione)	111-12-6	07.08	**R**
130.	p-Methylhydrocinnamic aldehyde	5406-12-2	(07.08)	**P**
131.	Methyl ionone, mixed isomers	1335-46-2 127-42-4 127-43-5 127-51-5 7779-30-8	07.08	**R**
132.	Methyl methacrylate	80-62-6	(07.08)	**P**
133.	Methyl N-methylanthranilate (Dimethyl anthranilate)	85-91-6	07.09	**R**
134.	Methyl beta-naphtyl ketone	93-08-3	04.05	**R**
135.	3-Methyl-2(3)-nonenenitrile (Citgrenile)	53153-66-5	05.07 (07.08)	**P**

	Substance	CAS	Last Amended	Standard
136.	Methyl octine carbonate (MOC)	111-80-8	07.08	**R**
137.	3-Methyl-2-(pentyloxy)cyclopent-2-en-1-one	68922-13-4	06.11	**R**
138.	p-Methyltetrahydroquinoline	91-61-2	07.09	**R**
139.	Moskene (1,1,3,3,5-Pentamethyl-4,6-dinitroindane)	116-66-5	04.05 (07.08)	**P**
140.	Musk ambrette	83-66-9	12.95 (05.06)	**P**
141.	Musk ketone	81-14-1	06.10	**S**
142.	Musk tibetene (1-tert-Butyl-2,6-dinitro-3,4,5-trimethylbenzene)	145-39-1	04.05 (07.08)	**P**
143.	Musk Xylene	81-15-2	07.09	**P**
144.	Nitrobenzene	98-95-3	06.74 (05.06)	**P**
145.	2,4-Nonadienal	6750-03-4	07.09	**P**
146.	2-Nonyl-1-al dimethyl acetal	13257-44-8	06.11	**R**
147.	Nootkatone	4674-50-4	05.06	**S**
148.	Oak moss extracts	90028-68-5 9000-50-4 68917-10-2	07.08	**R-S**
149.	2,4-Octadienal	30361-28-5	06.11	**P**
150.	1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone (OTNE)	54464-57-2	07.08	**R**
151.	1-Octen-3-yl acetate (Amyl vinyl carbinyl acetate)	2442-10-6	07.08	**R**
152.	Opoponax		07.94 (04.99)	**R**
153.	1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl)ethan-1-one	13144-88-2	06.11	**R**

	Substance	CAS	Last Amended	Standard
154.	2-Pentylidene cyclohexanone	25677-40-1	05.83 (05.06)	**P**
155.	Peru balsam crude	8007-00-9	12.91 (05.07)	**P**
156.	Peru balsam extracts and distillates	8007-00-9	07.08	**R**
157.	Phenylacetaldehyde (Hyacinthin)	122-78-1	05.06	**R**
158.	Phenyl acetone (Methyl benzyl ketone)	103-79-7	(07.08)	**P**
159.	Phenyl benzoate	93-99-2	(07.08)	**P**
160.	3-Phenylbutanal	16251-77-7	06.10	**R**
161.	2-Phenylpropionaldehyde	93-53-8	07.09	**R**
162.	Pinacea derivatives		07.94	**S**
163.	3-Propylidene phthalide	17369-59-4	07.08	**R**
164.	Pseudoionone (2,6-Dimethylundeca-2,6,8-trien-10-one)	141-10-6	04.89 (05.06)	**P-S**
165.	Pseudo Methylionones	26651-96-7 72968-25-3 1117-41-5	07.09	**P**
166.	Quinoline	91-22-5	06.10	**P**
167.	Rose Ketones	23696-85-7 23726-93-4 43052-87-5 24720-09-0 23726-94-5 23726-92-3 23726-91-2 57378-68-4 71048-82-3 39872-57-6 70266-48-7 33673-71-1 35087-49-1 35044-68-9	07.09	**R**

	Substance	CAS	Last Amended	Standard
168.	Rue oil	8014-29-7	04.01 (07.02)	**R**
169.	Safrole, Isosafrole, Dihydrosafrole	94-59-7 120-58-1 94-58-6	07.87 (04.99)	**P** **R**
170.	Santolina oil	84961-58-0	(07.08)	**P**
171.	Savin oil	8024-00-8	06.82	**P-S**
172.	Sclareol	515-03-7	04.05	**S**
173.	Styrax		07.94	**P-R**
174.	Tagetes oil and absolute	91722-29-1 8016-84-0	04.01 (04.05)	**R**
175.	Tea leaf absolute (camellia sinensis leaf extract)	84650-60-2	05.06	**R**
176.	1,2,3,4-Tetrahydro-4-methylquinoline	19343-78-3	07.09	**R**
177.	Toluene	108-88-3	04.04	**P**
178.	Treemoss extracts	90028-67-4 68648-41-9 68917-40-8	07.08	**R-S**
179.	2,6,6-Trimethylcyclohexa-1,3-dienyl methanal (Safranal)	116-26-7	12.98	**R**
180.	2,4-Undecadienal	13162-46-4	07.09	**P**
181.	Verbena absolute (Lippia citriodora)	8024-12-2	06.10	**R**
182.	Verbena oil	8024-12-2	12.81 (05.06)	**P**
183.	Vetiveryl Acetate (the former specification Standard on Acetylated vetiver oil is replaced by this one)	117-98-6 62563-80-8 68917-34-0 73246-97-6 84082-84-8	07.09	**R-S**
184.	Ylang Ylang Extracts	8006-81-3 68606-83-7 83863-30-3	07.08	**R**

Acetyl ethyl tetramethyl tetralin

CAS N°: 88-29-9

Empirical formula: $C_{18}H_{26}O$

Synonyms:
7-Acetyl-6-ethyl-1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphthalene
AETT
Ethanone, 1-(3-ethyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-
Versalide (trade name)

History:

Initial reviews:	November 1977, February 1980	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products: N/A

Leave-on products:

Rinse-off products:
Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: N/A

Acetyl ethyl tetramethyl tetralin

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards)

Critical effect: **Neurotoxicity**
RIFM Summaries:

LLNA weighted mean EC3 values ($\mu g/cm^2$) [no. studies]	**Potency Classification** Based on Animal Data[2]	**Human Data**			**WoE NESIL**[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	**NOEL – HMT** (induction) ($\mu g/cm^2$)	**LOEL**[1] (induction) ($\mu g/cm^2$)	
N/A	N/A	N/A	N/A	N/A	N/A

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1]Data derived from HRIPT or HMT.
[2]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[3]WoE NESIL limited to two significant figures.
[4]EC3 value from one LLNA, not the mean.
[5]LOEL from human maximization test, not a human repeated insult patch test.

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Opdyke, D.L.J. (1979), Food and Cosmetics Toxicology 17, 357-360.
Spencer, P.S., Sterman, A.B et al. (1979), Neurotoxicology 1(1), 221-37.

5-Acetyl-1,1,2,3,3,6-hexamethyl indan (AHMI)

CAS N°: 15323-35-0 **Empirical formula:** $C_{17}H_{24}O$

Synonyms: Acetyl hexamethyl indan
6-Acetyl-1,1,2,3,3,5-hexamethylindane
1-(2,3-Dihydro-1,1,2,3,3,6-hexamethyl-1h-inden-5-yl)ethanone
Ethanone,1-(2,3-dihydro-1,1,2,3,3,6-hexamethyl-1H-inden-5-yl)-
1,1,2,3,3,6-Hexamethylindan-5-yl Methylketone
Phantolid

History:			
	Initial reviews:	October 1978, October 1987	
	Current revision date:	September 2001	
	Implementation date:	For new submissions*:	N/A
		For existing fragrance compounds*:	N/A
	Next review date	2006	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: 2% Rinse-off products: No restriction

Including household cleaning products

Non skin contact products: No restriction

Note box:

The Standard is set due to the phototoxic effects of the material. The limit only applies to applications on skin, excluding rinse-off products.
If combinations of phototoxic fragrance ingredients are used, the use levels have to be reduced accordingly. The sum of the concentrations of all phototoxic ingredients, expressed in % of their recommended maximum level in the consumer product shall not exceed 100.

Fragrance material specifications: N/A

5-Acetyl-1,1,2,3,3,6-hexamethyl indan (AHMI)

Contribution from other sources: None known

Critical effect: **Phototoxicity**

RIFM Summaries:

Human studies – phototoxicity.

The IFRA Standard is based upon two photoirritation studies in humans. In the first study, 10 volunteers were treated with 10% solution of AHMI in 75% ethanol plus 25% diethyl phthalate on each forearm. Twenty-four hours later, one arm was irradiated (UVA) and the other served as a control. Observations immediately after radiation, at 24 hrs, and at 48 hours showed no phototoxic effects (RIFM, 1986). In the second study, 10 volunteers were treated with a 10% solution in 75% ethanol plus 25% diethyl phthalate on the back. After 30 minutes, the site was irradiated (UVA and UVB). Observations at 5 minutes after irradiation, and at 3, 24, 48, and 72 hours showed no phototoxic effects (RIFM, 1987).

Animal studies – phototoxicity

- 5, 20, 50 % in guinea pigs, photoirritation observed 20 and 50% (RIFM, 1978a).
- 5, 20% in rabbits, photoirritation observed at 5 and 20% (RIFM, 1978a).
- 1, 5, 10, 20% in guinea pigs and rabbits, photoirritation observed in guinea pigs and rabbits at 5, 10, and 20% (Ogoshi, et al, 1980; Ohkoshi, et al, 1981).
- 10% in guinea pigs, no photoirritation observed (Guillot, et al, 1985).
- 1% in rabbits, photoirritation observed (RIFM, 1978).
- 1, 2, 4 % in rabbits, photoirritation observed (RIFM, 1985a; 1985b).
- 0.01, 1, 10, 25, 50% in hairless mice, photoirritation observed at 10, 25, 50% (RIFM, 1978c).

Animal studies – photoallergy

2% in guinea pigs, no photoallergy observed, 1/10 showed sensitization (RIFM, 1985c).

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for AHMI and recommended no change to the Standard (September 2001).

References:

Guillot, J.P., Gonnet, J.F., Loquerie, J.F., Martini, M.C., Convert, P., and Cotte, J. (1985). Anew method for the assessment of phototoxic and photoallergic potentials by topical applications in the albino guinea pig. J. Toxicol.-Cut. Ocu. Toxcicol., 4(2), 117-133.

Ogoshi, K., Tanaka, N., and Sekine, A. (1980). A study on the phototoxicity of musk type fragrances. Unpublished. Presented at Society of Cosmetic Chemists, Japan. Report number 7465, 17 November.

5-Acetyl-1,1,2,3,3,6-hexamethyl indan (AHMI)

Ohkoshi, K., Watanabe, A., and Tanaka, N. (1981). Phototoxicity of musks in perfumery. J. Society Cosmetic Chemists, Japan, 15(3), 207-213.

Research Institute for Fragrance Materials, Inc. (1978a). Phototoxicity of synthetic musks. Unpublished report from Shiseido laboratories. Report number 4415, 26 August.

Research Institute for Fragrance Materials, Inc. (1978b). Phototoxicity tests with 5-acetyl-1,1,2,3,3,6-hexamethylindan in albino rabbits. Unpublished report from Quest International. Report number 8055, 1 January.

Research Institute for Fragrance Materials, Inc. (1978c). Phototoxicity studies. RIFM report number 2042, 12 May.

Research Institute for Fragrance Materials, Inc. (1985a). Photosensitization test with 2% and 4% 5-acetyl-1,1,2,3,3,6-hexamethylindan in albino rabbits. Unpublished report from PFW Aroma Chemicals. Report number 29705, 1 November.

Research Institute for Fragrance Materials, Inc. (1985b). Photosensitization test with 1% 5-acetyl-1,1,2,3,3,6-hexamethylindan in albino rabbits. Unpublished report from PFW Aroma Chemicals. Report number 29706, 1 November.

Research Institute for Fragrance Materials, Inc. (1985c). Photosensitization test with 5-acetyl-1,1,2,3,3,6-hexamethylindan (17179) in guinea pigs. Unpublished report from PFW Aroma Chemicals. Report number 29704, 1 November.

Research Institute for Fragrance Materials, Inc. (1986). Phototoxicity testing in human subjects. RIFM report number 5748, 19 December.

Research Institute for Fragrance Materials, Inc. (1987). Phototoxicity testing in human subjects. RIFM report number 5743, 23 January.

Acetyl isovaleryl (5-methyl-2,3-hexanedione)

CAS N°: 13706-86-0

Empirical formula: $C_7H_{12}O_2$
CH_3-CO-CO-CH_2-CH(CH_3)-CH_3

Synonyms: 2,3-Hexanedione, 5-methyl-
Acetyl isopentanoyl

History:

Initial reviews:	February 1980, May 1983	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A

Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: N/A

Acetyl isovaleryl (5-methyl-2,3-hexanedione)

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Sensitisation**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Opdyke, D.L.J., Letizia, C. (1982), Food and Chemical Toxicology 20, 637.

Alantroot oil

CAS N°: 97676-35-2 **Empirical formula:** N/A

Synonyms: Alantroot oil (*Inula helenium)*
Elecampane oil
Inula helenium oil

History:

Initial reviews:	June 1975	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: N/A

Alantroot oil

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: Sensitization

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Opdyke, D.L.J. (1976), Food and Chemical Toxicology 14, 307.

4-methoxy-α-methylbenzenepropanal

CAS N°: 5462-06-6 **Empirical formula:** $C_{11}H_{14}O_2$

Synonyms: 2-Anisylpropional
Benzenepropanal, 4-methoxy-α-methyl-
Hydrocinnamaldehyde, *p*-methoxy-a-methyl
p-Methoxyhydratropaldehyde
4-Methoxy-α-methylbenzenepropanal
p-Methoxy-α-methylhydrocinnamaldehyde
3-(4-Methoxyphenyl)-2-methylpropanal
3-(*p*-Methoxyphenyl)-2-methylpropionaldehyde
2-Methyl-3-(*p*-methoxyphenyl)propanal
2-Methyl-3-(4-methoxyphenyl)propionaldehyde
Canthoxal, Fennaldehyde, Foliaver

History:

Initial reviews:	New Standard	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2011
Next review date	2014	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1	See Note box (1)	Category 7	0.45 %
Category 2	0.22 %	Category 8	2.00 %
Category 3	0.89 %	Category 9	5.00 %
Category 4	2.67 %	Category 10	2.50 %
Category 5	1.40 %	Category 11	See Note box (2)
Category 6	See Note box (1)	4.28 %	

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) (http://www.iofiorg.org/).

4-methoxy-α-methylbenzenepropanal

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.
Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards).**

Critical effect: Sensitization

RIFM Summaries:

LLNA weighted mean EC3 values ($\mu g/cm^2$) [No. Studies]	Potency Classification Based on Animal Data[2]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – HMT (induction) ($\mu g/cm^2$)	LOEL[1] (induction) ($\mu g/cm^2$)	
5900 [1][4]	Weak	5905	1380	NA	5900

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1] Data derived from HRIPT or HMT
[2] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[3] WoE NESIL limited to two significant figures
[4] EC3 value from one LLNA, not the mean

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for 4-Methoxy-α-methylbenzenepropanal and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 5900 mg/cm2. They recommend the limits for the 11 different product categories, which are the acceptable use levels of 4-Methoxy-α-methylbenzenepropanal in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 1980. Maximization study with 4-Methoxy-α-methylbenzenepropanal. RIFM report number 1790, August 26. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2004. Local Lymph Node Assay. Unpublished study from IFF Inc., 22 November. Report number 47809. (RIFM, Woodcliff Lake, NJ, USA).

4-methoxy-α-methylbenzenepropanal

RIFM (Research Institute for Fragrance Materials, Inc.), 2008. Human repeated insult patch test. RIFM report number 55562, July 30a. (RIFM, Woodcliff Lake, NJ, USA).

Allyl esters

CAS N°: N/A **Empirical formula:** N/A

Synonyms: N/A

History:

Initial reviews:	February 1977	
Current revision date:	2009	
Implementation date:	For new submissions*:	Not applicable
	For existing fragrance compounds*:	Not applicable
Next review date	2014	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: SPECIFICATION

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: Allyl esters should only be used when the level of free allylalcohol in the ester is less than 0.1%. This recommendation is based on the delayed irritant potential of allylalcohol.

Allyl esters

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards**)

Critical effect: See Fragrance material specification

REXPAN Rationale / Conclusion:

IFRA specification noted.

References:

Fd. Cosmet. Toxicol. 15,611-21 (1977)

Allyl heptine carbonate

CAS N°: 73157-43-4 **Empirical formula:** $C_{11}H_{16}O_2$

Synonyms: Allyl 2-octynoate
2-Octynoic acid,
2-propenyl ester

History:

Initial reviews:	Arpil 1989, April 1999, April 2005, May 2007	
Current revision date:	N/A	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Allyl heptine carbonate

Contribution from other sources: N/A

Critical effect: See Note box

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Reg. Tox & Pharm*., 31, 166-181, 2000

Allyl isothiocyanate

CAS N°: 57-06-7 **Empirical formula:** $C_4H_5N_5$

Synonyms: AITC
Allyl isosulfocyanate
Allyl thiocarbonimide
1-Propenal, 3-isothiocyanato-
2-Propenyl isothiocyanate

History:

Initial reviews:	N/A	
Current revision date:	N/A	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Allyl isothiocyanate

Contribution from other sources:

Critical effect: See Note box

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Reg. Tox & Pharm.*, 31, 166-181, 2000

Allyl phenoxyacetate

CAS N°: 7493-74-5 **Empirical formula:** $C_{11}H_{12}O_3$

Synonyms: Acetate PA
Acetic acid, phenoxy-, 2-propenyl ester
2-Propenyl phenoxyacetate

History:

Initial reviews:	New Standard	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2011
Next review date	2014	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: RESTRICTED / SPECIFICATION

RESTRICTIONS:

Limits in the finished product:

Category 1 - See Note box (1)	0.02 %	Category 7	0.05 %
Category 2	0.03 %	Category 8	0.70 %
Category 3	0.11 %	Category 9	3.50 %
Category 4	0.32 %	Category 10	2.50 %
Category 5	0.17 %	Category 11	See Note box (2)
Category 6	0.51 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry - www.iofiorg.org)
(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to negligible skin contact the concentration of a fragrance ingredient should not exceed the usual concentration of the fragrance compound in the finished product.

Fragrance material specifications:	Please also refer to the IFRA Standard ALLYL ESTERS. Purity requirement: Allyl esters should only be used when the level of free allylalcohol in the ester is less than 0.1%. This recommendation is based on the delayed irritant potential of allylalcohol.

Allyl phenoxyacetate

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards**)

Critical effect: Sensitization

RIFM Summaries:

LLNA weighted mean EC3 values (µg/cm^2) [no. studies]	Potency Classification Based on Animal Data[2]	Human Data			WoE NESIL[3] (µg/cm^2)
		NOEL – HRIPT (induction) (µg/cm^2)	NOEL – HMT (induction) (µg/cm^2)	LOEL[1] (induction) (µg/cm^2)	
775 [1][4]	Moderate	709	690	NA	700

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1]Data derived from HRIPT or HMT.
[2]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[3]WoE NESIL limited to two significant figures.
[4]EC3 value from one LLNA, not the mean.
[5]LOEL from human maximization test, not a human repeated insult patch test.

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Allyl phenoxyacetate and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 700 mg/cm2. They recommend the limits for the 11 different product categories, which are the acceptable use levels of Allyl phenoxyacetate in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Food and Cosmetic Toxicology 15, 611-21 (1977)

RIFM (Research Institute for Fragrance Materials, Inc.), 1974a. Maximization study with allyl phenoxyacetate. RIFM report number 1801, April 16. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1974b. Maximization study with allyl phenoxyacetate. RIFM report number 1779, November 19. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2007. Local Lymph Node Assay. RIFM report number 52909, May 21. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2008. Human repeated insult patch test. RIFM report number 54680, April 16a. (RIFM, Woodcliff Lake, NJ, USA).

Angelica root oil

CAS N°: 8015-64-3 **Empirical formula:** N/A

Synonyms: Angelica archangelica oil
Angelica archangelica root oil
Angelica root oil (Angelica archangelica L.)

History:

Initial reviews:	June 1975, October 1978	
Current revision date:	September 2001	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	2006	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: 0.8% Rinse-off products: No restriction

Including household cleaning products

Non skin contact products: No restriction

Note box:

The Standard is set due to the phototoxic effects of the material. The limit only applies to applications on skin, excluding rinse-off products.
If combinations of phototoxic fragrance ingredients are used, the use levels have to be reduced accordingly. The sum of the concentrations of all phototoxic ingredients, expressed in % of their recommended maximum level in the consumer product shall not exceed 100.

Fragrance material specifications: N/A

Angelica root oil

Contribution from other sources: None known

Critical effect: **Phototoxicity**

RIFM Summaries:

Two human phototoxicity studies were conducted. In one study, the test material at concentrations of 1% and 5% was applied to the backs of 30 male volunteers for 48 hours, under occlusion. Twenty-three hours after patch removal the sites were irradiated. Observations were made at 72 and 96 hours after application. No phototoxic reactions were observed in any subjects with either 1 or 5% concentrations of the test material (RIFM, 1975a). In a second study, the test material was applied neat to 13 male and female volunteers. Six hours later, the test sites were exposed to UVA radiation. Positive reactions were observed in 5/13 subjects (Kaidbey and Kligman, 1978, 1980).

- 4% on guinea pigs, UVA, photoirritation observed in all animals, 20/20. (Guillot, et al, 1985).
- 100% on hairless mice, UV, photoirritation observed. (RIFM, 1974. Forbes, et al, 1977). 0.78, 1.56, 3.125, 6.25, 12.5, 25, 50% on hairless mice. UV. Photoirritation observed at concentrations of 1.56% and higher. (RIFM, 1975b).
- 0.375, 0.75, and 1.5% on hairless mice. Photoirritation observed at all concentrations. (RIFM, 1987).

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for angelica root oil and has no concerns with the current limit of 0.8% (September 2001).

References:

Forbes P.D., Urbach F., and Davies R.E. (1977). Phototoxicity testing of fragrance raw materials. Food and Cosmetics Toxicology, 15, 55-60.

Guillot, J.P., Gonnet, J.F., Loquerie, J.F., Martini, M.C., Convert, P., and Cotte, J. (1985). A new method for the assessment of phototoxic and photoallergic potentials by topical applications in the albino guinea pig. Journal of Toxicology: Cutaneous and Ocular Toxicology, 4(2), 117-133.

Kaidbey, K.H. and Kligman, A.M. (1978). Identification of topical photosensitizing agents in humans. JID 70(3), 149-151.

Kaidbey, K.H. and Kligman, A.M. (1980). Identification of contact photosensitizers by human assay. Current Concepts in Cutaneous Toxicity, 55-68. Academic Press, NY.

Research Institute for Fragrance Materials, Inc. (1974). Phototoxicity and irritation test of fragrance materials in the mouse and miniature swine. RIFM report number 2037, 17 July.

Angelica root oil

Research Institute for Fragrance Materials, Inc. (1975a). Phototoxicity and irritation test of fragrance materials in the mouse and miniature swine. RIFM report number 2038, 4 February.

Research Institute for Fragrance materials, Inc. (1975b). Primary skin irritation and phototoxicity evaluation in human subjects with fragrance materials. RIFM report number 15092, December.

Research Institute for Fragrance Materials, Inc. (1987). Phototoxicity dilution assay of angelica root oil in hairless mice. RIFM report number 5147, 26 May.

alpha-Amyl cinnamic alcohol

CAS N°: 101-85-9

Empirical formula: $C_{14}H_{20}O$
C_6H_5-CH=C(CH_2-[CH_2]$_3$-CH_3)-CH_2OH

Synonyms:
Amylcinnamyl alcohol
α-Amylcinnamyl alcohol
2-Amyl-3-phenyl-2-propen-1-ol
2-Benzylideneheptanol
1-Heptanol, 2-(phenylmethylene)-
α-Pentylcinnamyl alcohol

History:

Initial reviews:	New Standard	
Current revision date:	2007	
Implementation date:	For new submissions*:	June 16, 2007
	For existing fragrance compounds*:	June 16, 2009
Next review date	2012	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Category 1	0.1 %	Category 7	0.3 %
Category 2	0.1 %	Category 8	2.0 %
Category 3	0.5 %	Category 9	5.0%
Category 4	1.6 %	Category 10	2.5 %
Category 5	0.8 %	Category 11	See Note box (2)
Category 6	2.5 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry). Further information about IOFI can be found on its website (http://www.iofiorg.org/).

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

alpha-Amyl cinnamic alcohol

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards**

Critical effect: **Sensitization**

RIFM Summaries:

LLNA weighted mean EC3 values (µg/cm²) [no. studies]	Potency Classification Based on Animal Data[2]	Human Data			WoE NESIL[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	NOEL – HMT (induction) (µg/cm²)	LOEL[1] (induction) (µg/cm²)	
>6250 [1]	Weak	3543	NA	NA	3500

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available

[1]Data derived from HRIPT or Human Max tests

[2]Gerberick *et al.*, 2001

[3]WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for alpha-amyl cinnamic alcohol and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 3500 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of alpha-amyl cinnamic alcohol in the various product categories. These were derived from the application of the exposurebased quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161)

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

RIFM (Research Institute for Fragrance Materials, Inc.), 2004a. Local Lymph Node Assay on alpha-Amylcinnamyl Alcohol. RIFM report number 45128, April 16. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2004b. Repeated Insult Patch Test on alpha-Amylcinnamyl Alcohol. RIFM report number 46097, July 7A. (RIFM, Woodcliff Lake, NJ, USA).

alpha-Amyl cinnamic aldehyde

CAS N°: 122-40-7 **Empirical formula:** $C_{14}H_{18}O$
C_6H_5-CH=C(CH_2-[CH_2]$_3$-CH_3)-CHO

Synonyms: Amyl cinnamal
Amyl cinnamic aldehyde
α-Amylcinnamaldehyde
α-Amyl ß-phenylacrolein
Heptanal, 2-phenylmethylene)-
Heptanal, 2-(phenylmethylene)
α-Pentylcinnamaldehyde
α-Pentyl-ß-phenylacrolein
2-(Phenylmethylene)heptanal
Flomine

History:

Initial reviews:	New Standard	
Current revision date:	2007	
Implementation date:	For new submissions*:	June 16, 2007
	For existing fragrance compounds*:	June 16, 2009
Next review date	2012	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Category 1	0.7 %	Category 7	1.8 %
Category 2	0.9 %	Category 8	2.0 %
Category 3	3.6 %	Category 9	5.0 %
Category 4	10.7 %	Category 10	2.5 %
Category 5	5.6 %	Category 11	See Note box (2)
Category 6 See Note box (1)	17.1 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry). Further information about IOFI can be found on its website (www.iofiorg.org).

alpha-Amyl cinnamic aldehyde

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards).**

Critical effect: Sensitization

RIFM Summaries:

alpha-Amyl cinnamic aldehyde - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values (µg/cm^2) [no. studies]	Potency Classification[2]	Human Data			WoE NESIL[3] (µg/cm^2)
		NOEL – HRIPT (induction) (µg/cm^2)	NOEL – MAX (induction) (mg/cm2)	LOEL[1] (induction) (µg/cm^2)	
2942 [3]	Extremely weak	23622	NA	NA	23600

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available

[1]Data derived from HRIPT or Human Max tests
[2]Gerberick *et al*., 2001
[3]WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for alpha-amyl cinnamic aldehyde and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 23600 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of alpha-amyl cinnamic aldehyde in the various product categories. These were derived from the application of the exposurebased quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Basketter, D.A. 2004. Unpublished data. Private communication to RIFM.

Elahi, E.N., Wright, Z., Hinselwood, D., Hotchkiss, S.A.M., Basketter D.A., Smith Pease , C.K., 2004. Protein binding and metabolism influence the relative skin sensitization potential of cinnamic compounds. Chemical Research in Toxicology, 17(3), 301-310.

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161

alpha-Amyl cinnamic aldehyde

RIFM (Research Institute for Fragrance Materials, Inc.), 1994. Repeated Insult Patch Test on alpha-Amylcinnamaldehyde. RIFM report number 26498, July 29. (RIFM, Woodcliff Lake, NJ, USA).
QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

RIFM (Research Institute for Fragrance Materials, Inc.), 2005. Repeated Insult Patch Test on alpha-Amylcinnamaldehyde. RIFM report number 47874, February 23. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2006. Local Lymph Node Assay on alpha-Amylcinnamaldehyde. DRAFT (RIFM, Woodcliff Lake, NJ, USA).

Smith, C. K. and Hotchkiss, S. A. M., 2001. Allergic Contact Dermatitis: Chemical and Metabolic Mechanisms. Taylor & Francis Ltd, London.

Amylcyclopentenone

CAS N°: 25564-22-1 **Empirical formula:** $C_{10}H_{16}O$

Synonyms: 2-Cyclopenten-1-one, 2-pentyl-
2-Pentyl-2-cyclopentenone
2-Pentylcyclopent-2-en-1-one

History:			
	Initial reviews:	Nov. 1987, July 1994, May 2007	
	Current revision date:	N/A	
	Implementation date:	For new submissions*:	N/A
		For existing fragrance compounds*:	N/A
	Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Amylcyclopentenone

Contribution from other sources: N/A

Critical effect: See Note box

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Reg. Tox & Pharm.*, 31, 166-181, 2000

Anisyl alcohol

CAS N°: 105-13-5

Empirical formula: $C_8H_{10}O_2$
$CH_3O\text{-}C_6H_4\text{-}CH_2OH$

Synonyms: Anisalcohol
Anise alcohol
Anisic alcohol
Benzyl alcohol, p-methoxy
p-Methoxybenzyl alcohol

History:

Initial reviews:	New Standard	
Current revision date:	2007	
Implementation date:	For new submissions*:	June 16, 2007
	For existing fragrance compounds*:	June 16, 2009
Next review date	2012	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Category 1	0.04 %	Category 7	0.1 %
Category 2	0.1 %	Category 8	1.5 %
Category 3	0.2 %	Category 9	5.0 %
Category 4	0.7 %	Category 10	2.5 %
Category 5	0.4 %	Category 11	See Note box (2)
Category 6 See Note box (1)	1.1 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry). Further information about IOFI can be found on its website (www.iofiorg.org).
(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Anisyl alcohol

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards).**

Critical effect: Sensitization

RIFM Summaries:

Anisyl alcohol - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values (µg/cm²) [no. studies]	Potency Classification[2]	Human Data			WoE NESIL[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	NOEL – MAX (induction) (µg/cm²)	LOEL[1] (induction) (µg/cm²)	
1475 [1]	Weak	NA	3448	NA	1500

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available

[1]Data derived from HRIPT or Human Max tests
[2]Gerberick *et al.*, 2001
[3]WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for anisyl alcohol and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 1500 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of anisyl alcohol in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161)

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

RIFM (Research Institute for Fragrance Materials, Inc.), 1971. Maximization Test on Anisyl Alcohol. RIFM report number 1805, May 24. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2005. Local Lymph Node Assay on Anisyl Alcohol. RIFM report number 48750, January 28. (RIFM, Woodcliff Lake, NJ, USA).

Anisylidene acetone (4-(p-methoxyphenyl)-3-butene-2-one)

CAS N°: 943-88-4

Empirical formula: $C_{11}H_{12}O_2$
$CH_3\text{-}O\text{-}C_6H_4\text{-}CH{=}CH\text{-}CO\text{-}CH_3$

Synonyms: 3-Butene-2-one, 4-(4-methoxyphenyl) ester
Methyl p-methoxycinnamyl ketone

History:

Initial reviews:	November 1974	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A

Rinse-off products: N/A
Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: N/A

Anisylidene acetone (4-(p-methoxyphenyl)-3-butene-2-one)

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Opdyke, D.L.J. (1975), Food and Chemical Toxicology 13, 456.

cis- and trans-Asarone

CAS N°: 2883-98-9
5273-86-9

Empirical formula: $C_{12}H_{16}O_3$

Synonyms: α-Asarone
Asarone ((E)-and (Z)-2,4,5-Trimethoxypropen-1-yl benzene)
trans-Asarone
Benzene, 1,2,4-trimethoxy-5-(1-propenyl)-, (E)-
trans-Isoasarone

ß-Asarone
cis-ß-Asarone
Benzene, 1,2,4-trimethoxy-5-(1-propenyl)-, (Z)-
cis-Isoasarone

History:

Initial reviews:	Dec. 1991	
Current revision date:		
Implementation date:	For new submissions*:	
	For existing fragrance compounds*:	December 1991
Next review date		

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED** / **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	
Non skin contact products:	N/A		

Note box:

cis- and trans-Asarone as such should not be used as fragrance ingredients; essential oils containing cis- or trans-asarone (e.g. calamus oils) should not be used at a level such that the total concentration of cis- and trans-asarone exceeds 0.01% in consumer products.
This recommendation is based on similar biological effects to those of safrole (R.W. Wiseman, E.C. Miller et al. (1987), Cancer Res. 47,2275-2283).

Fragrance material specifications: N/A

cis- and trans-Asarone

Contribution from other sources: N/A

Critical effect: See Note box

REXPAN Rationale / Conclusion:

N/A

References:

N/A

Benzaldehyde

CAS N°: 100-52-7 **Empirical formula:** C_7H_6O

Synonyms: Benzenecarbonal
Benzene carboxaldehyde
Benzenecarboxaldehyde
Benzenemethylal
Benzoic aldehyde
Bitter almond oil, synthetic
Phenylformaldehyde
Phenylmethanol aldehyde

History:

Initial reviews:	New Standard	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2011
Next review date	2014	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1 See Note box (1)	0.02 %	Category 7	0.05 %
Category 2	0.02 %	Category 8	0.60 %
Category 3	0.09 %	Category 9	3.00 %
Category 4	0.27 %	Category 10	2.50 %
Category 5	0.14 %	Category 11	See Note box (2)
Category 6 See Note box (1)	0.43 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry - www.iofiorg.org)
(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to negligible skin contact the concentration of a fragrance ingredient should not exceed the usual concentration of the fragrance compound in the finished product.

Fragrance material specifications: N/A

Benzaldehyde

Contribution from other sources: See **Annex I**

Critical effect: **Sensitization**

RIFM Summaries:

LLNA weighted mean EC3 values (µg/cm^2) [no. studies]	Potency Classification Based on Animal Data[2]	Human Data			WoE NESIL[3] (µg/cm^2)
		NOEL – HRIPT (induction) (µg/cm^2)	NOEL – HMT (induction) (µg/cm^2)	LOEL[1] (induction) (µg/cm^2)	
> 6250 [1][4]	Weak	590	NA	2760[5]	590

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1]Data derived from HRIPT or HMT.
[2]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[3]WoE NESIL limited to two significant figures.
[4]EC3 value from one LLNA, not the mean.
[5]LOEL from human maximization test, not a human repeated insult patch test.

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Benzaldehyde and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 590 µg/cm2. They recommend the limits for the 11 different product categories, which are the acceptable use levels of Benzaldehyde in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Basketter, D.A., Wright, Z., Gilmour, N.J., Ryan, C.A., Gerberick, G.F., Robinson, M.K., Dearman, R.J., Kimber, I., 2002. Prediction of human sensitization potency using local lymph node assay EC3 values. The Toxicologist, 66(1-S), 240.

RIFM (Research Institute for Fragrance Materials, Inc.), 1973. Maximization study with benzaldehyde. RIFM report number 1802, October 11a. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2009. Human repeated insult patch test. RIFM report number 57360. (RIFM, Woodcliff Lake, NJ, USA).

Benzene

CAS N°: 71-43-2 **Empirical formula:** C_6H_6

Synonyms: Benzol

History:

Initial reviews:	1988	
Current revision date:	January 2004	
Implementation date:	For new submissions*:	May 6, 2004
	For existing fragrance compounds*:	May 6, 2005
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material should not be used as fragrance ingredient for any application.

Fragrance material specifications:

The level of benzene has to be kept as low as practicable and should never exceed **1 ppm** in the fragrance compound.

Since the introduction of the original restriction on the use of benzene by IFRA in 1988, there have been significant changes in manufacturing practices that permit the reduction of the maximum permitted level of this substance. These include use of technological improvements allowing replacement of this solvent for the extraction of fragrance materials and in eliminating its presence as an impurity in alternative extraction solvents.

Benzene

Contribution from other sources: None to consider

Critical effect: **Carcinogenicity**

REXPAN Rationale / Conclusion:

IFRA ban noted - REXPAN, January 2004

References:

1) IARC (International Agency for Research on Cancer) Monographs Vol 7, p. 203 (1974); Vol 29, p. 93 and 391 (1982); Suppl. 7, p. 120 (1987)

2) CSTEE (Scientific Committee on Toxicity, Ecotoxicity and the Environment), Opinion on the results of the Risk Assessment of Benzene carried out in the framework of Council Regulation (EEC) 793/93 as adopted on Feb., 6, 2003

Benzyl alcohol

CAS N°: 100-51-6

Empirical formula: C_7H_8O
$C_6H_5\text{-}CH_2OH$

Synonyms:
Benzenemethanol
Benzylic alcohol
alpha-Hydroxytoluene
Phenylcarbinol
Phenyl carbinol
Phenylmethanol
Phenylmethyl alcohol
alpha-Toluenol

History:

Initial reviews:	New Standard	
Current revision date:	2007	
Implementation date:	For new submissions*:	June 16, 2007
	For existing fragrance compounds*:	June 16, 2009
Next review date	2012	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Category 1 See Note box (1)	0.2 %	Category 7	0.4 %
Category 2	0.2 %	Category 8	2.0 %
Category 3	0.9 %	Category 9	5.0 %
Category 4	2.7 %	Category 10	2.5 %
Category 5	1.4 %	Category 11 See Note box (2)	
Category 6 See Note box (1)	4.3 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry). Further information about IOFI can be found on its website (www.iofiorg.org).
(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product

Benzyl alcohol

Fragrance material specifications: N/A

Contribution from other sources: See **Annex 1**

Critical effect: **Sensitization**

RIFM Summaries:

LLNA weighted mean EC3 values (µg/cm²) [no. studies]	Potency Classification[2]	Human Data			WoE NESIL[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	NOEL – MAX (induction) (µg/cm²)	LOEL[1] (induction) (µg/cm²)	
>12500 [1]	Weak	5906	6897	8858	5900

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available

[1]Data derived from HRIPT or Human Max tests
[2]Gerberick *et al.*, 2001
[3]WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for benzyl alcohol and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 5900 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of benzyl alcohol in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161.

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

RIFM (Research Institute for Fragrance Materials, Inc.), 1970. Maximization test on Benzyl Alcohol. RIFM report number 1760, October 7. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2004. Repeated Insult Patch Test on Benzyl Alcohol. RIFM report number 45131, April 30. (RIFM, Woodcliff Lake, NJ, USA).

Benzyl alcohol

RIFM (Research Institute for Fragrance Materials, Inc.), 2005a. Local Lymph Node Assay on Benzyl Alcohol. RIFM report number 47376, January 20. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2005b. Repeated Insult Patch Test on Benzyl Alcohol. RIFM report number 47873, March 16. (RIFM, Woodcliff Lake, NJ, USA).

Benzyl benzoate

CAS N°: 120-51-4 **Empirical formula:** $C_{14}H_{12}O_2$ $C_6H_5\text{-}CO_2\text{-}CH_2\text{-}C_6H_5$

Synonyms: Benylate
Benzoic acid, benzyl ester
Benzoic acid, phenylmethyl ester
Benzyl phenylformate
Phenylmethyl benzoate

History:

Initial reviews:	New Standard	
Current revision date:	2007	
Implementation date:	For new submissions*:	June 16, 2007
	For existing fragrance compounds*:	June 16, 2009
Next review date	2012	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Category 1 See Note box (1)	1.7 %	Category 7	4.5 %
Category 2	2.2 %	Category 8	2.0 %
Category 3	8.9 %	Category 9	5.0 %
Category 4	26.7 %	Category 10	2.5 %
Category 5	14 %	Category 11	See Note box (2)
Category 6 See Note box (1)	42.8 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry). Further information about IOFI can be found on its website (www.iofiorg.org).
(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Benzyl benzoate

Contribution from other sources: **See Annex 1**

Critical effect: **Sensitization**

RIFM Summaries:

LLNA weighted mean EC3 values (µg/cm²) [no. studies]	Potency Classification[2]	Human Data			WoE NESIL[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	NOEL – MAX (induction) (µg/cm²)	LOEL[1] (induction) (µg/cm²)	
>12500 [1]	Extremely weak	59050	20690	NA	59000

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available

[1]Data derived from HRIPT or Human Max tests
[2]Gerberick *et al.*, 2001
[3]WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for benzyl benzoate and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 59000 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of benzyl benzoate in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

RIFM (Research Institute for Fragrance Materials, Inc.), 1970. Maximization test on Benzyl Benzoate. RIFM report number 1760, June 1. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2004. Repeated Insult Patch Test on Benzyl Benzoate. RIFM report number 47159, July 7A. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2005. Local Lymph Node Assay

Benzyl benzoate

on Benzyl Benzoate. RIFM report number 47377, January 20. (RIFM, Woodcliff Lake, NJ, USA).

Benzyl cinnamate

CAS N°: 103-41-3 **Empirical formula:** $C_{16}H_{14}O_2$
C_6H_5-CH_2-CO_2-CH=CH-C_6H_5

Synonyms: Benzyl gamma-phenylacrylate
Benzyl 3-phenylpropenoate
Cinnamein
Cinnamic acid, benzyl ester
Phenylmethyl 3-phenyl-2-propenoate
2-Propenoic acid, 3-phenyl-, phenylmethyl ester

History:

Initial reviews:	New Standard	
Current revision date:	2007	
Implementation date:	For new submissions*:	June 16, 2007
	For existing fragrance compounds*:	June 16, 2009
Next review date	2012	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Informational Booklet.

Category 1 See Note box (1)	0.1 %	Category 7	0.4 %
Category 2	0.2 %	Category 8	2.0 %
Category 3	0.7 %	Category 9	5.0 %
Category 4	2.1 %	Category 10	2.5 %
Category 5	1.1 %	Category 11	See Note box (2)
Category 6 See Note box (1)	3.4 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry). Further information about IOFI can be found on its website (www.iofiorg.org).
(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Benzyl cinnamate

Contribution from other sources: **See Annex 1**

Critical effect: **Sensitization**

RIFM Summaries:

LLNA weighted mean EC3 values (µg/cm²) [no. studies]	Potency Classification[2]	Human Data			WoE NESIL[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	NOEL – MAX (induction) (µg/cm²)	LOEL[1] (induction) (µg/cm²)	
4600 [1]	Weak	4720	5517	NA	4700

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available

[1]Data derived from HRIPT or Human Max tests
[2]Gerberick *et al.*, 2001
[3]WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for benzyl cinnamate and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 4700 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of benzyl cinnamate in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

RIFM (Research Institute for Fragrance Materials, Inc.), 1972. Maximization test on Benzyl Cinnamate. RIFM report number 1804, June 1. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1975. Maximization test on Benzyl Cinnamate. RIFM report number 1799, March 27A. (RIFM, Woodcliff Lake, NJ, USA).

Benzyl cinnamate

RIFM (Research Institute for Fragrance Materials, Inc.), 2005a. Local Lymph Node Assay on Benzyl Cinnamate. RIFM report number 48751, January 26. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2005b. Repeated Insult Patch Test on Benzyl Cinnamate. RIFM report number 49109, June 23. RIFM, Woodcliff Lake, NJ, USA).

Benzyl cyanide

CAS N°: 140-29-4

Empirical formula: C_8H_7N
$C_6H_5\text{-}CH_2\text{-}CN$

Synonyms: Benzeneacetonitrile
Benzylnitrile
Phenylacetonitrile
Phenyl acetyl nitrile

History:

Initial reviews:	New Standard**	
Current revision date:	October 2003	
Implementation date:	For new submissions*:	N/A**
	For existing fragrance compounds*:	N/A**
Next review date	N/A**	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	
Non skin contact products:	N/A		

Note box:

The material as such should not be used as fragrance ingredient for any application.

**This material has previously been included in the list of 'Other Materials'; the material therefore has already been prohibited before.

Fragrance material specifications: N/A

Benzyl cyanide

Contribution from other sources:

On the basis of established maximum levels of this substance in commercially available natural sources (like essential oils and extracts), exposure to this substance from the use of these oils and extracts is not significant and the use of these oils is authorised as long as the level of benzyl cyanide in the finished product does not exceed 100 ppm. Furthermore, these natural extracts should not be used as substitutes for this substance. Examples for potential natural sources (with maximum levels) of benzyl cyanide are provided below:
Fleur d'oranger absolute 1%
Frangipani (plumeria acutifolia) absolute 0.2%
Jasmine grandiflorum (Egypt) absolute traces
Jasmine multiflorum (India) absolute 0.3%
Karo karoundé absolute (CAS 68916-95-0) 4.75%
Tuberose (India) absolute 0.8%

Critical effect: **Release of cyanide**

REXPAN Rationale / Conclusion:

IFRA ban noted - REXPAN, October 2003

References:

Potter et al., 2001, Food and Chemical Toxicology 39 (2), page 141-146.

Potter et al., 2001, Food and Chemical Toxicology 39 (2), page 147-151.

Benzylidene acetone (4-Phenyl-3-buten-2-one)

CAS N°: 122-57-6

Empirical formula: $C_{10}H_{10}O$
C_6H_5-CH=CH-CO-CH_3

Synonyms: 3-Buten-2-one, 4-phenyl-
Benzilideneacetone
Methyl styryl ketone

History:

Initial reviews:	June 1974	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A

Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: N/A

Benzylidene acetone (4-Phenyl-3-buten-2-one)

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Opdyke, D.L.J. (1973), Food and Chemical Toxicology 11, 1021.

Private communication to IFRA.

Benzyl salicylate

CAS N°: 118-58-1 **Empirical formula:** $C_{14}H_{12}O_3$
$C_6H_5\text{-}CH_2\text{-}OCO\text{-}C_6H_4\text{-}OH$

Synonyms: Benzoic acid, 2-hydroxy-, phenylmethyl ester
Benzyl 2-hydroxybenzoate
Benzyl o-hydroxybenzoate
2-Hydroxybenzoic acid, benzyl ester
Phenylmethyl 2-hydroxybenzoate
Salicylic acid, benzyl ester

History:

Initial reviews:	New Standard	
Current revision date:	2007	
Implementation date:	For new submissions*:	June 16, 2007
	For existing fragrance compounds*:	June 16, 2009
Next review date	2012	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Informational Booklet.

Category 1	See Note box (1)	Category 7	1.3 %
Category 2	0.7 %	Category 8	2.0 %
Category 3	2.7 %	Category 9	5.0 %
Category 4	8.0 %	Category 10	2.5 %
Category 5	4.2 %	Category 11	See Note box (2)
Category 6	See Note box (1) 12.8 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry). Further information about IOFI can be found on its website (www.iofiorg.org).

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Benzyl salicylate

Fragrance material specifications: N/A

Contribution from other sources: **See Annex 1**

Critical effect: **Sensitization**

RIFM Summaries:

LLNA weighted mean EC3 values (µg/cm²) [no. studies]	Potency Classification[2]	Human Data			WoE NESIL[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	NOEL – MAX (induction) (µg/cm²)	LOEL[1] (induction) (µg/cm²)	
725 [1]	Weak	17717	20690	NA	17700

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available

[1]Data derived from HRIPT or Human Max tests
[2]Gerberick *et al.*, 2001
[3]WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for benzyl salicylate and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 17700 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of benzyl salicylate in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161

RIFM (Research Institute for Fragrance Materials, Inc.), 1970. Maximization test on Benzyl Salicylate. RIFM report number 1760, October 7. (RIFM, Woodcliff Lake, NJ, USA).

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

RIFM (Research Institute for Fragrance Materials, Inc.), 1975a. Maximization test on Benzyl Salicylate. RIFM report number 1798, March 28. (RIFM, Woodcliff Lake, NJ, USA).

Benzyl salicylate

RIFM (Research Institute for Fragrance Materials, Inc.), 1975b. Maximization test on Benzyl Salicylate. RIFM report number 1799, March 27. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2004. Repeated Insult Patch Test on Benzyl Salicylate. RIFM report number 45129, May 3. RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2005. Local Lymph Node Assay on Benzyl Salicylate. RIFM report number 47378, January 20. (RIFM, Woodcliff Lake, NJ, USA)

Bergamot oil expressed

CAS N°: 908007-75-8 **Empirical formula:** N/A

Synonyms: N/A

History:			
	Initial reviews:	October 1974, June 1992	
	Current revision date:	N/A	
	Implementation date:	For new submissions*:	N/A
		For existing fragrance compounds*:	N/A
	Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:		
Skin contact products:	0.4% (excl. wash off prod.)	
Leave-on products:		Rinse-off products: *Including household cleaning products*
Non skin contact products:	No limitation	
Note box:		
Fragrance material specifications:	N/A	

Contribution from other sources:

Critical effect:

REXPAN Rationale / Conclusion:

For applications on areas of skin exposed to sunshine, excluding bath preparations, soaps and other products which are washed off the skin, bergamot oil expressed should not be used such that the level in the consumer products exceeds 0.4%.

Note: See remark on phototoxic ingredients in the introduction to the Standards (Appendix 8 to the IFRA Code of Practice) and the Standard on Citrus oil and other furocoumarins-containing essential oils.

It is further recommended that, for qualities of the expressed oil in which the less volatile

Bergamot oil expressed

components have been concentrated by partial or total removal of the terpene fraction, this limit should be reduced in proportion to the degree of concentration.

References:

These recommendations are based on the published literature on the phototoxicity of this material, summarized by D.L. Opdyke, Fd. Cosm. Toxicol. 11,1031(1973) and other investigations published in Contact Dermatitis 3,225 (1977).

Birch wood pyrolysate

CAS N°: 8001-88-5
84012-15-7
85940-29-0
68917-50-0

Empirical formula: N/A

Synonyms:

For the crude material banned:
Birch tar oil, crude

For the distillates specified:
Birch tar oil dephenolated
Birch tar oil rectified
Essence bouleau dephenolisée
Essence bouleau (Goudron) rect.

History:

Initial reviews:	December 1996	
Current revision date:	October 2003	
Implementation date:	For new submissions*:	May 6, 2004
	For existing fragrance compounds*:	May 6, 2005
Next review date	October 2008	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: SPECIFICATION / **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	

Non skin contact products: N/A

Note box:

Crude birch wood (bark) pyrolysates (oils) derived by pyrolysis (destructive distillation) of the wood or bark of *Betula Pubescens*, *Betula Pendula*, *Betula Lenta* or *Betula Alba* **should not be used as a fragrance ingredient**.

Only rectified (purified) birch tar oils being in compliance with the below limitations for polynuclear aromatic hydrocarbons should be used.

Fragrance material specifications:	Limit content of polynuclear aromatic hydrocarbons (PAH) resulting from the use of rectified oils according to Good Manufacturing Practice. If used alone or in combination with rectified cade oil,

Birch wood pyrolysate

	benzopyrene and 1, 2-benzanthracene are to be used as markers for PAHs. The total concentration of both of these should not exceed **1 ppb** in the final product.

Contribution from other sources: N/A

Critical effect: **Carcinogenicity, Genotoxicity***

*Some of the polynuclear aromatic hydrocarbons are known to be carcinogen or genotoxic materials.

REXPAN Rationale / Conclusion:

IFRA ban noted - REXPAN, October 15, 2003

Bitter orange peel oil expressed

CAS N°: 68916-04-1
72968-50-4

Empirical formula: N/A

Synonyms: Orange Peel Oil, Bitter (*Citrus aurantium* L. subsp amara L.)
Bitter orange oil (*Citrus aurantium* L. subsp. amara L.)
Citrus aurantium peel oil
Curacao peel oil (*Citrus aurantium* L.)
Daidai peel oil (*Citrus aurantium* L.)

History:

Initial reviews:	October 1975, June 1992	
Current revision date:	July 2002	
Implementation date:	For new submissions*:	July 3, 2002
	For existing fragrance compounds*:	July 3, 2003
Next review date	July 2007	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	1.25%*	Rinse-off products:	No Restriction
		Including household cleaning products	
Non skin contact products:	No Restriction		

Note box:

*Applications on skin areas exposed to sunshine.
If combinations of phototoxic fragrance ingredients are used, the use levels have to be reduced accordingly. The sum of the concentrations of all phototoxic fragrance ingredients, expressed in % of their recommended maximum level in the consumer product, shall not exceed 100.
For Bitter Orange Peel Oil Expressed, the general Standard on '**Citrus oils and other furocoumarin containing essential oils' also needs to be taken into account.**

Fragrance material specifications: N/A

Bitter orange peel oil expressed

Contribution from other sources: None known

Critical effect: Photoirritation

RIFM Summaries:

Human Studies: The material was tested for phototoxic potential in human volunteers (Kaidbey and Kligman, 1980). Five µL/cm² of 100% bitter orange oil was applied to 2 cm² under occlusive tape. One cm circular sites were exposed to visible light or 20 J/ cm² UVA.

Reactions were read at 24 and 48 hours. All 8 subjects reacted.

Animal studies: The NOEL was based on studies conducted with pooled samples of bitter orange oil in one miniature swine and hairless mice, which showed NOEL of 6.25%.

LLNA weighted mean EC3 values (µg/cm²) [no. studies]	**Potency Classification** Based on Animal Data[2]	**Human Data**			**WoE NESIL**[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	**NOEL – HMT** (induction) (µg/cm²)	**LOEL**[1] (induction) (µg/cm²)	
N/A	N/A	N/A	N/A	N/A	N/A

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1]Data derived from HRIPT or HMT.
[2]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[3]WoE NESIL limited to two significant figures.
[4]EC3 value from one LLNA, not the mean.
[5]LOEL from human maximization test, not a human repeated insult patch test.

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for orange peel oil, bitter, and recommended that the skin contact level should change to 1.25%, incorporating a 5 fold uncertainty factor.

References:

P.D. Forbes, F. Urbach and R.E. Davies (1977). Phototoxicity testing of fragrance raw materials. Food and Cosmetics Toxicology, 15, 55-60. Report number 1422.

Kaidbey, K.H. and Kligman, A.M. (1980). Identification of contact photosensitizers by human assay. Current Concepts in Cutaneous Toxicity, 55-68. Academic Press, NY. Report number 1995.

Bitter orange peel oil expressed

Research Institute for Fragrance Materials, Inc. (1972). Phototoxicity and irritation studies of fragrance materials in hairless mice and miniature swine. RIFM report number 2034, May 26.

Research Institute for Fragrance Materials, Inc. (1978). Phototoxicity and irritation studies of mice and pigs with fragrance materials. RIFM report number 2042, April 14.

Boldo oil

CAS N°: 8022-81-9 **Empirical formula:** N/A

Synonyms: Boldo leaf oil (Peumus boldus Mol.)
Oil, boldo leaf
Peumus boldus oil

History:

Initial reviews:	New Standard	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2010
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: N/A

Boldo oil

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards**)

Critical effect: **Insufficient Data**

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.

This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Regulatory Toxicology and Pharmacology*, 31, 166-181, 2000

3-Bromo-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one

CAS N°: 76-29-9 **Empirical formula:** $C_{10}H_{15}BrO$

Synonyms: Bicyclo[2.2.1]heptan-2-one, 3-bromo-
1,7,7-trimethyl-
2-Bornanone, 3-bromo-
3-Bromobornan-2-one
3-Bromo-2-bornanone
3-Bromocamphor
Camphor bromide
Camphor, 3-bromo-

History:

Initial reviews:	N/A	
Current revision date:	N/A	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

3-Bromo-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one

Contribution from other sources: N/A

Critical effect: See Note box

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Reg. Tox & Pharm*., 31, 166-181, 2000

Bromostyrene

CAS N°: 103-64-0 **Empirical formula:** C_8H_7Br

Synonyms: Benzene, (2-bromoethenyl)-
α-Bromo-ß-phenylethylene
ß-Bromostyrene
ß-Bromovinylbenzene
Omega-Bromstyrene
Bromstyrol
Bromstyrolene

History:

Initial reviews:	N/A	
Current revision date:	N/A	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Bromostyrene

Contribution from other sources: N/A

Critical effect: See Note box

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

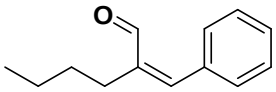
Human Health Criteria Document, *Reg. Tox & Pharm*., 31, 166-181, 2000

α-Butylcinnamaldehyde

CAS N°: 7492-44-6 **Empirical formula:** $C_{13}H_{16}O$

Synonyms: 2-Benzylidenehexanal
Butyl cinnamic aldehyde
α-Butyl-β-phenylacrolein
Hexanal, 2-(phenylmethylene)-alpha-butylcinnamaldehyde

Structure:



History:

Initial reviews:	New Standard	
Current revision date:	June 20, 2011	
Implementation date:	For new submissions*:	August 20, 2011
	For existing fragrance compounds*:	August 20, 2012
Next review date:	2016	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: RESTRICTED

RESTRICTIONS:

Limits in the finished product:			
Category 1 See Note box (1)	0.03%	Category 7	0.08%
Category 2	0.04%	Category 8	1.01%
Category 3	0.15%	Category 9	5.00%
Category 4	0.45%	Category 10	2.50%
Category 5	0.24%	Category 11	See Note box (2)
Category 6 See Note box (1)	0.72%		

Note box:
(1) See the IFRA Code of Practice (Appendix 8, Introduction to the IFRA Standards) regarding the Note on Oral Care Products and other products with the potential of ingestion.
(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Indicative contribution from other sources: None known at the time of the publication of the Standard

---

Critical effect: Sensitization

α-Butylcinnamaldehyde

RIFM Summaries:

LLNA weighted mean EC3 values (µg/cm²) [no. studies]	Potency Classification Based on Animal Data[1]	Human Data[2]			WoE NESIL[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	NOEL – HMT (induction) (µg/cm²)	LOEL (induction) (µg/cm²)	
2775 [2]	Weak	NA	5520	NA	1000

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[2]Data derived from HRIPT or HMT.
[3]WoE NESIL limited to two significant figures. A default value based on the LLNA data was employed because the material is used a very low volume and there are no HRIPT data.

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for α-butylcinnamaldehyde and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 1000 µg/cm², which is a default value based on the LLNA data. They recommend the limits for the 11 different product categories, which are the acceptable use levels of α-butylcinnamaldehyde in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the publication by Api *et al*., 2008.

References:

Api AM, Basketter DA, Cadby PA, Cano M-F, Ellis G, Gerberick G, et al. Dermal Sensitization Quantitative Risk Assessment (QRA) For Fragrance Ingredients. *Regulatory Toxicology and Pharmacology* 2008;52(1): 3-23.

p-tert-Butyldihydrocinnamaldehyde (Bourgeonal)

CAS N°: 18127-01-0 **Empirical formula:** $C_{13}H_{18}O$ $(CH_3)_3C\text{-}C_6H_4\text{-}CH_2CH_2CHO$

Synonyms: Benzenepropanal, 4-(1,1-dimethylethyl)-
3-(4-tert-Butylphenyl)propionaldehyde
Bourgeonal

History:

Initial reviews:	April 1991, July 1994, May 2007 (42nd Amendment)	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

For a description of the categories, refer to the QRA Informational Booklet.

Category 1 See Note box (1)	0.03 %	Category 7	0.1 %
Category 2	0.04 %	Category 8	0.6 %
Category 3	0.2 %	Category 9	0.6 %
Category 4	0.5 %	Category 10	0.6 %
Category 5	0.3 %	Category 11	Not Restricted (2)
Category 6 See Note box (1)	0.8 %		

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.
(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry)http://www.iofiorg.org/.

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

p-tert-Butyldihydrocinnamaldehyde (Bourgeonal)

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards).**

Critical effect: Sensitization

RIFM Summaries:

p-tert-Butyl-dihydrocinnamaldehyde - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values (µg/cm²) [no. studies]	Potency Classification[2]	Human Data			WoE NESIL[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	NOEL – MAX (induction) (µg/cm²)	LOEL[1] (induction) (µg/cm²)	
1075 [1]	Weak	1181	4138	7087	1100

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available

[1]Data derived from HRIPT or Human Max tests
[2]Gerberick *et al.*, 2001
[3]WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for p-tert-butyldihydrocinnamaldehyde and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 1100 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of p-tertbutyldihydrocinnamaldehyde in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161

RIFM (Research Institute for Fragrance Materials, Inc.), 1980. Maximization test on p-tert- Butyldihydrocinnamaldehyde. RIFM report number 1790, June 25a. (RIFM, Woodcliff Lake, NJ, USA).

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

p-tert-Butyldihydrocinnamaldehyde (Bourgeonal)

RIFM (Research Institute for Fragrance Materials, Inc.), 2002. Repeated Insult Patch Test on p-tert-Butyldihydrocinnamaldehyde. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2003. Repeated Insult Patch Test on p-tert-Butyldihydrocinnamaldehyde. RIFM report number 47269, March 21. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2003. Repeated Insult Patch Test on p-tert-Butyldihydrocinnamaldehyde. RIFM report number 47272, February 10. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2004. Repeated Insult Patch Test on p-tert-Butyldihydrocinnamaldehyde. RIFM report number 45134, March 11. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2006. Local Lymph Node Assay on p-tert-Butyldihydrocinnamaldehyde. DRAFT. (RIFM, Woodcliff Lake, NJ, USA).

p-tert-Butyl-alpha-methylhydrocinnamic aldehyde (BMHCA)

CAS N°: 80-54-6 **Empirical formula:** $C_{14}H_{20}O$
$(CH_3)_3C\text{-}C_6H_4\text{-}CH_2\text{-}CH(CH_3)\text{-}CHO$

Synonyms: Benzenepropanal, 4-(1,1-dimethylethyl)-alpha-methyl-
p-t-Bucinal
2-(4-tert-Butylbenzyl)propionaldehyde
p-t-Butyl-alpha-methylhydrocinnamaldehyde
Butylphenyl methylpropional
alpha-Methyl-ß-(p-t-butylphenyl)propionaldehyde
Lilestralis, Lilial, Lysmeral

History:

Initial reviews:	April 2003 (37th Amendment), May 2007 (42nd Amendment)	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Informational Booklet.

Category 1 See Note box (1)	0.1 %	Category 7	0.3 %
Category 2	0.2 %	Category 8	2.0 %
Category 3	0.6 %	Category 9	2.5 %
Category 4	1.9 %	Category 10	2.5 %
Category 5	1.0 %	Category 11	Not Restricted (2)
Category 6 See Note box (1)	3.0 %		

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.
(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor

p-tert-Butyl-alpha-methylhydrocinnamic aldehyde (BMHCA)

Industry)http://www.iofiorg.org/.

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards).**

Critical effect: Sensitization

RIFM Summaries:

p-tert-Butyl-alpha-methylhydrocinnamic aldehyde - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values (µg/cm²) [no. studies]	Potency Classification[2]	Human Data			WoE NESIL[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	NOEL – MAX (induction) (µg/cm²)	LOEL[1] (induction) (µg/cm²)	
2372 [6]	Weak	4125	NA	29528	4100

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available

[1]Data derived from HRIPT or Human Max tests
[2]Gerberick *et al.*, 2001
[3]WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for p-tert-butyl-alphamethylhydrocinnamic aldehyde and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 4100 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of p-tert-butylalpha-methylhydrocinnamic aldehyde in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161

Kimber, I., Ryan, C. A., Gerberick, G. F., White, I. R., 2001. Human potency predictions for aldehydes using the local lymph node assay. Contact Dermatitis, 45(2), 89-94.

p-tert-Butyl-alpha-methylhydrocinnamic aldehyde (BMHCA)

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

RIFM (Research Institute for Fragrance Materials, Inc.), 1980. Repeated Insult Patch Test on BMHCA. Unpublished report from IFF, Inc., 14 February. Report number 15029. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1999. Repeated Insult Patch Test on BMHCA. RIFM report number 34405, May 4. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2001a. Local Lymph Node Assay on BMHCA. RIFM report number 37065, March 12. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2001b. Local Lymph Node Assay on BMHCA. RIFM report number 37066, May 9. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2001c. Local Lymph Node Assay on BMHCA. RIFM report number 37068, May 9. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2001d. Local Lymph Node Assay on BMHCA. RIFM report number 37067, May 9. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2001e. Local Lymph Node Assay on BMHCA. RIFM report number 41235, September 27. (RIFM, Woodcliff Lake, NJ, USA).

p-tert-Butylphenol

CAS N°: 98-54-4

Empirical formula: $C_{10}H_{14}O$
$HO\text{-}C_6H_4\text{-}C(CH_3)_3$

Synonyms: 4-tert-Butylphenol
4-(1,1-Dimethylethyl) phenol
1-Hydroxy-4-tert-butylbenzene
Phenol, 4-(1,1-dimethylethyl)-
Phenol, p-tert-butyl

History:

Initial reviews:	June 1975	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A

Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Sensitization** and **Depigmentation**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Opdyke, D.L.J. (1975), Food and Chemical Toxicology 12, 835.

Cade oil

CAS N°: 8013-10-3
90046-02-9

Empirical formula: N/A

Synonyms: For the **crude material banned:**
Juniper tar (CAS)

For the **distillates specified:**
Juniper tar oil
Juniperus oxycedrus oil

History:

Initial reviews:	July 1990	
Current revision date:	October 2003	
Implementation date:	For new submissions*:	May 6, 2004
	For existing fragrance compounds*:	May 6, 2005
Next review date	October 2008	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: SPECIFICATION / **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	

Non skin contact products: N/A

Note box:

Crude cade oil derived by pyrolysis of the wood and twigs of *Juniperus oxycedrus* L. should not be used as a fragrance ingredient.

Only rectified (purified) cade oils being in compliance with the maximum limit for polynuclear aromatic hydrocarbons should be used.

Fragrance material specifications:	Limit content of polynuclear aromatic hydrocarbons (PAH) resulting from the use of rectified oils according to Good Manufacturing Practice. If used alone or in combination with rectified birch tar oils, benzopyrene and 1,2-benzanthracene are to be used as markers for PAHs. The total concentration of both of these should not exceed **1 ppb** in the final product.

Cade oil

Contribution from other sources: N/A

Critical effect: **Carcinogenicity**, **Genotoxicity**·
* Some of the polynuclear aromatic hydrocarbons are known to be carcinogenic or genotoxic materials.

REXPAN Rationale / Conclusion:

IFRA ban noted - REXPAN, October 15, 2003

Carvone

CAS N°: Carvone: 99-49-0
d-Carvone: 2244-16-8
l-Carvone: 6485-40-1

Empirical formula: $C_{10}H_{14}O$

Synonyms: 2-Cyclohexen-1-one, 2-methyl-5-(1-methylethenyl)-
6,8(9)-p-Menthadien-2-one
p-Mentha-6,8-dien-2-one
1-Methyl-4-isopropenyl-6-cyclohexen-2-one

History:			
	Initial reviews:	New Standard	
	Current revision date:	2008	
	Implementation date:	For new submissions*:	August 16, 2008
		For existing fragrance compounds*:	August 16, 2010
	Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Informational Booklet.

Category 1 See Note box (1)	0.08 %	Category 7	0.2 %
Category 2	0.1 %	Category 8	2.0 %
Category 3	0.4 %	Category 9	5.0 %
Category 4	1.2 %	Category 10	2.5 %
Category 5	0.6 %	Category 11	Not Restricted (2)
Category 6 See Note box (1)	1.9 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) (http://www.iofiorg.org/).

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Carvone

Contribution from other sources: See **Annex I**

Critical effect: Sensitization

RIFM Summaries:

EC3 value from one LLNA (not the mean) (µg/cm2)	**Potency Classification** Based on Animal Data[1]	**Human Data**			**WoE NESIL**[3] (µg/cm^2)
		NOEL – HRIPT (induction) (µg/cm^2)	**NOEL – HMT** (induction) (µg/cm^2)	**LOEL**[2] (induction) (µg/cm^2)	
2675	Weak	2657[4]	1379[4]	NA	2650

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[2] Data derived from HRIPT or HMT
[3] WoE NESIL limited to three significant figures
[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Carvone and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 2650 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of Carvone in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 1976 . Human Maximization Test RIFM report number 1797, April 9. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2007a. Local Lymph Node Assay. RIFM report number 52902, May 10. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2007b. Human Repeated Insult Patch Test. RIFM report number 52896, May 15. (RIFM, Woodcliff Lake, NJ, USA).

Carvone oxide

CAS N°: 33204-74-9 **Empirical formula:** $C_{10}H_{14}O_2$

Synonyms: Carvone epoxide
1,6-Epoxy-p-menth-8-en-2-one
1-Methyl-4-(1-methylvinyl)-7-oxabicyclo[4.1.0]heptan-2-one
7-Oxabicyclo[4.1.0]heptan-2-one, 1-methyl-4-(1-methylethenyl)-

---

History:

Initial reviews:	New Standard**	
Current revision date:	October 2003	
Implementation date:	For new submissions*:	N/A**
	For existing fragrance compounds*:	N/A**
Next review date	N/A**	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

This material **should not be used as fragrance ingredient for any application.**

**This material has previously been included in the list of 'Other Materials', the material therefore has already been prohibited before.

Fragrance material specifications: N/A

Contribution from other sources: None to consider

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:

IFRA ban noted - REXPAN, October 2003

References:

Carvone oxide

Letizia et al., 2000, Food and Chemical Toxicology, Volume 38, Supplement 3, Special Issue IX, pages S25-26.

Chenopodium oil

CAS N°: 8006-99-3 **Empirical formula:** N/A

Synonyms: American wormseed oil
Chenopodium ambrosioides L. var anthelminticum

History:

Initial reviews:	N/A	
Current revision date:	N/A	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: See Note box

Chenopodium oil

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Reg. Tox & Pharm*., 31, 166-181, 2000

Cinnamic alcohol

CAS N°: 104-54-1

Empirical formula: $C_9H_{10}O$
C_6H_5-CH=CH-CH_2-OH

Synonyms: Cinnamyl alcohol
3-Phenylallyl alcohol
3-Phenyl-2-propen-1-ol
2-Propen-1-ol, 3-phenyl-
Styrone
Styryl alcohol
Zimtalcohol
Styryl carbinol

History:

Initial reviews:	October 1987, June 1992, September 2002, May 2007 (42nd Amendment)	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

For a description of the categories, refer to the QRA Informational Booklet.

Category 1 See Note box (1)	0.09 %	Category 7	0.2 %
Category 2	0.1 %	Category 8	0.4 %
Category 3	0.4 %	Category 9	0.4 %
Category 4	0.4 %	Category 10	0.4 %
Category 5	0.4 %	Category 11	Not Restricted (2)
Category 6 See Note box (1)	2.2 %		

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.
(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid

Cinnamic alcohol

down in the Code of Practice of IOFI (International Organisation of the Flavor Industry)www.iofiorg.org.

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

There is also a separate Standard for **Styrax** that should be taken into account.

Fragrance material specifications: N/A

Contribution from other sources: See **Annex I**

Critical effect: Sensitization

RIFM Summaries:

Cinnamic alcohol - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values (mg/cm^2) [no. studies]	Potency Classification[2]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – MAX (induction) ($\mu g/cm^2$)	LOEL[2] (induction) ($\mu g/cm^2$)	
5250 [1]	Weak	3000	2759	4724	3000

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available

[1] Data derived from HRIPT or HMT
[2]Gerberick *et al*., 2001
[3]WoE NESIL limited to three significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for cinnamic alcohol and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 3000 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of cinnamic alcohol in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Basketter, D.A., Wright, Z., Gilmour, N.J., Ryan, C.A., Gerberick, G.F., Robinson, M.K., Dearman, R.J., Kimber, I., 2002. Prediction of human sensitization potency using local lymph node assay EC3 values. *The Toxicologist*, 66(1-S), 240.

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. *American Journal of Contact Dermatitis*, 12(3), 156-161

Cinnamic alcohol

Greif, N., 1967. Cutaneous safety of fragrance materials as measured by the maximization test. *American Perfumer and Cosmetics*, 82, 54.

RIFM (Research Institute for Fragrance Materials, Inc.), 1979. Human Maximization Test on Cinnamyl Alcohol. RIFM report number 1697, July 6a. (RIFM, Woodcliff Lake, NJ, USA).

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

RIFM (Research Institute for Fragrance Materials, Inc.), 2001a. Repeated Insult Patch Test on Cinnamyl Alcohol. RIFM report number 40696, August 20. (RIFM, WoodcliffLake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2001b. Repeated Insult Patch Test on Cinnamyl Alcohol. RIFM report number 40695, August 20. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2002. Repeated Insult Patch Test on Cinnamyl Alcohol. RIFM report number 40697, March 5. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2004. Repeated Insult Patch Test on Cinnamyl Alcohol. RIFM report number 47241, December 16. (RIFM, Woodcliff Lake, NJ, USA).

Cinnamic aldehyde

CAS N°: 104-55-2 **Empirical formula:** C_9H_8O

Synonyms: Cinnamal
Cinnamaldehyde
Phenylacrolein
3-Phenyl-2-propenal
3-Phenyl-2-propen-1-al
'Cassia aldehyde'

History:

Initial reviews:	March 1978, April 2004 (38th Amendment), May 2006 (40th Amendment), May 2007 (42nd Amendment)	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date		

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

For a description of the categories, refer to the QRA Informational Booklet.

Category 1 See Note box (1)	0.02 %	Category 7	0.4 %
Category 2	0.02 %	Category 8	0.05 %
Category 3	0.05 %	Category 9	0.05 %
Category 4	0.05 %	Category 10	0.05 %
Category 5	0.05 %	Category 11	Not Restricted (2)
Category 6 See Note box (1)	0.4 %		

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry)

Cinnamic aldehyde

http://www.iofiorg.org/.

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

The Standard on cinnamic aldehyde covers and replaces the former existing Standards on cassia oil, cinnamon bark oil as well as cinnamic aldehyde – methyl anthranilate schiff base. The existing Standards for cinnamic aldehyde, cassia oil, cinnamic aldehyde – methyl anthranilate schiff base and cinnamon bark oil are no longer valid.

Fragrance material specifications: N/A

Contribution from other sources: See **Annex I**

Critical effect: Sensitization

RIFM Summaries:

LLNA weighted mean EC3 values (µg/cm2) [No. Studies]	Potency Classification Based on Animal Data[1]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – HMT (induction) ($\mu g/cm^2$)	LOEL[2] (induction) ($\mu g/cm^2$)	
262 [23]	Moderate	591[4]	NA	775	590

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[2] Data derived from HRIPT or HMT
[3] WoE NESIL limited to three significant figures
[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Cinnamic aldehyde and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 590 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of Cinnamic aldehyde in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

Cinnamic aldehyde

References:

Basketter, D.A., Wright, Z.M., Warbrick, E.V. Dearman, R.J., Kimber, I., Ryan, C.A., Gerberick, G.F., White, I.R., 2001. Human potency predictions for aldehydes using the local lymph node assay. *Contact Dermatitis*, 45(2), 89-94.

Basketter, D.A., Wright, Z., Gilmour, N.J., Ryan, C.A., Gerberick, G.F., Robinson, M.K., Dearman, R.J., Kimber, I., 2002. Prediction of human sensitization potency using local lymph node assay EC3 values. *The Toxicologist*, 66(1-S), 240.

Elahi, E.N., Wright, Z., Hotchkiss, S.A.M., Basketter, D.A., Smith Pease, C.K., 2002. Protein binding and metabolic inhibition reveals clues on the mechanisms surrounding relative potency of sensitizing cinnamic compounds. Toxicology, 178, 52.

Elahi, E.N., Wright, Z., Hinselwood, D., Hotchkiss, S.A.M., Basketter D.A., Smith Pease , C.K., 2004. Protein binding and metabolism influence the relative skin sensitization potential of cinnamic compounds. *Chemical Research in Toxicology*, 17(3), 301-310.

RIFM (Research Institute for Fragrance Materials, Inc.), 1973. Repeated Insult Patch Test on Cinnamaldehyde. RIFM report number 12509, January 23. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2002a. Repeated Insult Patch Test on Cinnamaldehyde. RIFM report number 41692, August 27. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2002b. Repeated Insult Patch Test on Cinnamaldehyde. RIFM report number 41693, August 27. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2003a. Local Lymph Node Assay on Cinnamaldehyde. RIFM report number 42032, February 18. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2003b. Local Lymph Node Assay on Cinnamaldehyde. RIFM report number 42033, February 18. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2003c. Local Lymph Node Assay on Cinnamaldehyde. RIFM report number 42040, February 18. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2003d. Local Lymph Node Assay on Cinnamaldehyde. RIFM report number 42034, February 18. (RIFM, Woodcliff Lake, NJ, USA).

Cinnamic aldehyde

RIFM (Research Institute for Fragrance Materials, Inc.), 2003e. Local Lymph Node Assay on Cinnamaldehyde. RIFM report number 42036, February 18. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2003f. Local Lymph Node Assay on Cinnamaldehyde. RIFM report number 42035, February 18. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2003g. Local Lymph Node Assay on Cinnamaldehyde. RIFM report number 42037, February 18. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2003h. Local Lymph Node Assay on Cinnamaldehyde. RIFM report number 42038, February 18. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2003i. Local Lymph Node Assay on Cinnamaldehyde. RIFM report number 42039, February 18. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2003j. Local Lymph Node Assay on Cinnamaldehyde. RIFM report number 42041, February 18. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2004. Repeated Insult Patch Test on Cinnamaldehyde. RIFM report number 47158, April 22a. (RIFM, Woodcliff Lake, NJ, USA).

Smith, C.K., Hotchkiss, S.A.M., 2001. Allergic Contact Dermatitis. Chemical and Metabolic Mechanisms. *Taylor and Francis*, London.

Wright, Z.M., Basketter, D.A., Blaikie, L., Cooper, K.J., Warbrick, E.V., Dearman, R.J., Kimber, I., 2001. Vehicle effects on skin sensitization potency of four chemicals assessment using the local lymph node assay. *Journal International Journal of Cosmetic Science*, 23(2), 75-83.

Cinnamic aldehyde dimethyl acetal

CAS N°: 4364-06-1 **Empirical formula:** $C_{11}H_{14}O_2$

Synonyms: Benzene, (3,3-dimethoxy-1-propenyl)-
Cinnamic aldehyde dimethyl acetal
(3,3-Dimethoxypropen-1-yl)benzene
(3,3-Dimethoxyprop-1-en-1-yl)benzene
3-Phenyl-2-propenal dimethyl acetal

History:

Initial reviews:	New Standard	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2011
Next review date	2014	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Informational Booklet.

Category 1 See Note box (1)	0.02 %	Category 7	0.06 %
Category 2	0.03 %	Category 8	0.80 %
Category 3	0.12 %	Category 9	4.10 %
Category 4	0.37 %	Category 10	2.50 %
Category 5	0.20 %	Category 11	See Note box (2)
Category 6 See Note box (1)	0.59 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry www.iofiorg.org)

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Cinnamic aldehyde dimethyl acetal

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards**)

Critical effect: Sensitization

RIFM Summaries:

LLNA weighted mean EC3 values ($\mu g/cm^2$) [No. Studies]	Potency Classification Based on Animal Data[2]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – HMT (induction) ($\mu g/cm^2$)	LOEL[1] (induction) ($\mu g/cm^2$)	
NA	NA	827	NA	1938	820

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available

[1] Data derived from HRIPT or HMT
[2] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[3] WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Cinnamic aldehyde dimethyl acetal and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 820 µg/cm2. They recommend the limits for the 11 different product categories, which are the acceptable use levels of Cinnamic aldehyde dimethyl acetal in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 1965. Human repeated insult patch test. Unpublished study from IFF Inc., 7 September. Report number 48396. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2008. Human repeated insult patch test. RIFM report number 55346, July 30. (RIFM, Woodcliff Lake, NJ, USA).

Cinnamylidene acetone

CAS N°: 4173-44-8 **Empirical formula:** $C_{12}H_{12}O$

Synonyms: 3,5-Hexadien-2-one, 6-phenyl-
Methyl 4-phenyl-1,3-butadienyl ketone
1-Phenyl-3,5-hexadien-5-one
6-Phenyl-3,5-hexadien-2-on

History:

Initial reviews:	N/A	
Current revision date:	N/A	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: See Note box

Cinnamylidene acetone

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Reg. Tox & Pharm*., 31, 166-181, 2000

Cinnamyl nitrile

CAS N°: 1885-38-7
4360-47-8

Empirical formula: C_9H_7N

Synonyms: Cinnamonitrile (E)
Cinnamyl nitrile
trans-.β.-Phenylacrylonitrile
2-Propenenitrile, 3-phenyl-, (E)-

History:

Initial reviews:	March 2002 (36th Amendment)	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Informational Booklet.

Category 1 See Note box (1)	0.03 %	Category 7	0.08 %
Category 2	0.04 %	Category 8	0.125 %
Category 3	0.125 %	Category 9	0.125 %
Category 4	0.125 %	Category 10	0.125 %
Category 5	0.125 %	Category 11	Not Restricted (2)
Category 6 See Note box (1)	0.80 %		

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) (http://www.iofiorg.org/).

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due

Cinnamyl nitrile

to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.
Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards).**

Critical effect: Sensitization

RIFM Summaries:

EC3 value from one LLNA (not the mean) (µg/cm2) [No. Studies]	**Potency Classification** Based on Animal Data[1]	**Human Data**			**WoE NESIL**[3] (µg/cm^2)
		NOEL – HRIPT (induction) (µg/cm^2)	**NOEL – HMT** (induction) (µg/cm^2)	**LOEL**[2] (induction) (µg/cm^2)	
>2500	Weak	1063[4]	3448[4]	1938	1060

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[2] Data derived from HRIPT or HMT
[3] WoE NESIL limited to three significant figures
[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Cinnamyl nitrile and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 1060 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of Cinnamyl nitrile in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

Cinnamyl nitrile

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 1965. Human Repeated Insult Patch Test. Unpublished report from IFF International, 1 April. Report number 1981 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1981. Human Maximization Test. RIFM report number 1792, October 27 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2005. Local Lymph Node Assay. RIFM report number 51626, January 28 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2007. Human Repeated Insult Patch Test. RIFM report number 54076, December 13 (RIFM, Woodcliff Lake, NJ, USA).

Citral

CAS N°: 5392-40-5
141-27-5
106-26-3

Empirical formula: $C_{10}H_{16}O$
$(CH_3)_2C=CH(CH_2)_2C(CH_3)=CH-CHO$

Synonyms: 3,7-Dimethyl-2,6-octadienal
Geranial (trans-citral)
Neral
Lemarome
Neral and Geranial

History:

Initial reviews:	October 1975, February 1980	
Current revision date:	2006	
Implementation date:	For new submissions*:	June 11, 2007
	For existing fragrance compounds*:	June 11, 2008
Next review date	2011	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

For a description of the categories, refer to the QRA Informational Booklet.

Category 1	0.04 %	Category 7	0.1 %
Category 2	0.05 %	Category 8	1.4 %
Category 3	0.2 %	Category 9	5.0 %
Category 4	0.6 %	Category 10	2.5 %
Category 5	0.3 %	Category 11	See Note box
Category 6	1.0 %		

Note box:

Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

This Standard cancels and replaces the existing one on citral, which was based on the no longer supported 'quenching' phenomenon.

Fragrance material specifications: N/A

Citral

Contribution from other sources: See **Annex 1**

Critical effect: Sensitization

RIFM Summaries:

Citral - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values (mg/cm^2) [no. studies]	Potency Classification[2]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – MAX (induction) ($\mu g/cm^2$)	LOEL[1] (induction) ($\mu g/cm^2$)	
1414 [11]	Weak	1400	NA	3876	1400 $\mu g/cm^2$

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available

[1] Data derived from HRIPT or Human Max Tests
[2] Gerberick *et al*., 2001
[3] WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for citral and based on the weight of evidence established the No Expected Sensitization Induction Level (NESIL) as 1400 µg/cm².They recommend the limits for the 11 different product categories, which are the acceptable use levels of citral in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of March 15, 2006.

References:

Basketter, D. A., Wright, Z., Gilmour, N. J., Ryan, C. A., Gerberick, G. F., Robinson, M. K., Dearman, R. J., Kimber, I., 2002a. Prediction of human sensitization potency using local lymph node assay EC3 values. The Toxicologist, 66(1-S), 240.

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161.

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

Research Institute for Fragrance Materials, Inc (1964). Repeated insult patch test of citral in human subjects. Unpublished report from International Flavors and Fragrances Inc., Report number 14576 (RIFM, Woodcliff Lake, NJ USA).

Citral

Research Institute for Fragrance Materials, Inc (2004). Repeated insult patch test in human subjects with citral. RIFM report number 47157 (RIFM, Woodcliff Lake, NJ USA).

Research Institute for Fragrance Materials, Inc (2004). Local Lymph Node Assay on Citral. RIFM report number 45126 (RIFM, Woodcliff Lake, NJ USA).

Citronellol

CAS N°: 106-22-9
1117-61-9
26489-01-0
6812-78-8
141-25-3
68916-43-8
7540-51-4

Empirical formula: $C_{10}H_{20}O$

Synonyms: 106-22-9
Citronellol
dl-Citronellol
Dihydrogeraniol
3,7-Dimethyl-6-octen-1-ol
6-Octen-1-ol, 3,7-dimethyl-

1117-61-9
(+)-ß-Citronellol
(+)-(R)-Citronellol
(R)-3,7-Dimethyloct-6-en-1-ol
6-Octen-1-ol, 3,7-dimethyl-, (R)-

26489-01-0
dl-Citronellol

6812-78-8
α-Citronellol

141-25-3
3,7-Dimethyl-(6-or 7-)octen-1-ol
3,7-Dimethyl-7-octen-1-ol
7-Octen-1-ol, 3,7-dimethyl-,(S)-
7-Octen-1-ol, 3,7-dimethyl- (isomer unspecified)
Rhodinol

68916-43-8
Geranium oil, saponified
Rhodinol

7540-51-4
l-Citronellol
(-)-3,7-Dimethyloct-6-en-1-ol
(S)-3,7-Dimethyl-6-octen-1-ol
6-Octen-1-ol, 3,7-dimethyl-, (S)-

Citronellol

History:	Initial reviews:	New Standard	
	Current revision date:	2007	
	Implementation date:	For new submissions*:	June 16, 2007
		For existing fragrance compounds*:	June 16, 2009
	Next review date	2012	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

For a description of the categories, refer to the QRA Informational Booklet.

Category 1 See Note box (1)	0.8 %	Category 7	2.2 %
Category 2	1.1 %	Category 8	2.0 %
Category 3	4.4 %	Category 9	5.0 %
Category 4	13.3 %	Category 10	2.5 %
Category 5	7.0 %	Category 11	See Note box (2)
Category 6 See Note box (1)	21.4 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry). Further information about IOFI can be found on its website (www.iofiorg.org).

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Contribution from other sources: See **Annex 1**

Critical effect: **Sensitization**

Citronellol

RIFM Summaries:

dl-Citronellol - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values (mg/cm^2) [no. studies]	Potency Classification[2]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – MAX (induction) ($\mu g/cm^2$)	LOEL[1] (induction) ($\mu g/cm^2$)	
10875 [1]	Extremely weak	29528	4138	NA	29500

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available

[1] Data derived from HRIPT or Human Max Tests
[2] Gerberick *et al*., 2001
[3] WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for dl-citronellol and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 29500 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of dl-citronellol in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161.

Greif, N., 1967. Cutaneous safety of fragrance materials as measured by the maximization test. American Perfumer and Cosmetics, 82, 54.

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

RIFM (Research Institute for Fragrance Materials, Inc.), 2005a. Repeated Insult Patch Test on dl-Citronellol. RIFM report number 47277, January 28. (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2005b. Local Lymph Node Assay on dl-Citronellol. RIFM report number 48752, January 6. (RIFM, Woodcliff Lake, NJ, USA).

Citrus oils and other furocoumarins - containing essential oils

CAS N°:

Synonyms:

History: Initial reviews: December 1996

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:		
Skin contact products:	15 ppm 5-MOP (excl. rinse-off products)	
Leave-on products:		Rinse-off products: *Including household cleaning products*
Non skin contact products:	No limitation	
Note box:		
Fragrance material specifications:		

Where the bergapten (5-methoxypsoralen) content of all relevant oils present in a compound has been determined, it is recommended that for applications on areas of skin exposed to sunshine, excluding bath preparations, soaps and other products which are washed off the skin, the total level of bergapten in the consumer products should not exceed 0.0015% (15 ppm). This is equivalent to 0.0075% (75 ppm) in a fragrance compound used at 20% in the consumer product.

Where the level of bergapten has not been determined by appropriate methods, the limits specified in the guidelines on individual oils should apply.

In those cases, where such oils are used in combination with other phototoxic ingredients, the additive effect has to be taken into consideration and the use levels have to be reduced
accordingly. The sum of the concentrations of all phototoxic fragrance ingredients, expressed in % of their recommended maximum level in the consumer product, shall not exceed 100.

Restrictions for furocoumarin containing essential oils have been recommended for:

Angelica root oil,
Bergamot oil expressed,
Bitter orange oil expressed,
Cumin oil,
Grapefruit oil expressed,
Lemon oil cold pressed,

Citrus oils and other furocoumarins - containing essential oils

Lime oil expressed,
Rue oil.

The following essential oils contain small amounts of phototoxic furocoumarins. These levels are not high enough to require special restrictions if used alone, but if used in combination with one or the other phototoxic essential oil, attention should be paid that the total level of bergapten (5-MOP) in the consumer product does not exceed 15 ppm. It is the responsibility of fragrance manufacturers to ensure that the level is observed.

Typical levels of 5-MOP are the following:
Petitgrain Mandarin oil - 50 ppm,
Tangerine oil cold pressed - 50 ppm,
Mandarin oil cold pressed - 250 ppm,
Parsley leaf oil - 20 ppm.

References:

These recommendations are based on the published phototoxic effects of bergapten and the established dose-effect relationships (Young at al., J. Photochem. Photobiol. B,7, 231 (1990); Dubertret et al.ibid 7, 251 (1990), idem, ibid, 7, 362 (1990).

Colophony

CAS N°: 8050-09-7 **Empirical formula:** N/A

Synonyms: Colophony
Colophonium
Rosin

History:

Initial reviews:	December 1992	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: N/A

Colophony

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Hausen. B.M. (1989), Contact Dermatitis (20), 41-50; 133-143; 295-301.

Costus root oil, absolute and concrete

CAS N°: 8023-88-9 **Empirical formula:** N/A

Synonyms: Costus root essential oil, absolute and concrete (*Saussurea lappa* Clarke)
Oils, costus
Saussurea lappa root oil
Spiral flag oil

History:

Initial reviews:	October 1974, May 1998	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: N/A

Costus root oil, absolute and concrete

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Opdyke D.L. (1974), Food and Cosmetics Toxicology 12, 867.

Mitchell J.C. and Epstein W.L (1974), Archives of Dermatology, 110, 871-872.

Foussereau, J., Muller J.C. and Benezra C. (1975), Contact Dermatitis, 1, 223-230.

Epstein, W.L., Reynolds G.W. and Rodriguez, E. (1980), Archives of Dermatology, 116, 59-60.

Cheminat, A., Benezra, C., Farral M.J. and Frechet, J.M.J. (1981), Canadian Journal of Chemistry, 59, 1405-1414.

Coumarin

CAS N°: 91-64-5 **Empirical formula:** $C_9H_6O_2$

Synonyms: 2H-1-Benzopyran-2-one
1,2-Benzopyrone
cis-o-Coumaric acid lactone
Coumarin
Coumarinic anhydride
2-Oxo-1,2-benzopyran
Tonka bean camphor

History:

Initial reviews:	New Standard	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

For a description of the categories, refer to the QRA Informational Booklet.

Category 1	See Note box (1)	Category 7	0.3 %
Category 2	0.13 %	Category 8	2.0 %
Category 3	0.5 %	Category 9	5.0 %
Category 4	1.6 %	Category 10	2.5 %
Category 5	0.8 %	Category 11	Not Restricted (2)
Category 6	See Note box (1)	2.5 %	

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) http://www.iofiorg.org/.

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Coumarin

Contribution from other sources: See **Annex I**

Critical effect: Sensitization

RIFM Summaries:

LLNA weighted mean EC3 values (µg/cm2) [No. Studies]	Potency Classification Based on Animal Data[1]	Human Data			WoE NESIL[3] (µg/cm^2)
		NOEL – HRIPT (induction) (µg/cm^2)	NOEL – HMT (induction) (µg/cm^2)	LOEL[2] (induction) (µg/cm^2)	
>12 500 [2]	Weak	3 543[4]	5517[4]	8 858	3 500

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[2] Data derived from HRIPT or HMT
[3] WoE NESIL limited to three significant figures
[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Coumarin and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 3 500 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of Coumarin in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Greif , N., 1967. Cutaneous safety of fragrance material as measured by the maximization test. *American Perfumer and Cosmetics*, 82, 54-57.

RIFM (Research Institute for Fragrance Materials, Inc.), 2003. Local Lymph Node Assay with coumarin. Unpublished report from Rhodia Services, 26a May. Report number 47072. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2004a. Human Repeated Insult Patch Test with coumarin. RIFM report number 47161, March 10. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2004b. Local Lymph Node Assay with coumarin. Unpublished report from Rhodia Services, 3a December. Report number 47073. (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2005. Human Repeated Insult Patch Tests with coumarin. RIFM report number 47274, January 6 and 6b. (RIFM, Woodcliff Lake, NJ, USA).

Cumin oil

CAS N°: 8014-13-9 **Empirical formula:** N/A

Synonyms: Cumin seed oil
Cuminum cyminum (Cumin) seed oil
Cuminum cyminum L.
Cuminum cyminum oil
Oils, cumin (*Cuminum cyminum*)

History:

Initial reviews:	October 1975, June 1986	
Current revision date:	September 2001	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	2010	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	0.4%	Rinse-off products:	No restriction
		Including household cleaning products	

Non skin contact products: No restriction

Note box:

The Standard is set due to the phototoxic effects of the material. The limit only applies to applications on skin, excluding rinse-off products.

If combinations of phototoxic fragrance ingredients are used, the use levels have to be reduced accordingly. The sum of the concentrations of all phototoxic ingredients, expressed in % of their recommended maximum level in the consumer product shall not exceed 100.

Fragrance material specifications: N/A

Cumin oil

Contribution from other sources: None known

Critical effect: **Phototoxicity**

RIFM Summaries:

The NOEL for phototoxicity is 50% based on a study in 23 volunteers patched under occlusion on the back for 24 hours. Patches were removed after 10 minutes followed by irradiation with 16-20 J/cm2 of UVA. Readings were made at 1, 24, 48 & 72 hours after irradiation. No photoirritation was observed (RIFM, 1986).

- 100% in miniature swine, UV, distinct photoirritant effects were observed (RIFM 1972; Forbes et al., 1977)
- 100% in hairless mice, UV, distinct photoirritant effects were observed (RIFM 1972; Forbes et al., 1977).
- 100% and 25% in hairless mice, UV, no reactions at 25% 0/12, 6/12 reactions at 100% (RIFM, 1983).
- 100%, 75%, 50%, and 25% in hairless mice, UV, no reactions 0/6 at 25%, 5/6 reactions at 50%, 6/6 reactions at 75% and 100% (RIFM, 1983).
- 30% in guinea pigs, UV, no reactions 0/10 (RIFM, 1984)
- 3% and 10% in guinea pigs, UV, no reactions 0/10 at 3%, and 4/10 reactions at 10% (RIFM, 1984).

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for cumin oil and has no concerns with the current limit of 0.4% (September 2001).

References:

Research Institute for Fragrance Materials, Inc. (1986). Human phototoxicity study of cumin oil, tagetes minuta absolute, thyme concrete and pentyl acetate. RIFM report number 4348, 21 August.

Research Institute for Fragrance Materials, Inc. (1985). Cumin oil: A photoirritation test in humans. Unpublished report from the Givaudan-Roure Corp. Report number 3877, 7 January.

Research Institute for Fragrance Materials, Inc. (1972). Phototoxicity and irritation tests of fragrance materials in the hairless mice and miniature swine. Report number 2035, 26 July.

P.D.Forbes, F.Urbach and R.E.Davies. (1977). Phototoxicity testing of fragrance raw materials. Food and Cosmetics Toxicology, 15, 55-60. Report number 1422.

Cumin oil

K.H.Kaidbey and A.M.Kligman (1978). Identification of topical photosensitizing agents in humans. Journal of Investigative Dermatology, 70(3), 149-151. Report number 3090.

Research Institute for Fragrance Materials, Inc. (1983). Phototoxicity study of fragrance materials in hairless mice. RIFM report number 2043, 31 January.

Research Institute for Fragrance Materials, Inc. (1984). Determination of phototoxicity of cumin oil in guinea pigs. Unpublished report from the Givaudan-Roure Corp. Report number 3875, 23 February.

Research Institute for Fragrance Materials, Inc. (1984). Determination of phototoxicity of cumin oil in guinea pigs. Unpublished report from the Givaudan-Roure Corp. Report number 3876, 17 July.

Cyclamen alcohol (3-(4-isopropylphenyl)-2-methylpropanol)

CAS N°: 4756-19-8

Synonyms: Benzenepropanol, .β.-methyl-4-(1-methylethyl)-
Cyclamen alcohol
3-(*p*-Isopropyl)phenyl-2-methyl-1-propanol
3-(4-Isopropylphenyl)-2-methylpropan-1-ol

History: Initial reviews: November 1977, October 1978

RECOMMENDATION: PROHIBITED / SPECIFICATION

RESTRICTIONS:

Cyclamen alcohol should not be used as a fragrance ingredient as such, but a level of up to 1.5% in cyclamen aldehyde is accepted.

References:

This recommendation is based on the sensitizing potential of cyclamen alcohol and the absence of sensitization reaction in a sample of cyclamen aldehyde containing 1.5% cyclamen alcohol. (D.L.J. Opdyke (1979), Fd. Cosmet. Toxicol. 17, 267).

2,4-Decadienal

CAS N°: 2363-88-4
(Including all geometric isomers)

Empirical formula: $C_{10}H_{16}O$

Synonyms: Deca-2,4-dienal

History:			
	Initial reviews:	New Standard	
	Current revision date:	2009	
	Implementation date:	For new submissions*:	August 7, 2009
		For existing fragrance compounds*:	August 7, 2010
	Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:		
Skin contact products:	N/A	
Leave-on products:		Rinse-off products: *Including household cleaning products*
Non skin contact products:	N/A	
Note box:		
Fragrance material specifications:	N/A	

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards)

Critical effect: **Insufficient Data**

REXPAN Rationale / Conclusion:
The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.

This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material.

2,4-Decadienal

References:

Human Health Criteria Document, *Regulatory Toxicology and Pharmacology*, 31, 166-181, 2000

Dibenzyl ether

CAS N°: 103-50-4 **Empirical formula:** $C_{14}H_{14}O$

Synonyms: Benzene, 1,1'-[oxybis(methylene)]bis-
Benzyl ether
Benzyl oxide
Dibenzyl oxide
1,1'-[Oxybis(methylene)]dibenzene

History:

Initial reviews:	New Standard	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2011
Next review date	2014	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Category 1 See Note box (1)	0.07 %	Category 7	0.17 %
Category 2	0.08 %	Category 8	2.00 %
Category 3	0.35 %	Category 9	5.00 %
Category 4	1.04 %	Category 10	2.50 %
Category 5	0.55 %	Category 11	See Note box (2)
Category 6 See Note box (1)	1.67 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry http://www.iofiorg.org/)

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Dibenzyl ether

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards**)

Critical effect: Sensitization

RIFM Summaries:

LLNA weighted mean EC3 values (µg/cm2) [No. Studies]	Potency Classification Based on Animal Data[1]	Human Data			WoE NESIL[3] (µg/cm^2)
		NOEL – HRIPT (induction) (µg/cm^2)	NOEL – HMT (induction) (µg/cm^2)	LOEL[2] (induction) (µg/cm^2)	
1575 [1][4]	Weak	2362	2760	NA	2300

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available

[1] Data derived from HRIPT or HMT
[2] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[3] WoE NESIL limited to three significant figures
[4] EC3 value from one LLNA, not the mean.

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Dibenzyl ether and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 2300 µg/cm2. They recommend the limits for the 11 different product categories, which are the acceptable use levels of Dibenzyl ether in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 1974. Maximization study with dibenzyl ether. RIFM report number 1779, June 4a. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2007. Local Lymph Node Assay. RIFM report number 52907, May 21. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2008. Human repeated insult patch test. RIFM report number 54679, April 16a. (RIFM, Woodcliff Lake, NJ, USA).

1,3-Dibromo-2-methoxy-4-nitro-5-(1,1-dimethylethyl)-6-methyl-benzene (Musk alpha)

CAS N°: 63697-53-0 **Empirical formula:** $C_{12}H_{15}Br_2NO_3$

Synonyms: Musk alpha
Benzene,1,3-dibromo-5-(1,1-dimethylethyl)-2- methoxy-4-methyl-6-nitro-

---

History:	Initial reviews:	N/A	
	Current revision date:	N/A	
	Implementation date:	For new submissions*:	N/A
		For existing fragrance compounds*:	N/A
	Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: See Note box

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or

1,3-Dibromo-2-methoxy-4-nitro-5-(1,1-dimethylethyl)-6-methyl-benzene (Musk alpha)

2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Reg. Tox & Pharm*., 31, 166-181, 2000

1,3-Dibromo-2-methoxy-4-methyl-5-nitrobenzene (Musk KS)

CAS N°: 62265-99-0 **Empirical formula:** $C_8H_7Br_2NO_3$

Synonyms: Benzene, 1,3-dibromo-2-methoxy-4-methyl-5-nitro-
Bromorose
1,3-Dibromo-2-methoxy-5-nitro-6-methylbenzene
2,4-Dibromo-3-methoxy-6-nitrotoluene
2,6-Dibromo-3-methyl-4-nitroanisole
6-Nitro-2,4-dibromo-3-methoxytoluene
Musk KS

History:

Initial reviews:	N/A	
Current revision date:	N/A	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: See Note box

1,3-Dibromo-2-methoxy-4-methyl-5-nitrobenzene (Musk KS)

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Reg. Tox & Pharm*., 31, 166-181, 2000

2,2-Dichloro-1-methylcyclopropylbenzene

CAS N°: 3591-42-2 **Empirical formula:** $C_{10}H_{10}Cl_2$

Synonyms: Benzene, (2,2-dichloro-1-methylcyclopropyl)-

History:

Initial reviews:	N/A	
Current revision date:	N/A	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: See Note box

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

2,2-Dichloro-1-methylcyclopropylbenzene

References:

Human Health Criteria Document, *Reg. Tox & Pharm.*, 31, 166-181, 2000

Diethyl maleate

CAS N°: 141-05-9 **Empirical formula:** $C_8H_{12}O_4$
C_2H_5-OCO-CH=CH-OCO-C_2H_5

Synonyms: 2-Butenedioic acid (2Z)-, diethyl ester
Ethyl maleate
Maleic acid, diethyl ester

History:

Initial reviews:	June 1975	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Opdyke, D.L.J. (1976), Food and Cosmetics Toxicology 14, 443.

Dihydrocoumarin

CAS N°: 119-84-6 **Empirical formula:** $C_9H_8O_2$

Synonyms: 1,2-Benzodihydropyrone
2H-1-Benzopyran-2-one, 3,4-dihydro-
2-Chromanone
3,4-Dihydro-2H-1-benzopyran-2-one
o-Hydroxydihydrocinnamic acid lactone
Melilotic acid lactone
Melilotine

History:

Initial reviews:	October 1974	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: PROHIBITED

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	
Non skin contact products:	N/A		

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: Sensitization

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Opdyke, D.L.J (1974), Food and Cosmetics Toxicology 12, 521.

2,4-Dihydroxy-3-methylbenzaldehyde

CAS N°: 6248-20-0 **Empirical formula:** $C_8H_8O_3$

Synonyms: Benzaldehyde, 2,4-dihydroxy-3-methyl-
4-Formyl-2-methylresorcinol

History:	Initial reviews:	February 1980, April 1989	
	Current revision date:	September 2002	
	Implementation date:	For new submissions*:	N/A
		For existing fragrance compounds*:	N/A
	Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Ford, R.A. (1988), Food and Chemical Toxicology 26, 303.

Dimethylcyclohex-3-ene-1-carbaldehyde (mixed isomers)

CAS N°: 68737-61-1 (mixed isomers)
68039-49-6
68039-48-5
27939-60-2
67801-65-4
36635-35-5
68084-52-6
35145-02-9

Empirical formula: $C_9H_{14}O$

Synonyms:
Dimethylcyclohex-3-ene-1-carbaldehyde (isomer mixture) (68737-61-1)
2,4-Dimethyl-3-cyclohexen-1-carboxaldehyde (68039-49-6)
3,5-Dimethylcyclohex-3-ene-1-carbaldehyde (68039-48-5)
Dimethylcyclohex-3-ene-1-carbaldehyde (isomer unspecified) (27939-60-2)
3,6-Dimethyl-3-cyclohexene-1-carboxaldehyde (67801-65-4)
3-Cyclohexene-1-carboxaldehyde, dimethyl- (isomer mixture)
2,4-Dimethyltetrahydro benzaldehyde
Dimethyltetrahydrobenzaldehyde (isomer mixture)
Triplal, Vertocitral (commercial names)

History:

Initial reviews:	New Standard	
Current revision date:	June 11, 2010	
Implementation date:	For new submissions*:	August 11, 2010
	For existing fragrance compounds*:	August 11, 2011
Next review date:	2015	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: RESTRICTED

RESTRICTIONS:

Limits in the finished product:				
Category 1	See Note box (1)	0.17%	Category 7	0.45%
Category 2		0.22%	Category 8	2.0%
Category 3		0.89%	Category 9	5.0%
Category 4		2.7%	Category 10	2.5%
Category 5		1.4%	Category 11	See Note box (2)
Category 6	See Note box (1)	4.3%		

Note box:
The above limits apply to Dimethylcyclohexen-3-ene-1-carbaldehyde (mixed isomers) used individually or in combination.

(1) See the IFRA Code of Practice (Appendix 8, Introduction to the IFRA Standards) regarding the Note on Oral Care Products and other products with the potential of ingestion.
(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Dimethylcyclohex-3-ene-1-carbaldehyde (mixed isomers)

Indicative contribution from other sources: None known at the time of the publication of the Standard

---

Critical effect: Sensitization

RIFM Summaries:

LLNA weighted EC3 values (µg/cm²) [no. studies]	Potency Classification Based on Animal Data[1]	Human Data[2]			WoE NESIL[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	NOEL – HMT (induction) (µg/cm²)	LOEL (induction) (µg/cm²)	
2500-5875 [7][4]	Weak	5905[5]	1380-6900[6]	N/A	5900

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[2]Data derived from HRIPT or HMT.
[3]WoE NESIL limited to two significant figures.
[4]A range of values and not the weighted mean was provided because the seven studies were performed on 7 different materials – all are isomers but the isomeric mixtures were different. There are currently 4 isomers of this material in the RIFM Database. Each material is typically a mixture of two or more isomers. In order to confirm the potency and characterization of these materials, a set of LLNAs was conducted on different commercial samples provided by individual suppliers with isomer ratios specified. The LLNA data showed all materials with similar dermal sensitization potency.
[5]MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL. The HRIPT MT-NOEL reported is for the fragrance material with the highest reported use in perfumery (IFRA Survey, 2004); the LLNA data showed all materials with similar dermal sensitization potency.
[6]A range of values was provided; three human maximization studies were conducted. No dermal sensitization was observed in any of the tests. The 3 studies were performed on 3 different isomer mixtures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for dimethylcyclohex-3-ene-1-carbaldehyde and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 5900 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of dimethylcyclohex-3-ene-1-carbaldehyde in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the publication by Api *et al*., 2008.

References:

Api AM, Basketter DA, Cadby PA, Cano M-F, Ellis G, Gerberick GF, et al. Dermal Sensitization Quantitative Risk Assessment (QRA) For Fragrance Ingredients. *Regulatory Toxicology and Pharmacology* 2008;52(1): 3-23.

RIFM (Research Institute for Fragrance Materials, Inc.), 2010a. Local Lymph Node Assay. RIFM report number 58108, Draft Report. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2010b. Local Lymph Node Assay. RIFM report number 58112, Draft Report. (RIFM, Woodcliff Lake, NJ, USA).

Dimethylcyclohex-3-ene-1-carbaldehyde (mixed isomers)

RIFM (Research Institute for Fragrance Materials, Inc.), 2010c. Local Lymph Node Assay. RIFM report number 58113, Draft Report. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2009. Human repeated insult patch test. RIFM report number 58150, December 14. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1982. Maximization study. RIFM report number 1643, October 5. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1978. Maximization study. RIFM report number 1698, February 27b. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1977. Maximization study. RIFM report number 1702, May 4c. (RIFM, Woodcliff Lake, NJ, USA).

1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one

CAS N°: 56973-85-4 **Empirical formula:** $C_{13}H_{20}O$

Synonyms: α-Dynascone
4-Penten-1-one, 1-(5,5-dimethyl-1-cyclohexen-1-yl)-
Galbascone

History:			
	Initial reviews:	New Standard	
	Current revision date:	2009	
	Implementation date:	For new submissions*:	August 7, 2009
		For existing fragrance compounds*:	August 7, 2011
	Next review date	2014	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1 See Note box (1)	0.07 %	Category 7	0.19 %
Category 2	0.09 %	Category 8	2.00 %
Category 3	0.38 %	Category 9	5.00 %
Category 4	1.13 %	Category 10	2.50 %
Category 5	0.60 %	Category 11	See Note box (2)
Category 6 See Note box (1)	1.81 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry http://www.iofiorg.org/)

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards**)

1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one

Critical effect: Sensitization

RIFM Summaries:

LLNA weighted mean EC3 values ($\mu g/cm^2$) [No. Studies]	Potency Classification Based on Animal Data[1]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – HMT (induction) ($\mu g/cm^2$)	LOEL[1] (induction) ($\mu g/cm^2$)	
745 [1] [4-5]	Moderate	2500	NA	NA	2500

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1] Data derived from HRIPT or HMT.
[2] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[3] WoE NESIL limited to two significant figures.
[4] EC3 value from one LLNA, not the mean.
[5] LLNA used a very wide spacing of doses. Based on the response at each dose the EC3 value would be slightly on the low side. The response in the LLNA was:
0.1% SI of 0.9
1.0% SI of 0.9
10% SI of 10.4
100% SI of 17.5

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for 1-(5,5-Dimethyl-1-cyclohexen-1- yl)pent-4-en-1-one and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 2500 mg/cm2. They recommend the limits for the 11 different product categories, which are the acceptable use levels of 1-(5,5-Dimethyl-1-cyclohexen-1-yl)pent-4-en-1-one in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 1999. Human repeated insult patch test. Unpublished study from Firmenich Inc., 29a June. Report number 42138. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2001a. Local Lymph Node Assay. Unpublished study from Givaudan, 16 May. Report number 42073. (RIFM, Woodcliff Lake,NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2001b. Human repeated insult patch test. Unpublished study from IFF Inc., 29 October. Report number 51118. (RIFM, Woodcliff Lake, NJ, USA).

4,6-Dimethyl-8-tert-butylcoumarin

CAS N°: 17874-34-9 **Empirical formula:** $C_{15}H_{18}O_2$

Synonyms: 2H-1-Benzopyran-2-one, 8-(1,1-dimethylethyl)-4,6-dimethyl-
Butolia

History:	Initial reviews:	February 1979, June 1981	
	Current revision date:	September 2002	
	Implementation date:	For new submissions*:	N/A
		For existing fragrance compounds*:	N/A
	Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: Photoallergy

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Opdyke, D.L.J. (1980), Food and Cosmetics Toxicology 18, 671.

3,7-Dimethyl-2-octen-1-ol

CAS N°: 40607-48-5 **Empirical formula:** $C_{10}H_{20}O$

Synonyms: 6,7-Dihydrogeraniol
2-Octen-1-ol, 3,7-dimethyl

History:			
	Initial reviews:	New Standard**	
	Current revision date:	October 2003	
	Implementation date:	For new submissions*:	N/A**
		For existing fragrance compounds*:	N/A**
	Next review date	N/A**	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	
Non skin contact products:	N/A		

Note box:

This material **should not be used as fragrance ingredient for any application.**

**This material has previously been included in the list of 'Other Materials', the material therefore has already been prohibited before.

Fragrance material specifications: N/A

Contribution from other sources: None known

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:

IFRA ban noted - REXPAN, October 2003.

References:

Ford et al., 1992, Food and Chemical Toxicology, Volume 30, Supplement, Special Issue VIII, page 19S.

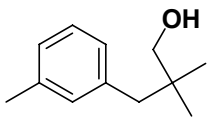
2,2-Dimethyl-3-(3-tolyl)propan-1-ol

CAS N°: 103694-68-4

Empirical formula: $C_{12}H_{18}O$

Synonyms: Benzenepropanol,.ß.,. ß.,3-trimethyl
2,2-Dimethyl-3-(3-methylphenyl)propanol
Majantol (commercial name)
Linlan alcohol (commercial name)

Structure:



History:

Initial reviews:	July 2008 (43rd Amendment), March 2010	
Current revision date:	June 11, 2010	
Implementation date:	For new submissions*:	January 11, 2011
	For existing fragrance compounds*:	January 11, 2012
Next review date:	March 2015	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED / SPECIFICATION**

RESTRICTIONS:

Limits in the finished product:

Category 1	See Note box (1)	0.28%	Category 7	0.8%
Category 2		0.36%	Category 8	2.0%
Category 3		1.5%	Category 9	5.0%
Category 4		4.5%	Category 10	2.5%
Category 5		2.4%	Category 11	See Note box (2)
Category 6	See Note box (1)	7.2%		

Note box:

(1) See the IFRA Code of Practice (Appendix 8, Introduction to the IFRA Standards) regarding the Note on Oral Care Products and other products with the potential of ingestion.
(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

This Standard replaces the existing one on 2,2-Dimethyl-3-(3-tolyl)propan-1-ol distributed with the 43rd Amendment, which only contained the restrictions based on the QRA.

Fragrance material specifications:

2,2-Dimethyl-3-(3-tolyl)propan-1-ol should only be used as a fragrance ingredient if traces of organochlorine compounds are restricted. Total chlorine, which can be measured by Atomic Absorption Spectroscopy, must not exceed 25 ppm in the raw material.

2,2-Dimethyl-3-(3-tolyl)propan-1-ol

Indicative contribution from other sources: None known at the time of the publication of the Standard

---

Critical effect: Sensitization

RIFM Summaries:

EC3 value from one **LLNA** (not the mean) **(µg/cm²)**	**Potency Classification** Based on Animal Data[1]	**Human Data**			**WoE NESIL**[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	**NOEL – HMT** (induction) (µg/cm²)	**LOEL**[2] (induction) (µg/cm²)	
>7500	Weak	9900[4]	N/A	N/A	9900

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[2]Data derived from HRIPT or HMT.
[3]WoE NESIL limited to two significant figures.
[4]MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Dose reported reflect the highest concentration tested, not necessarily the highest achievable NOEL.

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for 2,2-Dimethyl-3-(3-tolyl)propan-1-ol and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 9900 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of 2,2-Dimethyl-3-(3-tolyl)propan-1-ol in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 2002. Local Lymph Node Assay. Unpublished report from Symrise GmbH & Co. KG, 9 December. Report number 49523 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2005. Repeated Insult Patch Test. Unpublished report from Symrise GmbH & Co. KG,. Report number 49526 (RIFM, Woodcliff Lake, NJ, USA)

RIFM (Research Institute for Fragrance Materials, Inc.), 2007. Repeated Insult Patch Test. Unpublished report from Symrise GmbH & Co. KG, 26 September. Report number 53799 (RIFM, Woodcliff Lake, NJ, USA).

Dimethyl citraconate

CAS N°: 617-54-9 **Empirical formula:** $C_7H_{10}O_4$
CH_3-OOC-C(CH_3)=CH-COO-CH_3

Synonyms: 2-Butenedioic acid, 2-methyl-, dimethyl ester, (2Z)-
Dimethyl methyl maleate
Methylmaleic acid, dimethyl ester

History:

Initial reviews:	October 1976	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Opdyke, D.L.J. (1976), Food and Cosmetics Toxicology 14, 749.

Diphenylamine

CAS N°: 122-39-4 **Empirical formula:** $C_{12}H_{11}N$
C_6H_5-NH- C_6H_5

Synonyms: Benzeneamine, N-phenyl-

History:

Initial reviews:	New Standard**	
Current revision date:	October 2003	
Implementation date:	For new submissions*:	N/A**
	For existing fragrance compounds*:	N/A**
Next review date	N/A**	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

This material **should not be used as fragrance ingredient for any application.**

**This material has previously been included in the list of 'Other Materials', the material therefore has already been prohibited before.

Fragrance material specifications: N/A

Contribution from other sources: None known

Critical effect: **Toxicity and Teratogenicity**

REXPAN Rationale / Conclusion:

IFRA ban noted - REXPAN, October 2003

References:

Opdyke, 1978, Food and Cosmetics Toxicology, Volume 16, Supplement 1, Special Issue IV, page 723-727.

Esters of 2-octynoic acid (Except for methyl heptine carbonate)

CAS N°: 10484-32-9
10519-20-7

Empirical formula: $C_{13}H_{22}O_2$ & $C_{10}H_{16}O_2$

Synonyms: 10519-20-7:
Amyl heptine carbonate
2-Octynoic acid, pentyl ester
Pentyl 2-octynoic acid Principal
Vert de violette

10519-20-7:
Ethyl heptine carbonate
Ethyl 2-octynoate Principal
2-Octynoic acid, ethyl ester

History:

Initial reviews:	N/A	
Current revision date:	N/A	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A

Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Methyl heptine carbonate is not Prohibited because it is IFRA Restricted.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Esters of 2-octynoic acid (Except for methyl heptine carbonate)

Critical effect: See Note box

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Reg. Tox & Pharm*., 31, 166-181, 2000

Esters of 2-nonynoic acid (Except methyl octine carbonate)

CAS N°: e.g.:
10031-92-2

Empirical formula: N/A

Synonyms: e.g.:
Ethyl 2-nonynoate
Ethyl octine carbonate
Ethyl octyne carbonate
2-Nonynoic acid, ethyl ester

History:

Initial reviews:	N/A	
Current revision date:	N/A	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A

Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Methyl octine carbonate is not Prohibited because it is IFRA Restricted.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: See Note box

Esters of 2-nonynoic acid (Except methyl octine carbonate)

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Reg. Tox & Pharm*., 31, 166-181, 2000

Estragole

CAS N°: 140-67-0 **Empirical formula:** $C_{10}H_{12}O$

Synonyms: *p*-Allylanisole
1-Allyl-4-methoxybenzene
Benzene, 1-methoxy-4-(2-propenyl)-
Chavicyl methyl ether
Isoanethole
p-Methoxyallylbenzene
1-Methoxy-4-(2-propen-1-yl)benzene
Methyl chavicol

History:

Initial reviews:	New Standard	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2010
Next review date	2014	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: see note box Rinse-off products: see note box
Including household cleaning products

Non skin contact products: see note box

Note box:

The total concentration of Estragole should not exceed the following limitations in the finished product:
Fine fragrance : 0.2%
Eau de Toilette: 0.2%
Other leave on (incl. fragrancing cream): 0.01%
Rinse-off: 0.01%
Non skin (as defined in the introduction to the Standards): 0.2%
Other non cosmetic products not covered above: 0.2%

Fragrance material specifications: N/A

Estragole

Contribution from other sources: See **Annex I**

Critical effect: **Carcinogenicity**

REXPAN Rationale / Conclusion:

Although Estragole has been shown to cause tumors in laboratory animals (NTP, 2008) the studies have a number of limitations that have an impact on its direct application to human risk and particularly risk from dermal contact:

1. The current studies are confounded by high dose toxicity including significant hepatotoxicity, gastric damage and malnutrition in both mice and rats. This makes the distinction between primary and secondary mechanisms of tumour formation difficult.

2. Current scientific evidence supports a non-linear relationship between dose and the potential for carcinogenicity of Estragole and related substances (Smith et al., 2002). This is due to differences in the way that Estragole is metabolized at high versus low doses. Studies indicate that all these events are likely to be minimal in the dose range of 1- 10 mg/kg body weight (Zangouras et al., 1981; Anthony et al., 1987). The lowest dose in the NTP 90-day study used in this assessment was 37.5 mg/kg bw/d thus care needs to be taken in extrapolating to lower doses relevant to fragrance exposure. This non-linear response has also been used to support the risk assessment for exposure to Estragole in Flavours.

Consideration also needs to given to differences between dermal and oral exposure. Introduction of a bolus dose of test material into the stomach leads to higher peak blood plasma levels and increased metabolic demand compared with the slower, more steady absorption of the substance from the skin. Furthermore, although no data exist on the skin metabolism of Estragole or related compounds there is evidence that many enzymatic processes, particularly oxidative ones, are much lower in the skin than in the liver (Bronaugh et al., 1995). Thus the relevance of reported tumours resulting from skin painting studies or subcutaneous injection (Miller et al., 1983) with putative genotoxic metabolites of Estragole needs to be put into perspective. Although data indicate that the most potent metabolite for inducing skin tumours in rodents is the1′-hydroxy epoxide metabolite, characterization of dermal metabolism has not been established to show that the epoxide metabolites used in the skin painting and subcutaneous injection studies would be the metabolite of concern in either rat or mouse, nor has it been established that the level of exposure is relevant as it is unlikely that significant local tissue concentrations for metabolites would result from a realistic oral ingestion or dermal application of Estragole.
The total dermal exposure resulting from the limited use of Estragole as described in this Standard is 0.04 mg/kg body weight/day. Making the following conservative assumptions:

Estragole

- 100% dermal absorption
- Metabolism human = rodent
- Metabolism skin = liver
- Oral LOEL = 37.5 mg/kg/day – based on rat oral low dose observed hyperplasia (oval, bile cell) and it assumes that the hyperplasia will progress to tumor formation
- UF = 1,000 (10 for LOEL to NOAEL, 10 for species, 10 for inter-individual variability)

Worst Case Risk Assessment

- Systemic RfD = 37.5/1,000 = 0.04 mg/kg/day

The IFRA Standard reflects the potential for the higher presence of Estragole in hydroalcoholic and air freshener products whilst ensuring that the RfD for cumulative exposure through all product types will not be exceeded.

References:

Anthony, A., Caldwell, J., Hutt, A.J,. Smith R.L., 1987. Metabolism of Estragole in rat and mouse and influence of dose size on excretion of the proximate carcinogen 1'-hydroxyestragole. Food and Chemical Toxicology 25, 799-806.

Bronaugh, R.L., 1995. Methods for in Vitro Skin Metabolism Studies. Toxicology Mechanisms and Methods, Volume 5, Issue 4, pages 275 – 281

Miller, E.C., Swanson, A.B., Phillips, D.H., Fletcher, T.L., Liem, A., Miller, J.A., 1983. Structure-activity studies of the carcinogenicities in the mouse and rat of some naturally occurring and synthetic alkenylbenzene derivatives related to safrole and estragole. Cancer Research 43, 1124-1134.

National Toxicology Program, 2008. NTP Technical Report on the 3-month toxicity studies of estragole administered by gavage to rats and mice. National Toxicology Program Toxicity Report Series Number 82. NIH Publication No. 08-5966.

Phillips, D.H., Miller, J.A., Miller, E.C., Adams, B., 1981. Structures of the DNA adducts formed in mouse liver after administration of the proximate hepatocarcinogen 1'-hydroxyestragole. Cancer Research 41, 176-186.

Smith R.L., Adams T.B., Doullc J., Ferond V.J., Goodmane J.I., Marnettf L.J., Portogheseg P.S., Waddellh W.J., Wagneri B.M., Rogers A.E., Caldwellk J., and Sipes I.G. 2002. Safety assessment of allylalkoxybenzene derivatives used as flavoring substances — methyl eugenol and estragole. Food and Chemical Toxicology 40: 851–870

Estragole

Swanson, A.B., Miller, E.C., Miller, J.A., 1981. The side-chain epoxidation and hydroxylation of the hepatocarcinogens safrole and estragole and some related compounds by rat and mouse liver microsomes. Biochemica et Biophysica Acta 673, 504-516.

Wiseman, R.W., Fennell, T.R., Miller, J.A., Miller, E.C., 1985. Further characterization of the DNA adducts formed by electrophilic esters of the hepatocarcinogens 1'-hydroxysafrole and 1'-hydroxyestragole *in vitro* and in mouse liver *in vivo*, including new adducts at C-8 and N-7 of guanine residues. Cancer Research 45, 3096-3105.

Zangouras, A., Caldwell, J., Hutt, A.J., Smith, R.L., 1981. Dose dependent conversion of estragole in the rat and mouse to the carcinogenic metabolite, 1'-hydroxyestragole. Biochemical Pharmacology, 30, 1383-1386.

2-Ethoxy-4-methylphenol

CAS N°: 2563-07-7 **Empirical formula:** $C_9H_{12}O_2$

Synonyms: 2-Ethoxy-p-cresol
2-Ethoxy-4-methylphenol
4-Methyl-2-ethoxyphenol
Phenol, 2-ethoxy-4-methyl-
Supravanil, Ultravanil

History:			
	Initial reviews:	New Standard	
	Current revision date:	2008	
	Implementation date:	For new submissions*:	August 16, 2008
		For existing fragrance compounds*:	August 16, 2010
	Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1 See Note box (1)	0.01 %	Category 7	0.02 %
Category 2	0.01 %	Category 8	0.2 %
Category 3	0.03 %	Category 9	1.2 %
Category 4	0.1 %	Category 10	1.9 %
Category 5	0.1 %	Category 11	Not Restricted (2)
Category 6 See Note box (1)	0.2 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) (http://www.iofiorg/)

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

2-Ethoxy-4-methylphenol

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards**)

Critical effect: Sensitization

RIFM Summaries:

LLNA weighted mean EC3 values ($\mu g/cm^2$) [No. Studies]	Potency Classification Based on Animal Data[1]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – HMT (induction) ($\mu g/cm^2$)	LOEL[2] (induction) ($\mu g/cm^2$)	
	Moderate	236[4]	2362[4]	NA	230

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[2] Data derived from HRIPT or HMT.
[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[3] WoE NESIL limited to three significant figures.
[4] *MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL*

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for 2-Ethoxy-4-methylphenol and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 230 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of 2-Ethoxy-4-methylphenol in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 2003a. Human Repeated Insult Patch Test. RIFM report number 44237, December 10 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2003b. Human Repeated Insult Patch Test. RIFM report number 44238, December 10 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2004. Human Repeated Insult Patch Test. RIFM report number 45135, March 30 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2007. Human Repeated Insult Patch Test. RIFM report number 52894, May 15 (RIFM, Woodcliff Lake, NJ, USA).

Ethyl acrylate

CAS N°: 140-88-5 **Empirical formula:** $C_5H_8O_2$
CH_3-CH_2-OCO-CH=CH_2

Synonyms: Ethyl propenoate
2-Propenoic acid, ethyl ester

History:

Initial reviews:	November 1974	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards)

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Opdyke, D.L.J. (1975), Food and Cosmetics Toxicology 13, 801.

Ethylene glycol monoethyl ether and its acetate

CAS N°: 110-80-5
111-15-9 (acetate)

Empirical formula: $C_4H_{10}O_2$; $C_6H_{12}O_3$
$HOCH_2CH_2OC_2H_5$; $CH_3CH_2OCH_2CH_2OAc$

Synonyms: Ethylene glycol ethyl ether
2-Ethoxyethanol
Ethanol, 2-ethoxy-
Cellosolve
Oxitol

Ethylene glycol ethyl ether acetate
2-Ethoxyethyl acetate
Ethyl cellosolve acetate
Ethanol, 2-ethoxy-, acetate
1-Acetoxy-2-ethoxyethane

History:

Initial reviews:	New Standard**	
Current revision date:	October 2003	
Implementation date:	For new submissions*:	N/A**
	For existing fragrance compounds*:	N/A**
Next review date	N/A**	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A

Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

This material **should not be used as fragrance ingredient for any application.**

**This material has previously been included in the list of 'Other Materials', the material therefore has already been prohibited before.

Fragrance material specifications: N/A

Contribution from other sources: None to consider

Critical effect: **Reproductive toxicity**

Ethylene glycol monoethyl ether and its acetate

REXPAN Rationale / Conclusion:

IFRA ban noted - REXPAN, October 2003

References:

NIOSH, 1983, Current Intelligence bulletin, No. 39, page 1-20.

EPA, 1984b, EPA/540/1-86/052; PB86-134632.

ECETOC, 1985, ECETOC Technical Report, 17.

Ethylene glycol monomethyl ether and its acetate

CAS N°: 109-86-4
110-49-6 (acetate)

Empirical formula: $C_3H_8O_2$; $C_5H_{10}O_3$
$HOCH_2CH_2OCH_3$; $CH_3OCH_2CH_2OAc$

Synonyms: Ethylene glycol methyl ether
2-Methoxyethanol
Ethanol, 2-methoxy-
Methyl cellosolve

Ethylene glycol methyl ether acetate
2-Methoxyethanol acetate
2-Methoxyethyl acetate
Methyl cellosolve acetate
Ethanol, 2-methoxy-, acetate

History:

Initial reviews:	New Standard**	
Current revision date:	October 2003	
Implementation date:	For new submissions*:	N/A**
	For existing fragrance compounds*:	N/A**
Next review date	N/A**	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A

Rinse-off products: N/A
Including household cleaning products

Non skin contact products: N/A

Note box:

This material **should not be used as fragrance ingredient for any application.**

**This material has previously been included in the list of 'Other Materials', the material therefore has already been prohibited before.

Fragrance material specifications: N/A

Contribution from other sources: None known

Critical effect: **Reproductive toxicity**

Ethylene glycol monomethyl ether and its acetate

REXPAN Rationale / Conclusion:

IFRA ban noted - REXPAN, October 2003

References:

NIOSH, 1983, Current Intelligence bulletin, No. 39, page 1-20.

EPA, 1984b, EPA/540/1-86/052; PB86-134632.

ECETOC, 1985, ECETOC Technical Report, 17.

Eugenol

CAS N°: 97-53-0

Empirical formula: $C_{10}H_{12}O_2$
$HO\text{-}C_6H_3(OCH_3)\text{-}CH_2\text{-}CH{=}CH_2$

Synonyms:
4-Allylcatechol-2-methyl ether
1-Allyl-4-hydroxy-3-methoxybenzene
4-Allyl-2-methoxyphenol
Caryophyllic acid
2-Hydroxy-5-allylanisole
1-Hydroxy-2-methoxy-4-allylbenzene
4-Hydroxy-3-methoxy-1-allylbenzene
1-Hydroxy-2-methoxy-4-propenylbenzene
2-Methoxy-4-allylphenol
2-Methoxy-4-(2-propenyl)phenol
Phenol, 2-methoxy-4-(2-propenyl)-
Eugenic acid
Allylguaiacol, 4-Allylguaiacol

History:

Initial reviews:	April 2004 (38th Amendment), May 2006 (40th Amendment), May 2007 (42nd Amendment)	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1 See Note box (1)	0.2 %	Category 7	0.4 %
Category 2	0.2 %	Category 8	0.5 %
Category 3	0.5 %	Category 9	0.5 %
Category 4	0.5 %	Category 10	0.5 %
Category 5	0.5 %	Category 11	Not Restricted (2)
Category 6 See Note box (1)	4.3 %		

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year

Eugenol

monitoring phase. At the end of the 5 years the position will be reevaluated again.

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) http://www.iofiorg.org/

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Contribution from other sources: See **Annex 1**

Critical effect: Sensitization

RIFM Summaries:

Eugenol - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values ($\mu g/cm^2$) [No. Studies]	Potency Classification [2]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – MAX (induction) ($\mu g/cm^2$)	LOEL[1] (induction) ($\mu g/cm^2$)	
2703 [6]	Weak	5906	NA	NA	5900

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available
[1] Data derived from HRIPT or Human Max tests
[2] Gerberick *et al.*, 2001
[3] WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for eugenol and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 5900 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of eugenol in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Basketter, D.A., Lea, L.J., Dickens, A., Briggs, D., Pate, I., Dearman, R.J., Kimber, I., 1999. A comparison of statistical approaches to the derivation of EC3 values from local lymph node assay dose responses. Journal of Applied Toxicology, 19(4), 261-266.

Eugenol

Basketter, D.A., Gilmour, N., Dearman, R.J., Kimber, I., Ryan, C.A., Gerberick, F., 2003. Classification of skin sensitisation potency using the Local Lymph Node Assay. The Toxicologist, 72(S-1), 101.

Isola, D., Lalko, J., 2001a. Vehicle effects in the murine local lymph node assay (LLNA). American College of Toxicology Meeting, November 4-7. Washington DC.

Isola, D., Lalko, J., 2001b. Vehicle effects in the murine local lymph node assay (LLNA). International Journal of Toxicology, 20(6), 401.

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161.

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

RIFM (Research Institute for Fragrance Materials, Inc.), 2001. Repeated Insult Patch Test on dl-Citronellol. RIFM report number 39081, May 15. (RIFM, Woodcliff Lake, NJ, USA).

Farnesol

CAS N°: 4602-84-0

Empirical formula: $C_{15}H_{26}O$
$HOCH_2CH=C(CH_3)CH_2CH_2CH=C(CH_3)CH_2CH_2CH=C(CH_3)_2$

Synonyms: 2,6,10-Dodecatrien-1-ol, 3,7,11-trimethyl-
Farnesyl alcohol
Trimethyl dodecatrienol
3,7,11-Trimethyl-2,6,10-dodecatrien-1-ol

History:

Initial reviews:	October 1979, February 1980, 2002	
Current revision date:	2006	
Implementation date:	For new submissions*:	June 11, 2007
	For existing fragrance compounds*:	June 11, 2008
Next review date	2011	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: RESTRICTED / SPECIFICATION

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1	0.08 %	Category 7	0.2 %
Category 2	0.11 %	Category 8	2.0 %
Category 3	0.4 %	Category 9	5.0 %
Category 4	1.2 %	Category 10	2.5 %
Category 5	0.6 %	Category 11	See Note box
Category 6	2.0 %		

Note box:

Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

This Standard replaces the existing one on Farnesol, which only contained the purity criterion as outlined below.

Fragrance material specifications: Farnesol should only be used as a fragrance ingredient if it contains a minimum of 96% of farnesol isomers as determined by GLC.

Contribution from other sources: See **Annex 1**

Farnesol

Critical effect: Sensitization

RIFM Summaries:

Farnesol - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values ($\mu g/cm^2$) [No. Studies]	Potency Classification [2]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – MAX (induction) ($\mu g/cm^2$)	LOEL[1] (induction) ($\mu g/cm^2$)	
1200 [2]	Weak	2755	NA	68974	2700

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available
[1] Data derived from HRIPT or Human Max tests
[2] Gerberick *et al.*, 2001
[3] WoE NESIL limited to two significant figures
LOEL from human maximization test, not a human repeated insult patch test.

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Farnesol and based on the weight of evidence established the No Expected Sensitization Induction Level (NESIL) as 2700 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of Farnesol in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group, Technical Dossier of March 15, 2006.

References:

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161.

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

Research Institute for Fragrance Materials, Inc (1976). Human maximization test with Farnesol. RIFM report number 1797, 11b November (RIFM, Woodcliff Lake, NJ USA).

Research Institute for Fragrance Materials, Inc (1977). Human maximization test with Farnesol. RIFM report number 1702, 7 February (RIFM, Woodcliff Lake, NJ USA).

Research Institute for Fragrance Materials, Inc (2004). Local Lymph Node Assay on Farnesol. Unpublished report from Symrise GmbH & Co., Report number 47136 (RIFM, Woodcliff Lake, NJ USA).

Farnesol

Research Institute for Fragrance Materials, Inc (2004a). Local Lymph Node Assay on Farnesol. Unpublished report from Symrise GmbH & Co., Report number 47137 (RIFM, Woodcliff Lake, NJ USA).

Research Institute for Fragrance Materials, Inc (2004b). Repeated insult patch test of Farnesol in human subjects. Unpublished report from Symrise GmbH & Co., Report number 47190 (RIFM, Woodcliff Lake, NJ USA).

Fig leaf absolute

CAS N°: 68916-52-9 **Empirical formula:**

Synonyms: Ficus carica absolute
Fig leaf absolute (*Ficus carica*)

History:

Initial reviews:	October 1980, May 1983	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	
Non skin contact products:	N/A		

Note box:

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Sensitization and Phototoxicity**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Opdyke, D.L.J., Letizia, C. (1982), Food and Chemical Toxicology 20, 691.

Furfuryl alcohol

CAS N°: 98-00-0 **Empirical formula:** $C_5H_6O_2$

Synonyms: 2-Furancarbinol
2-Furanmethanol
Furfuralcohol
Furfuryl alcohol
α-Furylcarbinol
2-Furylcarbinol
2-Furylmethanol
2-Hydroxymethylfuran

History:			
	Initial reviews:	New Standard	
	Current revision date:	2009	
	Implementation date:	For new submissions*:	August 7, 2009
		For existing fragrance compounds*:	August 7, 2010
	Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	
Non skin contact products:	N/A		

Note box:

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Insufficient Data**

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:

Furfuryl alcohol

1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Regulatory Toxicology and Pharmacology*, 31, 166-181, 2000

Furfurylidene acetone

CAS N°: 623-15-4 **Empirical formula:** $C_8H_8O_2$

Synonyms: 3-Buten-2-one, 4-(2-furanyl)-
Furfuralacetone
4-(2-Furyl)-3-buten-2-one

History:

Initial reviews:	N/A	
Current revision date:	N/A	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: See Note box

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or

Furfurylidene acetone

3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Reg. Tox & Pharm*., 31, 166-181, 2000

Geraniol

CAS N°: 106-24-1 **Empirical formula:** $C_{10}H_{18}O$

Synonyms: 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)-

History:

Initial reviews:	New Standard	
Current revision date:	2007	
Implementation date:	For new submissions*:	June 16, 2007
	For existing fragrance compounds*:	June 16, 2009
Next review date	2012	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1	See Note box (1)	Category 7	0.9 %
Category 2	0.4 %	Category 8	2.0 %
Category 3	1.8 %	Category 9	5.0 %
Category 4	5.3 %	Category 10	2.5 %
Category 5	2.8 %	Category 11	See Note box (2)
Category 6	See Note box (1) 8.6 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry). Further information about IOFI can be found on its website (http://www.iofiorg.org)

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Geraniol

Fragrance material specifications: N/A

Contribution from other sources: See **Annex 1**

Critical effect: Sensitization

RIFM Summaries:

Eugenol - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values ($\mu g/cm^2$) [No. Studies]	Potency Classification [2]	Human Data			WoE NESIL [3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – MAX (induction) ($\mu g/cm^2$)	LOEL [1] (induction) ($\mu g/cm^2$)	
3525 [5]	Weak	11811	NA	NA	11800

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available
[1] Data derived from HRIPT or Human Max tests
[2] Gerberick *et al.*, 2001
[3] WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for geraniol and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 11800 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of geraniol in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Isola, D., Lalko, J., 2001a. Vehicle effects in the murine local lymph node assay (LLNA). American College of Toxicology Meeting, November 4-7. Washington DC.

Isola, D., Lalko, J., 2001b. Vehicle effects in the murine local lymph node assay (LLNA). International Journal of Toxicology, 20(6), 401.

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161.

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.
RIFM (Research Institute for Fragrance Materials, Inc.), 2004a. Repeated Insult Patch

Geraniol

Test on Geraniol. RIFM report number 46888, August 9a. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2004b. Local Lymph Node Assay on Geraniol. RIFM report number 43812, December 17. (RIFM, Woodcliff Lake, NJ, USA).

Geranyl nitrile

CAS N°: 5146-66-7
5585-39-7
31983-27-4

Empirical formula: $C_{10}H_{15}N$

Synonyms: 3,7-Dimethyl-2,6-octadienenitrile
Geranonitrile (isomer unspecified)
2,6-Octadienenitrile, 3,7-dimethyl-
Citranile, Citralva, Geranitrile

History:

Initial reviews:	November 2006 (41st Amendment)	
Current revision date:	N/A	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A

Rinse-off products: N/A
Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: **See Note box**

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:

Geranyl nitrile

1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Reg. Tox & Pharm., 31*, 166-181, 2000

Grapefruit oil expressed

CAS N°: 8016-20-4

Synonyms:

History: Initial reviews: June 1992

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:		
Skin contact products:	4% (excl. rinse-off prod.)	
Leave-on products:		Rinse-off products: *Including household cleaning products*
Non skin contact products:	No limitation	
Note box:		
Fragrance material specifications:		

For applications on areas of skin exposed to sunshine, excluding bath preparations, soaps and other products which are washed off the skin, grapefruit oil expressed should not be used such that the level in the consumer products exceeds 4%.

Note: See remark on phototoxic ingredients in the introduction to the Standards (Appendix 8 to the IFRA Code of Practice) and the Standard on Citrus oil and other furocoumarinscontaining essential oils.

For qualities of the expressed oil in which the less volatile components have been concentrated by partial or total removal of the terpene fraction, this limit should be reduced in proportion to the degree of concentration.

References:

These recommendations are made in order to promote good manufacturing practice (GMP) considering the large variations in the bergapten content of commercial samples of grapefruit oil expressed (private communication to IFRA).

2,4-Heptadienal

CAS N°: 5910-85-0
(Including all geometric isomers)

Empirical formula: $C_7H_{10}O$

Synonyms: Hepta-2,4-dienal

History:

Initial reviews:	New Standard	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2010
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A

Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards**)

Critical effect: **Insufficient Data**

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Regulatory Toxicology and Pharmacology*, 31, 166-181, 2000

trans-2-Heptenal

CAS N°: 18829-55-5

Empirical formula: $C_7H_{12}O$
CH_3-$(CH_2)_3$-CH=CH-CHO

Synonyms: beta-Butylacrolein
3-Butylacrolein
(E)-2-Hepten-1-al
2-Heptenal, (E)-

History:

Initial reviews:	February 1985, April 1989	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A

Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

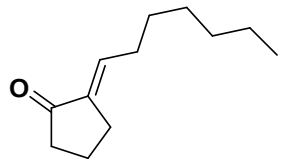
Ford, R.A. (1988), Food and Chemical Toxicology 26, 331.

2-Heptylidene cyclopentan-1-one

CAS N°: 39189-74-7 **Empirical formula:** $C_{12}H_{20}O$

Synonyms: 2-Heptylidenecyclopentanone
2-Heptylidenecyclopentan-1-one
Cyclopentanone, 2-heptylidene-

Structure:



History: Initial reviews: New Standard

Current revision date: June 20, 2011

Implementation date: For new submissions*: August 20, 2011

For existing fragrance compounds*: August 20, 2012

Next review date: 2016

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: RESTRICTED

RESTRICTIONS:

Limits in the finished product:			
Category 1 See Note box (1)	0.03%	Category 7	0.08%
Category 2	0.04%	Category 8	1.01%
Category 3	0.15%	Category 9	5.00%
Category 4	0.45%	Category 10	2.50%
Category 5	0.24%	Category 11	See Note box (2)
Category 6 See Note box (1)	0.72%		

Note box:
(1) See the IFRA Code of Practice (Appendix 8, Introduction to the IFRA Standards) regarding the Note on Oral Care Products and other products with the potential of ingestion.
(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Indicative contribution from other sources: None known at the time of the publication of the Standard

---

Critical effect: Sensitization

2-Heptylidene cyclopentan-1-one

RIFM Summaries:

LLNA weighted mean EC3 values (µg/cm²) [no. studies]	Potency Classification Based on Animal Data[1]	Human Data[2]			WoE NESIL[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	NOEL – HMT (induction) (µg/cm²)	LOEL (induction) (µg/cm²)	
4100 [1]	Weak	NA	NA	NA	1000

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[2]Data derived from HRIPT or HMT.
[3]WoE NESIL limited to two significant figures.

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for 2-Heptylidene cyclopentan-1-one and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 1000 µg/cm², which is a default value based on the LLNA data. They recommend the limits for the 11 different product categories, which are the acceptable use levels of 2-Heptylidene cyclopentan-1-one in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the publication by Api *et al*., 2008.

References:

Api AM, Basketter DA, Cadby PA, Cano M-F, Ellis G, Gerberick G, et al. Dermal Sensitization Quantitative Risk Assessment (QRA) For Fragrance Ingredients. *Regulatory Toxicology and Pharmacology* 2008;52(1): 3-23.

2,4-Hexadienal

CAS N°: 80466-34-8
(Including all geometric isomers)

Empirical formula: C_6H_8O

Synonyms: Hexa-2,4-dienal

History:			
	Initial reviews:	New Standard	
	Current revision date:	2009	
	Implementation date:	For new submissions*:	August 7, 2009
		For existing fragrance compounds*:	August 7, 2010
	Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A

Rinse-off products: N/A
Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards**)

Critical effect: **Insufficient Data**

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Regulatory Toxicology and Pharmacology*, 31, 166-181, 2000

Hexahydrocoumarin

CAS N°: 700-82-3 **Empirical formula:** $C_9H_{12}O_2$

Synonyms: 2H-1-Benzopyran-2-one, 3,4,5,6,7,8-hexahydro-
Coumarin, hexahydro-
Coumarin, 3,4,5,6,7,8-hexahydro-
1-Cyclohexene-1-propanoic acid, 2-hydroxy-, d-lactone
3,4,5,6,7,8-Hexahydro-2H-1-benzopyran-2-one

History:

Initial reviews:	February 1980	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Private communication to IFRA.

trans-2-Hexenal

CAS N°: 6728-26-3

Empirical formula: $C_6H_{10}O$
$CH_3(CH_2)_2CH=CHCHO$

Synonyms: 2-Hexenal, (E)-
Hexen-2-al
Leaf aldehyde
beta-Propyl acrolein

History:

Initial reviews:	April 1989, June 1992, May 2006 (40th Amendment), May 2007 (42nd Amendment)	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1 See Note box (1)	0.001 %	Category 7	0.002 %
Category 2	0.001 %	Category 8	0.002 %
Category 3	0.002 %	Category 9	0.002 %
Category 4	0.002 %	Category 10	0.002 %
Category 5	0.002 %	Category 11	Not Restricted (2)
Category 6 See Note box (1)	0.02 %		

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) (http://www.iofiorg.org)
(2) Category 11 includes all non-skin contact or incidental skin contact products. Due

trans-2-Hexenal

to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.
Fragrance material specifications: N/A

Contribution from other sources: See **Annex 1**

Critical effect: Sensitization

RIFM Summaries:

trans-2-Hexenal - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values (µg/cm^2) [No. Studies]	Potency Classification [2]	Human Data			WoE NESIL[3] (µg/cm^2)
		NOEL – HRIPT (induction) (µg/cm^2)	NOEL – MAX (induction) (µg/cm^2)	LOEL[1] (induction) (µg/cm^2)	
1012 [2]	Strong	24	NA	236	24

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available
[1] Data derived from HRIPT or Human Max tests
[2] Gerberick *et al.*, 2001
[3] WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for trans-2-hexenal and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 24 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of trans-2-hexenal in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Estrada, E., Patlewicz, G., Chamberlain, M., Basketter, D. and Larbey, S. (2003) Computer aided Knowledge Generation for Understanding Skin Sensitization Mechanisms: The TOPS-MODE Approach. Chem. Res. Toxicol., 16, 1226-1235

RIFM (Research Institute for Fragrance Materials, Inc.), 1989. Repeated Insult Patch Test on trans-2-Hexenal. RIFM report number 27821, May 22. (RIFM, Woodcliff Lake, NJ, USA).

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161.

trans-2-Hexenal

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

RIFM (Research Institute for Fragrance Materials, Inc.), 1990. Repeated Insult Patch Test on trans-2-Hexenal. RIFM report number 27822, January 9b. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2005a. Repeated Insult Patch Test on trans-2-Hexenal. RIFM report number 49111, July 14. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2005b. Local Lymph Node Assay on trans-2-Hexenal. RIFM report number 48756, January 26. (RIFM, Woodcliff Lake, NJ, USA).

trans-2-Hexenal diethyl acetal

CAS N°: 67746-30-9

Empirical formula: $C_{10}H_{20}O_2$
CH_3-CH_2-CH_2-CH=CH-CH(OCH_2CH_3)$_2$

Synonyms: 1,1-Diethoxy-trans-2-hexene
(E) 2-Hexenal diethyl acetal
2-Hexene, 1,1-diethoxy-, (2E)-

History:

Initial reviews:	February 1985, April 1989	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A

Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Ford, R.A. (1988), Food and Chemical Toxicology 26, 345.

trans-2-Hexenal dimethyl acetal

CAS N°: 18318-83-7

Empirical formula: $C_8H_{16}O_2$
CH_3-CH_2-CH_2-CH=CH-$CH(OCH_3)_2$

Synonyms: 1,1-Dimethoxy-trans-2-hexene
2-Hexene, 1,1-dimethoxy-, (2E)-

History:

Initial reviews:	February 1985, April 1989	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A

Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Ford, R.A. (1988), Food and Chemical Toxicology 26, 347.

alpha-Hexyl cinnamic aldehyde

CAS N°: 101-86-0

Empirical formula: $C_{15}H_{20}O$
C_6H_5-CH=C(CHO)-$[CH_2]_5$-CH_3

Synonyms:
2-Benzylideneoctanal
Hexyl cinnamal
α-Hexyl cinnamaldehyde
Hexyl cinnamic aldehyde
α-n-Hexylcinnamic aldehyde
Hexyl cinnamyl
α-n-Hexyl-β-phenylacrolein
Octanal, 2-(phenylmethylene)-
Jasmonal H

History:

Initial reviews:	New Standard	
Current revision date:	2007	
Implementation date:	For new submissions*:	June 16, 2007
	For existing fragrance compounds*:	June 16, 2009
Next review date	2012	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1 See Note box (1)	0.7 %	Category 7	1.8 %
Category 2	0.9 %	Category 8	2.0 %
Category 3	3.6 %	Category 9	5.0 %
Category 4	10.7 %	Category 10	2.5 %
Category 5	5.6 %	Category 11 See Note box (2)	
Category 6 See Note box (1)	17.1 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry). Further information about IOFI can be found on its website (http://www.iofiorg.org)

alpha-Hexyl cinnamic aldehyde

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.
Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards)

Critical effect: Sensitization

RIFM Summaries:

alpha-Hexyl cinnamic aldehyde - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values ($\mu g/cm^2$) [No. Studies]	Potency Classification [2]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – MAX (induction) ($\mu g/cm^2$)	LOEL[1] (induction) ($\mu g/cm^2$)	
2372 [>5]	Weak	23622	NA	NA	23600

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available
[1] Data derived from HRIPT or Human Max tests
[2] Gerberick *et al.*, 2001
[3] WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for alpha-hexyl cinnamic aldehyde and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 23600 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of alpha-hexyl cinnamic aldehyde in the various product categories. These were derived from the application of the exposure based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Basketter, D.A., Lea, L.J., Dickens, A., Briggs, D., Pate, I, Dearman, R.J., Kimber, I., 1999. A comparison of statistical approaches to the derivation of EC3 values from local lymph node assay dose responses. Journal of Applied Toxicology, 19(4), 261-266.
Basketter, D.A., Wright, Z.M., Warbrick, E.V., Dearman, R.J., Kimber, I., Ryan, C.A., Gerberick, G.F., White, I.R., 2001. Human potency predictions for aldehydes using the local lymph node assay. Contact Dermatitis, 45(2), 89-94.

alpha-Hexyl cinnamic aldehyde

Basketter, D.A., Gilmour, N., Dearman, R.J., Kimber, I., Ryan, C.A., and Gerberick, F., 2003. Classification of skin sensitisation potency using the Local Lymph Node Assay. The Toxicologist, 72(S-1), 101.

Dearman, R.J., Hilton, J., Evans, P., Harvey, P., Basketter,D.A., Kimber, I., 1998. Temporal stability of local lymph node assay responses to hexyl cinnamic aldehyde. Journal of Applied Toxicology, 18(4), 281-284.

Dearman, R.J., Wright, Z.M., Basketter, D.A., Ryan, C.A., Gerberick, G.F., Kimber, I, 2001. The suitability of hexyl cinnamic aldehyde as a calibrant for the murine local lymph node assay. Contact Dermatitis, 44(6), 357-361.

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161.

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

RIFM (Research Institute for Fragrance Materials, Inc.), 2005. Repeated Insult Patch Test on alpha-hexylcinnamaldehyde. RIFM report number 51047, November 11. (RIFM, Woodcliff Lake, NJ, USA).

alpha-Hexylidene cyclopentanone

CAS N°: 17373-89-6 **Empirical formula:** $C_{11}H_{18}O$

Synonyms: 2-Hexylidene cyclopentanone
Cyclopentanone, 2-hexylidene-
2-Hexylidene cyclopentanone
Jasmalone

History:

Initial reviews:	May 1983 (11th Amendment), July 1994 (28th Amendment)	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

For a description of the categories, refer to the QRA Informational Booklet.

Category 1 See Note box (1)	0.01 %	Category 7	0.02 %
Category 2	0.01 %	Category 8	0.06 %
Category 3	0.05 %	Category 9	0.06 %
Category 4	0.06 %	Category 10	0.06 %
Category 5	0.06 %	Category 11	Not Restricted (2)
Category 6 See Note box (1)	0.2 %		

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) http://www.iofiorg.org/.

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due

alpha-Hexylidene cyclopentanone

to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.
Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards).**

Critical effect: Sensitization

RIFM Summaries:

EC3 value from one LLNA (not the mean) (µg/cm2) [No. Studies]	**Potency Classification** Based on Animal Data[1]	**Human Data**			**WoE NESIL**[3] (µg/cm^2)
		NOEL – HRIPT (induction) (µg/cm^2)	**NOEL – HMT** (induction) (µg/cm^2)	**LOEL**[2] (induction) (µg/cm^2)	
600	Weak	300 [4]	NA	500	300

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[2] Data derived from HRIPT or HMT
[3] WoE NESIL limited to three significant figures
[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for alpha-Hexylidene cyclopentanone and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 300 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of alpha-Hexylidene cyclopentanone in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 1982. Human Repeated Insult Patch Test. Unpublished report from IFF Incorporated, 8 January and 27 August. Report number 15002 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2005. Human Repeated Insult Patch Test. Unpublished report from Firmenich Incorporated, 17 March. Report number 48712 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2008. Local Lymph Node Assay. RIFM report (RIFM, Woodcliff Lake, NJ, USA).

Hexyl salicylate

CAS N°: 6259-76-3

Empirical formula: $C_{13}H_{18}O_3$
CH_3-[CH_2]$_5$-OCO-C_6H_4-OH

Synonyms: Benzoic acid, 2-hydroxy-, hexyl ester
Hexyl o-hydroxybenzoate

History:

Initial reviews:	New Standard	
Current revision date:	2007	
Implementation date:	For new submissions*:	June 16, 2007
	For existing fragrance compounds*:	June 16, 2009
Next review date	2012	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1	See Note box (1)	Category 7	2.7 %
Category 2	1.3 %	Category 8	2.0 %
Category 3	5.3 %	Category 9	5.0 %
Category 4	16.0 %	Category 10	2.5 %
Category 5	8.4 %	Category 11	See Note box (2)
Category 6	See Note box (1) 25.7 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry). Further information about IOFI can be found on its website (http://www.iofiorg.org)

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards)

Hexyl salicylate

Critical effect: Sensitization

RIFM Summaries:

Hexyl salicylate - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values ($\mu g/cm^2$) [No. Studies]	Potency Classification [2]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – MAX (induction) ($\mu g/cm^2$)	LOEL[1] (induction) ($\mu g/cm^2$)	
45 [1]	Weak	35433	2069	NA	35400

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available
[1] Data derived from HRIPT or Human Max tests
[2] Gerberick *et al.*, 2001
[3] WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for hexyl salicylate and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 35400 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of hexyl salicylate in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161.

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

RIFM (Research Institute for Fragrance Materials, Inc.), 1975. Human Maximization Test on Hexyl Salicylate. RIFM report number 1798, January 31. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2004. Repeated Insult Patch Test on Hexyl Salicylate. RIFM report number 45130, May 3. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2006. Local Lymph Node Assay on Hexyl Salicylate. RIFM report number 51636, March 29a. (RIFM, Woodcliff Lake, NJ, USA).

Hydroabietyl alcohol
Dihydroabietyl alcohol

CAS N°: 13393-93-6
26266-77-3
1333-89-7

Empirical formula: $C_{20}H_{36}O$

Synonyms: Abitol (mixture of different hydroabietyl alcohols)

History:

Initial reviews:	October 1974, May 1976, December 1995	
Current revision date:	May 2003	
Implementation date:	For new submissions*:	May 6, 2004
	For existing fragrance compounds*:	May 6, 2005
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	N/A	Rinse-off products: *Including household cleaning products*
Non skin contact products:	N/A	

Note box:

So far only the use in cosmetic products was banned. This ban is now extended to all kinds of fragrance application (use).

Fragrance material specifications: N/A

Contribution from other sources: None known

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:

IFRA ban noted - REXPAN, May 2003

References:

RIFM Monograph 323, Fd. Cosmet. Toxicol. 12, 919-921 (1974)

Hydroquinone monoethyl ether

CAS N°: 622-62-8

Empirical formula: $C_8H_{10}O_2$
$HOC_6H_4OCH_2CH_3$

Synonyms: 1-Ethoxy-4-hydroxybenzene
p-Ethoxyphenol
Phenol, 4-ethoxy-

History:

Initial reviews:	June 1982, October 1983	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A

Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

So far only the use in cosmetic products was banned. This ban is now extended to all kinds of fragrance application (use).

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Depigmentation**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

Hydroquinone monoethyl ether

References:

E. Frenk, (1969), Arch. Klin. Exp. Derm. 235, 16.

E. Frenk (1970), Ann. Derm. Syph (Paris) 97, 287.

E. Frenk & F. Ott (1971), Journal of Investigative Dermatology 56, 287.

W. Wohlrab and R.P. Zaumseil (1976), Derm. Monatsschr. 162, 908.

Private communication to IFRA.

Hydroquinone monomethyl ether

CAS N°: 150-76-5

Empirical formula: $C_7H_8O_2$ $HO\text{-}C_6H_4\text{-}O\text{-}CH_3$

Synonyms:
4-Hydroxyanisole
p-Hydroxyanisole
4-Methoxyphenol
p-Methoxyphenol
Phenol, p-methoxy-

History:

Initial reviews:	October 1983	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	
Non skin contact products:	N/A		

Note box:

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Depigmentation**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Private communication to IFRA.

Hydroxycitronellal

CAS N°: 107-75-5 **Empirical formula:** $C_{10}H_{20}O_2$

Synonyms: Citronellalhydrate
3,7-Dimethyl-7-hydroxyoctanal
Octanal, 7-hydroxy-3,7-dimethyl-
Oxydihydrocitronellal
Laurinal, Laurine

History:

Initial reviews:	March 1987, September 2000, April 2005 (39th Amendment new format only), May 2007 (42nd Amendment)	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1	See Note box (1)	Category 7	0.4 %
Category 2	0.2 %	Category 8	1.0 %
Category 3	0.8 %	Category 9	1.0 %
Category 4	1.0 %	Category 10	1.0 %
Category 5	1.0 %	Category 11	Not Restricted (2)
Category 6	See Note box (1)	3.6 %	

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry). (http://www.iofiorg.org)

Hydroxycitronellal

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards)

Critical effect: Sensitization

RIFM Summaries:

LLNA weighted mean EC3 values ($\mu g/cm^2$) [No. Studies]	Potency Classification Based on Animal Data[1]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – HMT (induction) ($\mu g/cm^2$)	LOEL[2] (induction) ($\mu g/cm^2$)	
5612 [9]	Weak	5000[4]	NA	5906	5000

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[2] Data derived from HRIPT or HMT
[3] WoE NESIL limited to three significant figures
[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Hydroxycitronellal and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 5000 $\mu g/cm^2$. They recommend the limits for the 11 different product categories, which are the acceptable use levels of Hydroxycitronellal in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Ashby, J., Basketter, D. A., Paton, D., Kimber, I., 1995. Structure activity relationships in skin sensitization using the murine local lymph node assay. *Toxicology*, 103(3), 177-194.
Basketter, D. A., Wright, Z., Warbrick, E. V., Dearman, R. J., Kimber, I., Ryan, C. A.,

Gerberick, G. F., White, I. R., 2001. Comparison of the local lymph node assay with the guinea-pig maximization test for the detection of a range of contact allergens. *Food and Chemical Toxicology*, 30(1), 65-69.

Hydroxycitronellal

Basketter, D. A., Wright, Z., Gilmour, N. J., Ryan, C. A., Gerberick, G. F., Robinson, M. K., Dearman, R. J., Kimber, I., 2002. Prediction of human sensitization potency using local lymph node assay EC3 values. *Contact Dermatitis*, 45(2), 89-94.

Estrada, E., Patlewicz, G., Chamberlain, M., Basketter, D., Larbey, S., 2003. Computeraided knowledge generation for understanding skin sensitization mechanisms: The TOPSMODE approach. *Chemical Research in Toxicology*, 16(10), 1226-1235.

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. *American Journal of Contact Dermatitis*, 12(3), 156-161.

Isola, D., Lalko, J., 2001. Vehicle effects in the murine local lymph node assay (LLNA). *International Journal of Toxicology*, 20(6), 401

RIFM (Research Institute for Fragrance Materials, Inc.), 1990. Repeated insult patch testwith hydroxycitronellal in human subjects. RIFM report number 28267, October, 24. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1991. Repeated insult patch test with hydroxycitronellal in human subjects. RIFM report number 28273, April, 17. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Material, Inc.), 2006. Repeated insult patch test with hydroxycitronellal. RIFM report number 49736, January 5. (RIFM, Woodcliff Lake, NJ, USA).

Smith, C. K., Hotchkiss, S. A. M., 2001. Allergic Contact Dermatitis: Chemical and Metabolic Mechanisms. Taylor and Francis Ltd, London.

3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde (HMPCC)

CAS N°: 31906-04-4
51414-25-6

Empirical formula: $C_{13}H_{22}O_2$

Synonyms: 3-Cyclohexen-1-carboxaldehyde, 4-(4-hydroxy-4-methylpentyl)-
3-Cyclohexen-1-carboxaldehyde, 3-(4-hydroxy-4-methylpentyl)-
Hydroxyisohexyl 3-cyclohexene carboxaldehyde (INCI)
4-(4-Hydroxy-4-methylpenyl) cyclohex-3-enecarbaldehyde
3-(4-Hydroxy-4-methylpentyl) cyclohex-3-ene-1-carbaldehyde
Lyral, Kovanol, Mugonal, Landolal, Cyclohexal (trade names)

History:

Initial reviews:	April 2003, July 2008	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2011
Next review date	2014	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1	See Note box (1)	Category 7	0.02 %
Category 2	0.02 %	Category 8	0.2 %
Category 3	0.2 %	Category 9	0.2 %
Category 4	0.2 %	Category 10	0.2 %
Category 5	0.2 %	Category 11	See Note box (2)
Category 6	See Note box (1)	0.2 %	

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry - www.iofiorg.org).

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

3 and 4-(4-Hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde (HMPCC)

The restrictions as given for the individual categories are NOT based on the QRA but solely represent a pragmatic approach to address the specific situation for HMPCC. These pragmatic measures will be reviewed over time in view of the development of sensitization rates (clinical data) to the material.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards)**

Critical effect: **Sensitization**

RIFM Summaries:

See note box

REXPAN Rationale / Conclusion:

The RIFM Expert Panel approved the pragmatic approach proposed by IFRA.

p-Isobutyl-α-methyl hydrocinnamaldehyde

CAS N°: 6658-48-6 **Empirical formula:** $C_{14}H_{20}O$

Synonyms: p-Isobutyl-α-methyl hydro cinnamic aldehyde
Benzenepropanal, α-methyl-4-(2-methylpropyl)-
3-(4-Isobutyl-phenyl)-2-methyl-propionaldehyde
Rhodial
Suzaral

History:

Initial reviews:	New Standard	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2011
Next review date	2014	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1 See Note box (1)	0.07 %	Category 7	0.17 %
Category 2	0.08 %	Category 8	2.00 %
Category 3	0.35 %	Category 9	5.00 %
Category 4	1.04 %	Category 10	2.50 %
Category 5	0.55 %	Category 11	See Note box (2)
Category 6 See Note box (1)	1.67 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry). (http://www.iofiorg.org)

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

p-Isobutyl-α-methyl hydrocinnamaldehyde

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards)

Critical effect: **Sensitization**

RIFM Summaries:

LLNA weighted mean EC3 values (µg/cm^2) [No. Studies]	Potency Classification Based on Animal Data[2]	Human Data			WoE NESIL[3] (µg/cm^2)
		NOEL – HRIPT (induction) (µg/cm^2)	NOEL – HMT (induction) (µg/cm^2)	LOEL[1] (induction) (µg/cm^2)	
<2500 [1][4]	Weak	2362	5520	NA	2300

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.
[1] Data derived from HRIPT or HMT.
[2] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[3] WoE NESIL limited to two significant figures.
[4] EC3 value from one LLNA, not the mean.

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for *p*-Isobutyl-α-methyl hydrocinnamaldehyde and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 2300 mg/cm2. They recommend the limits for the 11 different product categories, which are the acceptable use levels of *p*-Isobutyl-α-methyl hydrocinnamaldehyde in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 1977. Maximization study with *p*-Isobutyl-α-methyl hydrocinnamaldehyde. RIFM report number 1702, May 9c. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2001. Local Lymph Node Assay. Unpublished study from Givaudan, 18 May. Report number 41055. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2008. Human repeated insult patch test. RIFM report number 55563, August 25a. (RIFM, Woodcliff Lake, NJ, USA).

Isobutyl N-methylanthranilate

CAS N°: 65505-24-0 **Empirical formula:** $C_{12}H_{17}NO_2$

Synonyms: Benzoic acid, 2-(methylamino)-, 2-methylpropyl ester
Isobutyl 2-(methylamino)benzoate

History:

Initial reviews:	New Standard	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2010
Next review date	2014	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material has been identified for having the potential of forming nitrosamines in nitrosating systems. Downstream users therefore have to be notified of the presence of the material and its potential to be able to consider adequate protective measures.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards**)

Critical effect: **Potential of nitrosamine formation**.

REXPAN Rationale / Conclusion:

IFRA measures regarding potential nitrosamine formation noted - REXPAN April 2009.

References:

Nitrosamine policy as contained in the EU Cosmetics Directive 76/768/EEC and its Amendments.

Isocyclocitral

CAS N°: 1335-66-6
1423-46-7
67634-07-5

Empirical formula: $C_{10}H_{16}O$

Synonyms: 1335-66-6
1-Formyl-[2,4,6-]&[3,5,6-]trimethyl-3-cyclohexene
Isocyclocitral
[2,4,6-]&[3,5,6-]Trimethyl-3-cyclohexene-1-carboxaldehyde

1423-46-7
3-Cyclohexene-1-carboxaldehyde, 2,4,6-trimethyl-
Neocyclocitral
2,4,6-Trimethylcyclohex-3-enecarbaldehyde
2,4,6-Trimethyl-3-cyclohexenylcarboxaldehyde
2,4,6-Trimethyl-3-cyclohexene-1-carbaldehyde

67634-07-5
3-Cyclohexene-1-carboxaldehyde, 3,5,6-trimethyl-
3,5,6-Trimethylcyclohex-3-ene-1-carbaldehyde

History:

Initial reviews:	New Standard	
Current revision date:	2007	
Implementation date:	For new submissions*:	June 16, 2007
	For existing fragrance compounds*:	June 16, 2009
Next review date	2012	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1	See Note box (1)	Category 7	0.5 %
Category 2	0.3 %	Category 8	2.0 %
Category 3	1.1 %	Category 9	5.0 %
Category 4	3.2 %	Category 10	2.5 %
Category 5	1.7 %	Category 11	See Note box (2)
Category 6	See Note box (1)	5.1 %	

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in

Isocyclocitral

compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry). Further information about IOFI can be found on its website (http://www.iofiorg.org)

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards)

Critical effect: Sensitization

RIFM Summaries:

Isocyclocitral - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values ($\mu g/cm^2$) [No. Studies]	Potency Classification [2]	Human Data			WoE NESIL [3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – MAX (induction) ($\mu g/cm^2$)	LOEL [1] (induction) ($\mu g/cm^2$)	
1825 [1]	Weak	7087	2759	NA	7000

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available
[1] Data derived from HRIPT or Human Max tests
[2] Gerberick *et al.*, 2001
[3] WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for isocyclocitral and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 7000 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of isocyclocitral in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

Isocyclocitral

References:

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161.

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

RIFM (Research Institute for Fragrance Materials, Inc.), 1972. The contact-sensitization potential of fragrance materials by maximization testing in humans. RIFM report number 1804, November 01 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2004. Repeated insult patch test with isocyclocitral. RIFM report number 47260, April 16 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2005. Repeated insult patch test with isocyclocitral. RIFM report number 47590, January 24 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2007. Murine local lymph node assay on isocyclocitral. RIFM DRAFT (RIFM, Woodcliff Lake, NJ, USA).

Isocyclogeraniol

CAS N°: 68527-77-5 **Empirical formula:** $C_{10}H_{18}O$

Synonyms: 3-Cyclohexene-1-methanol, 2,4,6-trimethyl-
2,4,6-Trimethyl-3-cyclohexene-1-methanol

History:	Initial reviews:	December 1995, April 2005 (39th Amendment, new format only)	
	Current revision date:	2008	
	Implementation date:	For new submissions*:	August 16, 2008
		For existing fragrance compounds*:	August 16, 2010
	Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

For a description of the categories, refer to the QRA Informational Booklet.

Category 1 See Note box (1)	0.11 %	Category 7	0.3 %
Category 2	0.14 %	Category 8	0.5 %
Category 3	0.5 %	Category 9	0.5 %
Category 4	0.5 %	Category 10	0.5 %
Category 5	0.5 %	Category 11	Not Restricted (2)
Category 6 See Note box (1)	2.8 %		

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) http://www.iofiorg.org/.

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Isocyclogeraniol

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards).**

Critical effect: Sensitization

RIFM Summaries:

EC3 value from one LLNA (not the mean) (µg/cm2) [No. Studies]	**Potency Classification** Based on Animal Data[1]	**Human Data**			**WoE NESIL**[3] (µg/cm^2)
		NOEL – HRIPT (induction) (µg/cm^2)	**NOEL – HMT** (induction) (µg/cm^2)	**LOEL**[2] (induction) (µg/cm^2)	
>6250	Weak	3898 [4]	NA	7752	3800

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[2] Data derived from HRIPT or HMT
[3] WoE NESIL limited to three significant figures
[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Isocyclogeraniol and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 3800 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of Isocyclogeraniol in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 1982. Evaluation of potential irritation and sensitization hazards by dermal contact of isocyclogeraniol in humans. Unpublished report from International Flavors and Fragrances, 22 July. Report number 21790 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1983. Evaluation of potential hazards by dermal contact of isocyclogeraniol in humans. Unpublished report from International Flavors and Fragrances, 06 January. Report number 21792 (RIFM, Woodcliff Lake, NJ, USA).

Isocyclogeraniol

RIFM (Research Institute for Fragrance Materials, Inc.), 2005. 2,4,6-Trimethyl-3-cyclohexene-1-methanol diluted with vehicle 1:3 EtOH:DEP: Local Lymph Node Assay. RIFM report number 48755, January 28 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2005a. Repeated insult patch test with 2,4,6-trimethyl-3-cyclohexene-1-methanol. RIFM report number 49110, September 07 (RIFM, Woodcliff Lake, NJ, USA).

Isoeugenol

CAS N°: 97-54-1 **Empirical formula:** $C_{10}H_{12}O_2$

Synonyms: 1-Hydroxy-2-methoxy-4-propen-1-ylbenzene
4-Hydroxy-3-methoxy-1-propen-1-ylbenzene
4-Hydroxy-3-methoxy-1-propenylbenzene
iso-Eugenol
3-Methoxy-4-hydroxy-1-propen-1-ylbenzene
2-Methoxy-4-propenylphenol
2-Methoxy-4-(1-propenyl)phenol
Phenol, 2-methoxy-4-(1-propenyl)-
4-Propenylguaiacol

History:

Initial reviews:	May 1980 (6th Amendment), May 1998 (31st amendment), 2001, April 2004 (38th Amendment), May 2007 (42nd Amendment)	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1 See Note box (1)	0.01 %	Category 7	0.02 %
Category 2	0.01 %	Category 8	0.02 %
Category 3	0.02 %	Category 9	0.02 %
Category 4	0.02 %	Category 10	0.02 %
Category 5	0.02 %	Category 11	Not Restricted (2)
Category 6 See Note box (1)	0.2 %		

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in

Isoeugenol

compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry).

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Contribution from other sources: See Annex 1

Critical effect: Sensitization

RIFM Summaries:

LLNA weighted mean EC3 values ($\mu g/cm^2$) [No. Studies]	Potency Classification Based on Animal Data[1]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – HMT (induction) ($\mu g/cm^2$)	LOEL[2] (induction) ($\mu g/cm^2$)	
498 [18]	Moderate	250[4]	NA	775	250

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[2] Data derived from HRIPT or HMT
[3] WoE NESIL limited to three significant figures
[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Isoeugenol and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 250 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of Isoeugenol in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Basketter, D. A., Lea, L. J., Dickens, A., Briggs, D., Pate, I., Dearman, R. J.,Kimber, I., 1999. A comparison of statistical approaches to the derivation of EC3 values from local lymph node assay dose responses. *Journal of Applied Toxicology*, 19(4), 261-266.

Isoeugenol

Basketter, D. A., Wright, Z., Gilmour, N. J., Ryan, C. A., Gerberick, G. F., Robinson, M. K.,Dearman, R. J.,Kimber, I., 2002. Prediction of human sensitization potency using local lymph node assay EC3 values. *The Toxicologist*, 66(1-S), 240

Loveless, S. E., Ladics, G. S., Gerberick, G. F., Ryan, C. A., Basketter, D. A., Scholes, E. W., House, R. V., Hilton, J., Dearman, R. J.,Kimber, I., 1996. Further evaluation of the local lymph node assay in the final phase of an international collaborative trial. *Toxicology*, 108 (1-2), 141-152

RIFM (Research Institute for Fragrance Materials, Inc.), 1991. Murine local lymph node assay on isoeugenol. Unpublished report from Firmenich Incorporated, 24 August. Report number 40676 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2001. Murine local lymph node assay with methoxy dicyclopentadiene carboxaldehyde. Unpublished report from Firmenich Incorporated, 08 October. Report number 42120 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2001a. Murine local lymph node assay with 3-cyclopentene-1-butanal, alpha,2,2,3-tetramethyl-.gamma.-methylene. Unpublished report from Firmenich Incorporated, 30 November. Report number 42122 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2001b. 4-Penten-2-ol, 3,3-dimethyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-: Murine local lymph node assay. Unpublished report from Firmenich Incorporated, 11 November. Report Number 42130 (RIFM, Woodcliff Lake, NJ, USA)

RIFM (Research Institute for Fragrance Materials, Inc.), 2002. Murine local lymph node assay with methyl hexadecanoate. Unpublished report from Firmenich Incorporated, 22 January. Report number 42123 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2002a. Murine local lymph node assay of delta-1-(2,6,6-trimethyl-3-cyclohexen-1-yl)-2-buten-1-one. Unpublished report from Firmenich Incorporated, 02 April. Report number 42139 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2002b. 2(3H)-Naphthalenone, 4,4a,5,6,7,8-hexahydro-4,4a-dimethyl-6-(1-methylethylidene)-, (4R,4aS)-: Murine Local Lymph Node Assay. Unpublished report from Firmenich Incorporated, 31 January. Report number 42145 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2002c. Methyl octanoate: Murine lymph node assay. Unpublished report from Firmenich Incorporated, 12 September. Report number 42131 (RIFM, Woodcliff Lake, NJ, USA).

Isoeugenol

Thompson, G. R., Booman, K. A., Dorsky, J., Kohrman, K. A., Rothenstein, A. S., Schwoeppe, E. A., Sedlak, R. I.,Steltenkamp, R. J., 1983. Isoeugenol: A survey of consumer patch-test sensitization. Food and Chemical Toxicology, 21(6), 735-740.

Wright, Z. M., Basketter, D. A., Blaikie, L., Cooper, K. J., Warbrick, E. V., Dearman, R. J.,Kimber, I., 2001. Vehicle effects on skin sensitization potency of four chemicals assessment using the local lymph node assay. *International Journal of Cosmetic Science*, 23(2), 75-83.

Isophorone

CAS N°: 78-59-1 **Empirical formula:** $C_9H_{14}O$

Synonyms: 2-Cyclohexen-1-one, 3,5,5-trimethyl-
Isoacetophorone
3,5,5-Trimethyl-2-cyclohexen-1-one

History:	Initial reviews:	N/A	
	Current revision date:	N/A	
	Implementation date:	For new submissions*:	N/A
		For existing fragrance compounds*:	N/A
	Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: **See Note box**

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

Isophorone

References:

Human Health Criteria Document, *Reg. Tox & Pharm.*, 31, 166-181, 2000

6-Isopropyl-2-decalol

CAS N°: 34131-99-2

Empirical formula: $C_{13}H_{24}O$

Synonyms: Decahydro-6-isopropyl-2-naphthol
Decahydro-6-(1-methylethyl)-2-naphthalenol
6-Isopropyl-2-decahydronaphthalenol
6-Isopropyldecalol
2-Naphthalenol, decahydro-6-(1-methylethyl)-
Decatol

History:

Initial reviews:	June 1979, April 1989	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A

Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Ford, R.A., (1988), Food and Chemical Toxicology 26, 367.

Jasmine absolute (grandiflorum)

CAS N°: 8022-96-6
8024-43-9
90045-94-6
84776-64-7

Empirical formula: N/A

Synonyms: Jasmine absolute (*Jasminum grandiflorum L.)*
Jasminum grandiflorum absolute
Jasmin officinale var. grandiflorum

History:

Initial reviews:	New Standard	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

For a description of the categories, refer to the QRA Informational Booklet.

Category 1 See Note box (1)	0.04 %	Category 7	0.1 %
Category 2	0.05 %	Category 8	1.5 %
Category 3	0.22 %	Category 9	5.0 %
Category 4	0.7 %	Category 10	2.5 %
Category 5	0.4 %	Category 11	Not Restricted (2)
Category 6 See Note box (1)	1.1 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) http://www.iofiorg.org/.

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Jasmine absolute (grandiflorum)

Contribution from other sources: N/A

Critical effect: Sensitization

RIFM Summaries:

EC3 value from one LLNA (not the mean) (µg/cm2)	Potency Classification Based on Animal Data[1]	Human Data			WoE NESIL[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	NOEL – HMT (induction) (µg/cm²)	LOEL[2] (induction) (µg/cm²)	
1475	Weak	1475 [4]	NA	2069	1470

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[2] Data derived from HRIPT or HMT
[3] WoE NESIL limited to three significant figures
[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Jasmine Absolute Grandiflorum and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 1470 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of Jasmine Absolute Grandiflorum in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 1972. Human Maximization Test. RIFM report number 1804, November 1c (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1977. Human Maximization Test. RIFM report number 1702, May 4a (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1980. Human Maximization Test. RIFM report number 1791, November 6 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2006. Local Lymph Node Assay. RIFM report number 53024, May 19 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2007. Human Repeated Insult Patch Test. RIFM report number 52893, May 18 (RIFM, Woodcliff Lake, NJ, USA).

Jasmine absolute (sambac)

CAS N°: 91770-14-8 **Empirical formula:** N/A

Synonyms: *Jasmin sambac* extract

History:			
	Initial reviews:	New Standard	
	Current revision date:	2008	
	Implementation date:	For new submissions*:	August 16, 2008
		For existing fragrance compounds*:	August 16, 2010
	Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

For a description of the categories, refer to the QRA Informational Booklet.

Category 1 See Note box (1)	0.25 %	Category 7	0.7 %
Category 2	0.32 %	Category 8	2.0 %
Category 3	1.33 %	Category 9	5.0 %
Category 4	4.0 %	Category 10	2.5 %
Category 5	2.1 %	Category 11	Not Restricted (2)
Category 6 See Note box (1)	6.4 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) http://www.iofiorg.org/.

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: **Sensitization**

Jasmine absolute (sambac)

RIFM Summaries:

EC3 value from one LLNA (not the mean) (µg/cm2)	**Potency Classification** Based on Animal Data[1]	**Human Data**			**WoE NESIL**[3] (µg/cm^2)
		NOEL – HRIPT (induction) (µg/cm^2)	**NOEL – HMT** (induction) (µg/cm^2)	**LOEL**[2] (induction) (µg/cm^2)	
9100	Weak	8858 [4]	NA	NA	8850

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[2] Data derived from HRIPT or HMT
[3] WoE NESIL limited to three significant figures
[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Jasmine absolute Sambac and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 8850 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of Jasmine absolute Sambac in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 2006. Local Lymph Node Assay. RIFM report number 52885, November 16 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2007. Human Repeated Insult Patch Test. RIFM report number 52897, May 15 (RIFM, Woodcliff Lake, NJ, USA).

Lemon oil cold pressed

CAS N°: 8008-56-8

Synonyms:

History: Initial reviews: October 1975, June 1992

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:		
Skin contact products:	2% (excl. rinse-off prod.)	
Leave-on products:		Rinse-off products: *Including household cleaning products*
Non skin contact products:	No limitation	
Note box:		
Fragrance material specifications:		

For applications on areas of skin exposed to sunshine, excluding bath preparations, soaps and other products which are washed off the skin, lemon oil cold pressed should not be used such that the level in the consumer products exceeds 2%.

Note: See remark on phototoxic ingredients in the introduction to the Standards (Appendix 8 to the IFRA Code of Practice) and the Standard on Citrus oil and other furocoumarins containing essential oils.

For qualities of the expressed oil in which the less volatile components have been concentrated by partial or total removal of the terpene fraction, this limit should be reduced in proportion to the degree of concentration.

References:

These recommendations are based on results of RIFM on the phototoxicity of lemon oil cold pressed (Fd. Cosm. Toxicol. 12,725(1974), its low bergapten content (C.K. Shu et al. VI Int. Congress of Essential oils 1974) and the observed no-effect level of pooled samples in tests using the animal model (private communication to IFRA).

Lime oil expressed

CAS N°: 8008-26-2

Synonyms:

History: Initial reviews: October 1975, June 1992

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:		
Skin contact products:	0.7% (excl. rinse-off prod.)	
Leave-on products:		Rinse-off products: *Including household cleaning products*
Non skin contact products:	No limitation	
Note box:		
Fragrance material specifications:		

For applications on areas of skin exposed to sunshine, excluding bath preparations, soaps and other products which are washed off the skin, lime oil expressed should not be used such that the level in the consumer products exceeds 0.7%.

Note: See remark on phototoxic ingredients in the introduction to the Standards (Appendix 8 to the IFRA Code of Practice) and the Standard on Citrus oil and other furocoumarins containing essential oils.

For qualities of the expressed oil in which the less volatile components have been concentrated by partial or total removal of the terpene fraction, this limit should be reduced in proportion to the degree of concentration.

References:

These recommendations are based on results of RIFM on the phototoxicity of lime oil expressed (Fd. Cosm. Toxicol. 12,731(1974), its bergapten content reported in J.A.O.A.C.52,(4),727(1969) and the observed no-effect level of pooled samples in tests using the animal model (private communication to IFRA).

Limonene

CAS N°: 138-86-3

Synonyms:

History: Initial reviews: December 1995

RECOMMENDATION: SPECIFICATION

d-, *l*-and *dl*-Limonene and natural products containing substantial amounts of it, should only be used when the level of peroxides is kept to the lowest practical level, for instance by adding antioxidants at the time of production. Such products should have a peroxide value of less than 20 millimoles peroxides per liter, determined according to the FMA method, which can be downloaded from the IFRA website (see Analytical Methods).

References:

This recommendation is based on the published literature, mentioning sensitizing properties when containing peroxides and oxidation products. (D.L.J. Opdyke(1975), Fd. Cosmet. Toxicol. 13,825).

Linalool

CAS N°: 78-70-6
126-90-9 (d-linalool)
126-91-0 (l-linalool)

Empirical formula: $C_{10}H_{18}O$

Synonyms: Coriandrol
2,6-Dimethyl-2,7-octadien-6-ol
3,7-Dimethyl-1,6-octadien-3-ol
Licareol
Linalol
Linalyl alcohol
1,6-Octadien-3-ol, 3,7-dimethyl (CAS)

History:

Initial reviews:	New Standard	
Current revision date:	November 2003	
Implementation date:	For new submissions*:	May 6, 2004
	For existing fragrance compounds*:	May 6, 2005
Next review date	November 2008	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: SPECIFICATION

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	
Non skin contact products:	N/A		

Note box:

Fragrance material specifications:	Limit peroxide level to 20 mmol/l. Linalool and natural products known to be rich in linalool, such as bois de rose, coriander or ho wood oil, should only be used when the level of peroxides is kept to the lowest practical level. It is recommended to add antioxidants at the time of production of the raw material. The addition of 0.1% BHT or alpha-tocopherol for example has shown great efficiency. The maximum peroxide level for products in use should be 20 mmol/l. The (hydro) peroxide content can be determined by using the

Linalool

FMA method.

Contribution from other sources: See fragrance material specification.

Critical effect: **Sensitization***

*Pure linalool is not a sensitizer while hydroperoxides and other oxidation products have shown sensitizing properties.

One of the major oxidation products of linalool was isolated and identified as 7-hydroperoxy-3,7-dimethyl-octa-1,5-diene-3-ol. In sensitization studies in guinea pigs, linalool of high purity gave no reactions, while linalool that had been oxidized for 10 weeks sensitized the animals. It was concluded that autoxidation of linalool is essential for its sensitizing potential (Skold et al., 2002).

REXPAN Rationale / Conclusion:

The GMP recommended by IFRA have been noted and approved by REXPAN, (November 17, 2003).

References:

M.Skold, A.Borje, M.Matura and A.-T.Karlberg., 2002. Studies on the autoxidation and sensitizing capacity of the fragrance chemical linalool, identifying a linalool hyperperoxide. Contact Dermatitis, 46(5), 267-272.

M.Skold, A.Borje, M.Matura and A.-T.Karlberg., 2002. Sensitization studies on the fragrance chemical linalool, with respect to auto-oxidation. Contact Dermatitis, 46 (Suppl. 4), 20.

Massoia bark oil

CAS N°: 85085-26-3 **Empirical formula:** N/A

Synonyms: Cryptocarya massoio oil
Cryptocarya massoy bark extract
Cryptocarya massoy, ext.
Massoia bark oil (*Cryptocarya massoio*)

History:

Initial reviews:	N/A	
Current revision date:	N/A	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: See Note box

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or

Massoia bark oil

3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Reg. Tox & Pharm.*, 31, 166-181, 2000

Massoia lactone

CAS N°: 54814-64-1 **Empirical formula:** $C_{10}H_{16}O_2$

Synonyms: 2-Decen-1,5-lactone
(-)-2-Decenoic acid, 5-hydroxy, δ-lactone
(R)-5,6-Dihydro-6-pentyl-2H-pyran-2-one
5,6-Dihydro-6-pentyl-2H-pyran-2-one
5-Hydroxy-2-decenoic acid δ-lactone
2H-Pyran-2-one, 5,6-dihydro-6-pentyl-, (R)-
Massoi lactone

History:			
	Initial reviews:	N/A	
	Current revision date:	N/A	
	Implementation date:	For new submissions*:	N/A
		For existing fragrance compounds*:	N/A
	Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: See Note box

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.

Massoia lactone

This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Reg. Tox & Pharm*., 31, 166-181, 2000

Melissa oil (genuine Melissa officinalis L.)

CAS N°: 8014-71-9
84082-61-1

Empirical formula: N/A

Synonyms: Balm oil (Melissa officinalis L.)
Lemon balm oil
Melissa officinalis leaf oil
Melissa oil (Melissa officinalis L.)
Oil of balm

History:

Initial reviews:	July 2008 (43th Amendment)	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2011
Next review date	2014	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1 See Note box (1)	0.04 %	Category 7	0.11 %
Category 2	0.05 %	Category 8	1.40 %
Category 3	0.21 %	Category 9	5.00 %
Category 4	0.63 %	Category 10	2.50 %
Category 5	0.33 %	Category 11	See Note box (2)
Category 6 See Note box (1)	1.01 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry - www.iofiorg.org).

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Melissa oil (genuine Melissa officinalis L.)

Contribution from other sources: N/A

Critical effect: Sensitization

RIFM Summaries:

LLNA weighted mean EC3 values (µg/cm²) [No. Studies]	Potency Classification Based on Animal Data[2]	Human Data			WoE NESIL[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	NOEL – HMT (induction) (µg/cm²)	LOEL[1] (induction) (µg/cm²)	
4500 [1] [5]	Weak	1470[4]	NA	NA	1400

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available

[1] Data derived from HRIPT or HMT
[2] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[3] WoE NESIL limited to two significant figures
[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL
[5] EC3 value from one LLNA, not the mean.

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Melissa oil and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 1400 mg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of Melissa oil in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 2001. Human repeated insult patch test. Unpublished study from Robertet, 21 February. Report number 36641. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2008a. Local Lymph Node Assay. Unpublished study from Robertet. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2008b. Human repeated insult patch test. Unpublished study from Robertet. (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2009 Repeated insult patch test on melissa oil in humans. Unpublished summary report from Robertet, June 2009 (RIFM, Woodcliff Lake, NJ, USA).

p-Mentha-1,8-dien-7-al (Perilla aldehyde)

CAS N°: 2111-75-3 **Empirical formula:** $C_{10}H_{14}O$

Synonyms: 1-Cyclohexene-1-carboxaldehyde, 4-(1-methylethenyl)-
Dihydrocuminic aldehyde
4-Isopropenylcyclohex-1-ene-1-carbaldehyde
4-Isopropenyl-1-cyclohexene-1-carboxaldehyde
p-Mentha-1,8-dien-7-al
Perilla aldehyde
Perillaldehyde

History:

Initial reviews:	Oct. 1979, July 1994	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1	See Note box (1)	Category 7	0.1 %
Category 2	0.03 %	Category 8	0.1 %
Category 3	0.1 %	Category 9	0.1 %
Category 4	0.1 %	Category 10	0.1 %
Category 5	0.1 %	Category 11	Not Restricted (2)
Category 6	See Note box (1) 0.5 %		

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) (http://www.iofiorg.org/).

p-Mentha-1,8-dien-7-al (Perilla aldehyde)

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Contribution from other sources: See **Annex I**

Critical effect: **Sensitization**

RIFM Summaries:

LLNA weighted mean EC3 values ($\mu g/cm^2$) [No. Studies]	Potency Classification Based on Animal Data[1]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – HMT (induction) ($\mu g/cm^2$)	LOEL[2] (induction) ($\mu g/cm^2$)	
2175 [2]	Moderate	709[4]	690[4]	2760	700

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[2] Data derived from HRIPT or HMT
[3] WoE NESIL limited to three significant figures
[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for p-Mentha-1,8-dien-7-al and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 700 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of p-Mentha-1,8-dien-7-al in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 1978. Human Maximization Tests. RIFM report number 1698, August 25 and November 21a (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1979. Human Maximization Test. RIFM report number 1697, August 31 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2007. Human Repeated Insult Patch Test. RIFM report number 53802, October 3 (RIFM, Woodcliff Lake, NJ, USA).

p-Mentha-1,8-dien-7-al (Perilla aldehyde)

RIFM (Research Institute for Fragrance Materials, Inc.), 2008. Local Lymph Node Assay. RIFM report 54428 (RIFM, Woodcliff Lake, NJ, USA).

Roberts, D.W., Patlewicz, G., Kern, P.S., Gerberick, F., Kimber, I., Dearman, R.J., Ryan, C.A., Basketter, D.A., Aptula, A.O., 2007. Mechanistic applicability domain classification of a local lymph node assay dataset for skin sensitization. *Chemical Research in Toxicology* 20, 1019-1030.

Menthadiene-7-methyl formate

CAS N°: 68683-20-5 **Empirical formula:** $C_{12}H_{18}O_2$

Synonyms: Cyclohexadiene-1-ethanol, 4-(1-methylethyl)-, formate
Isobergamate
4-(Isopropyl)cyclohexadiene-1-ethyl formate
2-(4-Isopropylcyclohexadienyl)ethyl formate
Menthadienyl formate
4-(1-Methylethyl)cyclohexadiene-1-ethyl formate

History:

Initial reviews:	Feb. 1986 (16th Amendment) , July 1994 (28th Amendment)	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1 See Note box (1)	0.03 %	Category 7	0.08 %
Category 2	0.04 %	Category 8	0.1 %
Category 3	0.1 %	Category 9	0.1 %
Category 4	0.1 %	Category 10	0.1 %
Category 5	0.1 %	Category 11	Not Restricted (2)
Category 6 See Note box (1)	0.8 %		

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) (http://www.iofiorg.org/).

Menthadiene-7-methyl formate

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards).**

Critical effect: Sensitization

RIFM Summaries:

LLNA weighted mean EC3 values ($\mu g/cm^2$) [No. Studies]	Potency Classification Based on Animal Data[1]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – HMT (induction) ($\mu g/cm^2$)	LOEL[2] (induction) ($\mu g/cm^2$)	
>2025	Weak	1063[4]	690[4]	6900	1060

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[2] Data derived from HRIPT or HMT
[3] WoE NESIL limited to three significant figures
[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Menthadiene-7-methyl formate and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 1060 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of Menthadiene-7-methyl formate in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22,2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 1977. Human Maximization Test. RIFM report number 1691, July 1b (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1978a. Human Maximization Test. RIFM report number 1698, April 28 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1978b. Human Maximization Test. RIFM report number 1787, October 26 (RIFM, Woodcliff Lake, NJ, USA).

Menthadiene-7-methyl formate

RIFM (Research Institute for Fragrance Materials, Inc.), 1979. Human Maximization Tests. RIFM report number 1775, September 11 and December 7 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2007. Human Repeated Insult Patch Test. RIFM report number 53723, August 22a (RIFM, Woodcliff Lake, NJ, USA).

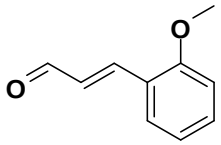
RIFM (Research Institute for Fragrance Materials, Inc.), 2008. Local Lymph Node Assay. DRAFT RIFM data, report 54429 (RIFM, Woodcliff Lake, NJ, USA).

o-Methoxycinnamaldehyde

CAS N°: 1504-74-1 **Empirical formula:** $C_{10}H_{10}O_2$

Synonyms: 2'-Methoxycinnamaldehyde
ortho-Methoxycinnamic aldehyde
β-(o-Methoxyphenyl)acrolein
3-(2-Methoxyphenyl)acrylaldehyde
3-(o-Methoxyphenyl)-2-propenal
2-Propenal, 3-(2-methoxyphenyl)-

Structure:



History:

Initial reviews:	New Standard	
Current revision date:	June 20, 2011	
Implementation date:	For new submissions*:	August 20, 2011
	For existing fragrance compounds*:	August 20, 2012
Next review date:	2016	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: RESTRICTED

RESTRICTIONS:

Limits in the finished product:			
Category 1 See Note box (1)	0.03%	Category 7	0.08%
Category 2	0.04%	Category 8	1.01%
Category 3	0.15%	Category 9	5.00%
Category 4	0.45%	Category 10	2.50%
Category 5	0.24%	Category 11	See Note box (2)
Category 6 See Note box (1)	0.72%		

Note box:
(1) See the IFRA Code of Practice (Appendix 8, Introduction to the IFRA Standards) regarding the Note on Oral Care Products and other products with the potential of ingestion.
(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Indicative contribution from other sources: See Annex I

Critical effect: Sensitization

o-Methoxycinnamaldehyde

RIFM Summaries:

LLNA weighted mean EC3 values (µg/cm²) [no. studies]	Potency Classification Based on Animal Data[2]	Human Data[2]			WoE NESIL[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	NOEL – HMT (induction) (µg/cm²)	LOEL (induction) (µg/cm²)	
NA	Weak	NA	2760	NA	1000

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[2]Data derived from HRIPT or HMT.
[3]WoE NESIL limited to two significant figures. A default value based on the LLNA data for α-butylcinnamaldehyde (CAS 7492-44-6) was employed because the material is used a very low volume and there are no HRIPT data.

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for *o*-methoxycinnamaldehyde and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 1000 µg/cm², which is a default value based on the LLNA data for a structurally related material, α-butylcinnamaldehyde (CAS 7492-44-6). They recommend the limits for the 11 different product categories, which are the acceptable use levels of *o*-methoxycinnamaldehyde in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the publication by Api *et al*., 2008.

References:

Api AM, Basketter DA, Cadby PA, Cano M-F, Ellis G, Gerberick G, et al. Dermal Sensitization Quantitative Risk Assessment (QRA) For Fragrance Ingredients. *Regulatory Toxicology and Pharmacology* 2008;52(1): 3-23.

7-Methoxycoumarin

CAS N°: 531-59-9 **Empirical formula:** $C_{10}H_8O_3$

Synonyms: 2H-1-Benzopyran-2-one, 7-methoxy-
Herniarin

History:

Initial reviews:	June 1979, April 1989	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2009
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material as such should not be used as a fragrance ingredient for any application.

On the basis of established maximum levels of this substance in commercially available natural sources (like essential oils, extracts and absolutes), exposure to this substance from the use of these oils and extracts is regarded acceptable as long as the level of 7-Methoxy-coumarin in the finished product **does not exceed 100 ppm**. Furthermore, these natural extracts should not be used as substitutes for this substance.

Examples for potential natural sources (with indicative maximum levels) of 7-Methoxycoumarin are:

- Camomilla matricaria EO 0,1 %
- Camomilla matricaria absolute (volatile part) : 5 %
- Lavandin absolute: 5 % (on the total absolute).
- Lavander and lavandin essential oils : <0,02 %
- Lavender absolute: 5 % (on the total absolute).
- Lime cold pressed oil: 0,1 %
- Tarragon absolute: volatile part: 5 %
- Tarragon essential oil : <0,1 %

Fragrance material specifications: N/A

7-Methoxycoumarin

Contribution from other sources: N/A

Critical effect: **Sentitization / Photo Sensitization**

REXPAN Rationale / Conclusion:

Based on the findings of RIFM on the potential for this material to induce allergic and photoallergic reactions (R.A. Ford et al. (1988), Fd. Chem. Toxic 26,375) **the material as such is prohibited for use in fragrance compounds.**

References:

R.A. Ford et al. (1988), *Fd. Chem. Toxic.* 26, 375

Methoxy dicyclopentadiene carboxaldehyde (Scentenal)

CAS N°: 86803-90-9 **Empirical formula:** $C_{12}H_{18}O_2$

Synonyms: 4,7-Methano-1H-indene-2-carboxaldehyde, octahydro-5-methoxy
8-Methoxytricyclo[5.2.2.1]decane-4-carboxaldehyde
Scentenal

History:

Initial reviews:	May 1998, May 2007 (42nd Amendment)	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1	See Note box (1)	Category 7	0.4 %
Category 2	0.2 %	Category 8	0.5 %
Category 3	0.5 %	Category 9	0.5 %
Category 4	0.5 %	Category 10	0.5 %
Category 5	0.5 %	Category 11	Not Restricted (2)
Category 6	See Note box (1)	3.6 %	

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) (http://www.iofiorg.org/).

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Methoxy dicyclopentadiene carboxaldehyde (Scentenal)

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards).**

Critical effect: Sensitization

RIFM Summaries:

Methoxy dicyclopentadiene carboxaldehyde - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values ($\mu g/cm^2$) [No. Studies]	Potency Classification [2]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – MAX (induction) ($\mu g/cm^2$)	LOEL[1] (induction) ($\mu g/cm^2$)	
>2500	Weak	5000 (DEP)	NA	NA	5000

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available
[1] Data derived from HRIPT or Human Max Test
[2] Gerberick *et al.*, 2001
[3] WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for methoxy dicyclopentadiene carboxaldehyde and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 5000 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of methoxy dicyclopentadiene carboxaldehyde in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161.

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

RIFM (Research Institute for Fragrance Materials, Inc.), 1997. Repeated insult patch test of methoxy dicyclopentadiene carboxaldehyde in human subjects. Unpublished report

Methoxy dicyclopentadiene carboxaldehyde (Scentenal)

from Firmenich, Inc., 23 January. RIFM report number 30026. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2001. Murine local lymph node assay with methoxy dicyclopentadiene carboxaldehyde. Unpublished report from Firmenich, Inc., 8 October. RIFM report number 42120. (RIFM, Woodcliff Lake, NJ, USA).

2-Methoxy-4-methylphenol

CAS N°: 93-51-6 **Empirical formula:** $C_8H_{10}O_2$

Synonyms: Creosol
p-Creosol
p-Cresol, 2-methoxy-
Homoguaiacol
1-Hydroxy-2-methoxy-4-methylbenzene
4-Hydroxy-3-methoxytoluene
2-Methoxy-p-cresol
3-Methoxy-4-hydroxytoluene
4-Methylguaiacol
p-Methylguaiacol
4-Methyl-2-methoxyphenol
Phenol, 2-methoxy-4-methyl-
Valspice

History:

Initial reviews:	January 1999, April 2005 (39th Amendment, new format only), May 2007 (42nd Amendment)	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1 See Note box (1)	0.003 %	Category 7	0.009 %
Category 2	0.004 %	Category 8	0.01 %
Category 3	0.01 %	Category 9	0.01 %
Category 4	0.01 %	Category 10	0.01 %
Category 5	0.01 %	Category 11	Not Restricted (2)
Category 6 See Note box (1)	0.09 %		

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.

2-Methoxy-4-methylphenol

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) (http://www.iofiorg.org/).

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards).**

Critical effect: Sensitization

RIFM Summaries:

2-Methoxy-4-methylphenol - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values ($\mu g/cm^2$) [No. Studies]	Potency Classification [2]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – MAX (induction) ($\mu g/cm^2$)	LOEL[1] (induction) ($\mu g/cm^2$)	
1450	Weak	118	NA	NA	118

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available
[1] Data derived from HRIPT or Human Max Test
[2] Gerberick *et al.*, 2001
[3] WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for 2-methoxy-4-methylphenol and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 118 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of 2-methoxy-4-methylphenol in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

2-Methoxy-4-methylphenol

References:

Basketter, D. A., Gilmour, N., Dearman, R. J., Kimber, I., Ryan, C. A., Gerberick, E., 2003. Classification of skin sensitisation potency using the Local Lymph Node Assay. The Toxicologist, 72(S-1), 101.

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161.

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

RIFM (Research Institute for Fragrance Materials, Inc.), 1998. Repeated insult patch test of 2-methoxy-4-methylphenol in human subjects. RIFM report number 33100, June 15. (RIFM, Woodcliff Lake, NJ, USA).

α-Methyl anisylidene acetone

CAS N°: 104-27-8

Empirical formula: $C_{12}H_{14}O_2$
$H_3CO\text{-}C_6H_4\text{-}CH{=}CH\text{-}CO\text{-}CH_2\text{-}CH_3$

Synonyms: 1-(p-Methoxyphenyl)-1-penten-3-one
p-Methoxystyryl ethyl ketone
alpha-Methylanisalacetone
1-Penten-3-one, 1-(4-(methoxyphenyl)-
Ethone

History:

Initial reviews:	November 1977, May 1980	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	
Non skin contact products:	N/A		

Note box:

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Sentitization**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Opdyke, D.L.J. (1979), Food and Chemical Toxicology 17, 863.

alpha-Methyl-1,3-benzodioxole-5-propionaldehyde (MMDHCA)

CAS N°: 1205-17-0

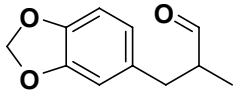
Empirical formula: $C_{11}H_{12}O_3$

Synonyms: Heliofolal, Heliogan, Helional, Tropional (commercial names)

1,3-Benzodioxole-5-propanal, α-methyl-

3-(1,3-Benzodioxol-5-yl)-2-methylpropanal

Structure:



2-Methyl-3-(3,4-methylenedioxyphenyl)- propionaldehyde

2-Methyl-3-(3,4-methylenedioxyphenyl)propanal

α-Methyl-3,4-(methylenedioxy)-hydrocinnamaldehyde

α-Methyl-1,3-benzodioxole-5-propanal

α-Methyl-1,3-benzodioxole-5-propionaldehyde

3-(3,4-Methylenedioxyphenyl)-2-methylpropanal

α-Methyl-3,4-methylene-dioxyhydrocinnamic aldehyde

History:

Initial reviews:	New Standard	
Current revision date:	June 11, 2010	
Implementation date:	For new submissions*:	August 11, 2010
	For existing fragrance compounds*:	August 11, 2011
Next review date:	2015	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:			
Category 1 See Note box (1)	0.34%	Category 7	0.89%
Category 2	0.43%	Category 8	2.0%
Category 3	1.78%	Category 9	5.0%
Category 4	5.3%	Category 10	2.5%
Category 5	2.8%	Category 11	See Note box (2)
Category 6 See Note box (1)	8.6%		

Note box:
(1) See the IFRA Code of Practice (Appendix 8, Introduction to the IFRA Standards) regarding the Note on Oral Care Products and other products with the potential of ingestion.
(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

alpha-Methyl-1,3-benzodioxole-5-propionaldehyde (MMDHCA)

Indicative contribution from other sources: None known at the time of the publication of the Standard

---

Critical effect: Sensitization

RIFM Summaries:

LLNA weighted EC3 values (µg/cm²) [no. studies]	Potency Classification Based on Animal Data[1]	Human Data[2]			WoE NESIL[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	NOEL – HMT (induction) (µg/cm²)	LOEL (induction) (µg/cm²)	
4100 [1][4]	Weak	11,811	13,800	15,000	11,800

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[2]Data derived from HRIPT or HMT.
[3]WoE NESIL limited to two significant figures.
[4]EC3 value from one LLNA, not the mean.

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for α-methyl-1,3-benzodioxole-5-propionaldehyde and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 11,800 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of α-methyl-1,3-benzodioxole-5-propionaldehyde in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the publication by Api *et al*., 2008.

References:

Api AM, Basketter DA, Cadby PA, Cano M-F, Ellis G, Gerberick GF, et al. Dermal Sensitization Quantitative Risk Assessment (QRA) For Fragrance Ingredients. *Regulatory Toxicology and Pharmacology* 2008;52(1): 3-23.

RIFM (Research Institute for Fragrance Materials, Inc.), 2009. Human repeated insult patch test. RIFM report number 57514, July 16. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2005. Local Lymph Node Assay. RIFM report number 50886, November 7. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2002. Human repeated insult patch test. Unpublished study from IFF, Inc., November 19. Report number 46969. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1985. Maximization study in humans. RIFM report number 1919, January 7c. (RIFM, Woodcliff Lake, NJ, USA).

α-Methyl cinnamic aldehyde

CAS N°: 101-39-3 **Empirical formula:** $C_{10}H_{10}O$

Synonyms: α-Methylcinnamaldehyde
α-Methylcinnamyl aldehyde
α-Methylcinnamic aldehyde
2-Methyl-3-phenyl-2-propenal
3-Phenyl-2-methylacrolein
2-Propenyl, 2-methyl-3-phenyl-

History:

Initial reviews:	New Standard	
Current revision date:	2007	
Implementation date:	For new submissions*:	June 16, 2007
	For existing fragrance compounds*:	June 16, 2009
Next review date	2012	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1	See Note box (1)	Category 7	0.3 %
Category 2	0.1 %	Category 8	2.0 %
Category 3	0.5 %	Category 9	5.0 %
Category 4	1.6 %	Category 10	2.5 %
Category 5	0.8 %	Category 11	See Note box (2)
Category 6	See Note box (1) 2.5 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) Further information about IOFI can be found on its website (http://www.iofiorg.org/).

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

α-Methyl cinnamic aldehyde

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards).**

Critical effect: Sensitization

RIFM Summaries:

alpha-Methyl cinnamic aldehyde - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values ($\mu g/cm^2$) [No. Studies]	Potency Classification [2]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – MAX (induction) ($\mu g/cm^2$)	LOEL[1] (induction) ($\mu g/cm^2$)	
1125 [1]	Extremely weak	3543	5517	NA	3500

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available
[1] Data derived from HRIPT or Human Max Test
[2] Gerberick *et al.*, 2001
[3] WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for alpha-methyl cinnamic aldehyde and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 3500 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of alpha-methyl cinnamic aldehyde in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Elahi, E. N., Wright, Z., Hinselwood, D., Hotchkiss, S. A. M., Basketter, D. A.,Pease, C. K. S., 2004. Protein binding and metabolism influence the relative skin sensitization potential of cinnamic compounds. Chemical Research in Toxicology, 17(3), 301-310.

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161.

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

RIFM (Research Institute for Fragrance Materials, Inc.), 1973. Report on human

maximization studies. RIFM report number 1802, July 10 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2003. Repeated insult patch test with alpha-methylcinnamaldehyde. RIFM report number 47264, February 28 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2003a. Repeated insult patch test with alpha-methylcinnamaldehyde. RIFM report number 47265, February 28 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2004. Repeated insult patch test with alpha-methylcinnamaldehyde. RIFM report number 45133, March 11 (RIFM, Woodcliff Lake, NJ, USA).

6-Methylcoumarin

CAS N°: 92-48-8 **Empirical formula:** $C_{10}H_8O_2$

Synonyms: 2H-1-Benzopyran-2-one, 6-methyl
6-Methyl-2h-1-benzopyran-2-one
6-Methylbenzopyrone
6-Methyl coumarin
6-Methyl-cis-o-coumarinic lactone
5-Methyl-2-hydroxyphenylpropenoic acid lactone
Toncarine

History:

Initial reviews:	March 1978, October 1978, February 1980
Current revision date:	September 2002
Implementation date:	For new submissions*:
	For existing fragrance compounds*:
Next review date	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:			
Skin contact products:			
Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	
Non skin contact products:	N/A		
Note box:			
Fragrance material specifications:	N/A		

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Photoallergy**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

6-Methylcoumarin

References:

Kaidbay, K.H. &. Kligman, A.M. (1978), Contact Dermatitis 4, No 5, 277.
Opdyke, D.L.J. (1979), Food and Cosmetics Toxicology 17, 275.

7-Methylcoumarin

CAS N°: 2445-83-2 **Empirical formula:** $C_{10}H_8O_2$

Synonyms: 2H-1-Benzopyran-2-one, 7-methyl-
7-Methyl-2-H-1-benzopyran-2-one

History:			
	Initial reviews:	February 1979, May 1983	
	Current revision date:	September 2002	
	Implementation date:	For new submissions*:	N/A
		For existing fragrance compounds*:	N/A
	Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications:

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards**).

Critical effect: **Sensitization and Photoallergy**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Opdyke, D.L.J., Letizia, C.S. (1982), Food and Chemical Toxicology 20, 747.

Methyl crotonate

CAS N°: 623-43-8

Empirical formula: $C_5H_8O_2$
CH_3-OOC-CH=CH-CH_3

Synonyms: 2-Butenoic acid, methyl ester, (E)-
Methyl trans-2-butenoate

History:	Initial reviews:	March 1978, May 1980	
	Current revision date:	September 2002	
	Implementation date:	For new submissions*:	N/A
		For existing fragrance compounds*:	N/A
	Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:			
Skin contact products:			
Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	
Non skin contact products:	N/A		
Note box:			
Fragrance material specifications:	N/A		

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards**).

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Opdyke, D.L.J. (1979), Food and Cosmetics Toxicology 17, 865.

4-Methyl-7-ethoxycoumarin

CAS N°: 87-05-8 **Empirical formula:** $C_{12}H_{12}O_3$

Synonyms: 2H-1-Benzopyran-2-one, 7-ethoxy-4-methyl-
Coumarin, 7-ethoxy-4-methyl-
7-Ethoxy-4-methylcoumarin
4-Methyl-7-ethoxybenzopyrone
Maraniol

History:

Initial reviews:	June 1979
Current revision date:	September 2002
Implementation date:	For new submissions*:
	For existing fragrance compounds*:
Next review date	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:			
Skin contact products:			
Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	
Non skin contact products:	N/A		
Note box:			
Fragrance material specifications:	N/A		

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards**).

Critical effect: **Photoallergy**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Private communication to IFRA.

Methyl eugenol

CAS N°: 93-15-2

Empirical formula: $C_{11}H_{14}O_2$
$CH_3O\text{-}C_6H_3(OCH_3)\text{-}CH_2\text{-}CH{=}CH_2$

Synonyms:
Eugenyl methyl ether
Methyl eugenol ether
Allylveratrole
Veratrole methyl ether
4-Allyl-1,2-dimethoxybenzene
Benzene, 1,2-dimethoxy-4-(2-propenyl)-
1,2-Dimethoxy-4-allylbenzene
1,2-dimethoxy-4-(2-propenyl)- benzene

History:

Initial reviews:	New Standard	
Current revision date:	N/A	
Implementation date:	For new submissions*:	July 3, 2002
	For existing fragrance compounds*:	July 3, 2003
Next review date	July 2007	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: See Note box

Rinse-off products: See Note box
Including household cleaning products

Non skin contact products: See Note box

Note box:

The Standard is based on long-term systemic effects and will therefore have a wider range of product type limitations as follows:
Fine fragrance: 0.02%
Eau de toilette: 0.008%
Fragrancing cream: 0.004%
Other leave on: 0.0004%
Rinse-off: 0.001%
Non skin (as defined in the introduction to the Standards): 0.02%*
Other non cosmetic products not covered above: 0.001%

*The limit of 0.02% applies to the concentration in the fragrance compound (see exposure calculation)

Methyl eugenol

The limitations apply to Methyleugenol (ME) originating from all sources. Contributions from essential oils can be significant. Names of essential oils, which should also be considered in the application of the Standard, are given below. Maximum percentage of the reference material is included for use when no analytical data is available.

Fragrance material specifications:

Contribution from other sources:
Contributions from essential oils (See also **Annex 1**)

Pimenta berry oil or leaf oil	< 15%	Basil oil	< 6%
Bay oil	< 4%	Rose oil	< 3.5%
Citronella oil	< 2%	Estragon oil	< 1.5%
Lovage leaf oil	< 1.5%	Cascarilla oil	< 1%
Hyssop oil	< 1%	Savory winter oil	< 1%
Nutmeg oil	< 1%	Calamus oil	< 1%
Clove oil	< 0.5%	Cananga oil	< 0.5%
Carrot oil	< 0.5%	Mace oil	< 0.5%
Cassia oil	< 0.1%		

This list is only indicative and should not be regarded as comprehensive. Maximum limits have been given. Variations to lower levels can result due to variations of species and time of harvest etc. It is recommended to base calculations on analytical data.

Critical effect: **Potential carcinogenic activity in animals**

RIFM Summaries:

The currently available metabolic, biochemical and toxicological data found for ME in laboratory species provide clear evidence of non-linearity in the dose-response relationship for ME with respect to metabolic activation and mechanisms associated with carcinogenic effects. Consideration of these data indicates a No-observed-Effect-Level for ME in the rat in the dose-range of 1-10 mg/kg body weight/day.
(Position Statement on Methyl Eugenol and Estragole as attached)

REXPAN Rationale / Conclusion:

Based on the lower end of the NOEL and applying a 1000 times safety factor for systemic effects a daily dose for ME of 60 µg/day is supported. Taking into account a dermal penetration factor of 40% leads to an acceptable dose of 150 µg/day.

This daily dose, applying the calculation table for dermal exposure as attached (contained in the Criteria Document), results in the maximum concentrations for ME in certain product categories as outlined in the section ‘limits’ of this Standard.

Methyl eugenol

Calculation table for dermal exposure

PRODUCT TYPE	Quantity per application g	Exposure events/day	Estimated retention factor	Skin surface residue of product g per day	Perfume level %	Skin surface residue of fragrance mg/event	Skin surface residue fragrance mg/day	Skin surface residue in body weight µg/kg b.w./d
BODY LOTION	8.00	0.71	1	5.68	0.40	32.0	22.7	378.0
FACE CREAM	0.80	2.0	1	1.60	0.30	2.4	4.8	80.0
EAU DE TOILETTE*	0.75	1.0	1	0.75	8.00	60.0	60.0	1000.0
PERFUME EXTRACTS*	0.30	1.0	1	0.30	20.0	60.0	60.0	1000.0
FRAGRANCING CREAM**	5.00	0.29	1	1.45	4.00	200.0	58.0	967.0
ANTI-PERSPIRANT/ DEODORANT	0.50	1.0	1	0.50	5.00	5.0	5.0	83.0
SHAMPOO	8.00	1.0	0.01	0.08	0.50	0.4	0.4	7.0
BATH PRODUCTS	17.00	0.29	0.001	0.005	2.00	0.34	0.1	2.0
SHOWER GEL	5.00	1.07	0.01	0.0535	1.20	0.6	0.6	10.0
TOILET SOAP	0.80	6.0	0.01	0.048	1.50	0.12	0.7	12.0
HAIR SPRAY	5.00	2.0	0.01	0.1	0.50	0.25	0.5	8.0
TOTAL				10.566				2547.0

*not used concurrently

**a cream designed for fragrance delivery

References:

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

Enclosure:

1. Position Statement on Methyl eugenol (attachment 1)
2. Calculation of finished product concentration for Methyl eugenol (attachment 2)

Research Institute for Fragrance Materials, Inc.
2 University Plaza, Suite 406,
Hackensack, New Jersey 07601-6209 USA
Phone: 201-488-5527 FAX: 201-488-5594

POSITION STATEMENT ON METHYL EUGENOL AND ESTRAGOLE: SAFETY WITH RESPECT TO USE AS FRAGRANCE INGREDIENTS (ADDED AS SUCH AND AS COMPONENTS OF NATURAL OILS)

INTRODUCTION

The Methyl Eugenol/Estragole Working Group of Scientific Experts (see attached list for composition) evaluated the current toxicological, metabolic, pharmacokinetic and exposure data for methyl eugenol (ME) and estragole (E) at a two-day Workshop sponsored by The Research Institute for Fragrance Materials and The Flavor and Extract Manufacturer's Association held in Washington, DC, May 1-2, 2000. The evaluation addressed questions raised by the issuance of the National Toxicology Program (NTP) Draft report of a chronic bioassay of ME in rats and mice. In particular the review raised major questions regarding the adequacy of the NTP study to address the safety assessment of ME, particularly at the low levels of exposure associated with its use as a fragrance ingredient. A summary of the outcome of this workshop has been previously circulated (see attached).

Since the safety review undertaken at the workshop focused on the exposure to ME when it was used as a component of essential oils and did not include exposure from its deliberate addition as such, that evaluation is regarded as being incomplete.

A second meeting of a sub-group of the original Working Party (referred to hereinafter) as the "Steering Group" was convened in New York on December 7-8, 2000 for the purposes of (1) to further discuss and determine exposure to ME from its use as such and as an ingredient of essential oils and (2) to identify and map out a sequence of further toxicology and metabolic/pharmacokinetic studies that were judged to be needed to assess definitively the safety of ME to humans at very low levels of exposure. The Steering Group also reviewed in detail a publication from the National Institutes of Environmental Health dealing with human biomonitoring studies, which have established the presence and levels of ME in the general U.S. population (Barr *et al.*, 2000, Environmental Health Perspectives, 108(4), 323-328).

EXPOSURE TO ME FROM FRAGRANCED PRODUCTS

The data for ME and E added as such (see Tables 1 and 2, respectively) are for average levels (using values greater than 1 ppm) and are for the 50 and 97.5 percentile use of fragrance compounds in fine fragrances. The data for ME and E in essential oils were similarly derived from typical essential oils containing ME and E in fine fragrances. Tables 1 and 2 also give the estimated total skin exposure from the use of multiple cosmetic products containing ME and E (added as such, from essential oils and total fragrance use).

TABLE 1: SUMMARY OF METHYL EUGENOL EXPOSURE IN FRAGRANCED PRODUCTS

Methyl Eugenol	Methyl Eugenol In Fragrance Compounds		Total Methyl Eugenol Human Dermal Exposure[3]	
	50th %ile	97.5%ile	50th %ile	97.5%ile
Added As Such[1]	0.061%	0.43%	1.55 μg/kg/day	11.21 μg/kg/day
From Essential Oils[2]	0.003%	0.05%	0.07 μg/kg/day	1.3 μg/kg/day
TOTAL			1.62 μg/kg/day	12.51 μg/kg/day

1 Reported by IFRA, August 30, 1999 (data from 2 members; 24/72 formulae contained ME directly added to fragrance compounds)

2 Reported by IFRA, October 19, 1999 (data from 6 members; typical essential oils containing ME in fine fragrances that were sold at more than 50 kg in 1998)

3 Calculated by exposure table detailed in Ford *et al*., 2000, Regulatory Toxicology and Pharmacology, 31, 166-181.

TABLE 2: SUMMARY OF ESTRAGOLE EXPOSURE IN FRAGRANCED PRODUCTS

Estragole	Estragole In Fragrance Compounds		Total Estragole Human Dermal Exposure[3]	
	50th %ile	97.5%ile	50th %ile	97.5%ile
Added As Such[1]	0.04%	0.8%	1.1 μg/kg/day	20.4 μg/kg/day
From Essential Oils[2]	0.02%	0.3%	0.5 μg/kg/day	7.6 μg/kg/day
TOTAL			1.6 μg/kg/day	28.0 μg/kg/day

1 Reported by IFRA, March 9, 1999 (data from 4 members; 739/2570 formulae contained E directly added to fragrance compounds)

2 Reported by IFRA, April 2, 2000 (data from 8 typical essential oils containing E in fine fragrances)

3 Calculated by exposure table detailed in Ford *et al*., 2000, Regulatory Toxicology and Pharmacology, 31, 166-181.

SAFETY ASSESSMENT OF ME IN FRAGRANCED PRODUCTS

For the purpose of the safety assessment of ME in fragranced products, the total human dermal exposure has been assumed to be 12.5 microgram/kg body weight/day. This is an extremely conservative assumption since it is derived from the 97.5 percentile use and it assumes 100% bioavailability through percutaneous absorption, which remains highly unlikely.

The currently available metabolic, biochemical and toxicological data found for ME in laboratory species provide clear evidence of non-linearity in the dose-response relationships for ME and E with respect to metabolic activation and mechanisms associated with the carcinogenic effects. Consideration of this data indicates, that in all probability, a No-Observed-Effect-Level (NOEL) for ME in the rat exists in the dose-range of 1-10 mg/kg body weight/kg. If the combined exposure to ME from its use in fragrance products (added as such and from essential oils) is taken as the conservative estimate of 12.5 microgram/kg body weight/day, then the margin of safety can be calculated to be in the range of 80-800, according to the NOEL. In the case of estragole there is metabolic evidence that the NOEL is likely to be significantly higher, perhaps in the region of 10-100 mg/kg. Thus, for a similar exposure, the margin of safety would be on the order of 360-3600.

CONCLUSION

Based on the available data, the ME Steering Group concluded, consistent with the conclusion from the May Meeting of the Working Group, that neither ME or E is likely to present a human cancer risk at current levels of exposure arising from their addition to fragranced products (added as such or from essential oils). However, in making this judgment, the ME Working Group also concluded that it is essential to undertake additional studies to characterize the lower-end of the dose-response curves for metabolic and toxicity endpoints. In addition, sub-chronic and chronic studies should be undertaken in order to characterize the NOEL at low levels of exposure and where damage to the glandular stomach does not occur as a confounding factor. This future work will allow a more reliable risk assessment to be based on proper hazard identification data.

The May Meeting of the Working Group agreed that NTP bioassays are hazard identifications, not safety assessments. The WG noted that NTP bioassays may provide relevant data for safety assessment, if they are appropriately designed and conducted. It was concluded that the data from this NTP bioassay were not adequate for assessing the safety of methyl eugenol at the very low levels of exposure consistent with its use as a flavoring substance or fragrance ingredient.

Approved by the RIFM EXPERT PANEL
May 7, 2001
Helmut A. Greim, Chairperson
David R. Bickers
Peter Calow
Jon M. Hanifin
Adrianne E. Rogers
Jean H. Saurat
I. Glenn Sipes
Robert L. Smith
Hachiro Tagami

International Workshop on p-Alkoxyallylbenzene Derivatives – Methyl Eugenol and Estragole

Ritz Carlton Hotel
Tyson's Corner, Virginia
May 1 and 2, 2000

Chairman of the Workshop	Dr. Robert Smith	Imperial College School of Medicine London, United Kingdom
Panel Moderators		
Metabolism/Pharmacokinetics/ Detoxication/Intoxication Mechanisms	Dr. Philip Portoghese	University of Minnesota Minneapolis, Minnesota
Toxicology/Pathology	Dr. Adrianne Rogers[*]	Boston University School of Medicine Boston, Massachusetts
Assessment of Exposures	Dr. Ron Walker	University of Surrey Surrey, United Kingdom
Researchers	Dr. Kamal Abdo[*∞]	National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina
	Dr. Tim Adams[*]	Flavor and Extract Manufacturers' Association (FEMA), District of Columbia
	Dr. Anne Marie Api[*]	The Research Institute for Fragrance Materials (RIFM), Hackensack, New Jersey
	Dr. John Bucher[∞]	National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina
	Dr. John Caldwell[*]	Imperial College School of Medicine London, United Kingdom
	Dr. Mike Cunningham[*∞]	National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina
	Dr. Jay Goodman[*]	Michigan State University East Lansing, Michigan
	Dr. Thomas Guenthner[*]	University of Illinois Chicago, Illinois
	Dr. Gerry Kenna[*]	Astra-Zeneca Corporation London, United Kingdom
	Dr. Jim Knaak[*]	State University of New York at Buffalo Buffalo, New York
	Dr. Scott Masden[*∞]	National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina
	Dr. Glenn Sipes[*]	University of Arizona Tucson, Arizona
	Dr. Ladd Smith	The Research Institute for Fragrance Materials (RIFM), Hackensack, New Jersey

[*] Presenters
[∞] NTP representatives were in attendance, but were not involved in any way in the preparation of the report.

Methyl Eugenol Steering Committee

December 7-8, 2000
RIFM Offices

Chairman of the Steering Committee	Dr. Robert Smith	Imperial College School of Medicine London, United Kingdom
	Dr. Tim Adams	Flavor and Extract Manufacturers' Association (FEMA), District of Columbia
	Dr. Anne Marie Api	The Research Institute for Fragrance Materials (RIFM), Hackensack, New Jersey
	Dr. John Caldwell	Imperial College School of Medicine London, United Kingdom
	Dr. Lawrence J. Marnett*	Vanderbilt University Nashville, Tennessee
	Dr. Adrianne Rogers	Boston University School of Medicine Boston, Massachusetts
	Dr. Glenn Sipes	University of Arizona Tucson, Arizona

* Not present at the December 2000 Steering Committee Meeting

IFRA - INTERNATIONAL FRAGRANCE ASSOCIATION
49, Square Marie-Louise
B - 1000 Brussels, Belgium

CALCULATION OF FINISHED PRODUCT CONCENTRATION FOR METHYLEUGENOL

NOEL: 1 mg/kg body weight/day (lower end of dose range) – based on the evaluation of the RIFM Working Group of Scientific Experts

Applying a safety factor of 1000 for systemic effects leads to an acceptable dose of 1μg/kg body weight/day

Taking into account **40% dermal penetration** results in an acceptable dose of **2,5** μg/kg body weight /day for Methyleugenol
(1μg/kg body weight/day = 0,4 x 2,5 μg/kg body weight /day)

This corresponds to 150 μg/day Methyleugenol for a typical 60 kg person.

Based on the exposure table as given in the RIFM Criteria Document percentages are assigned to the contributions of certain product categories to the total exposure of a fragrance compound / ingredient per day:

Body lotion:	0.378 mg/kg body weight /day correspond to 14,84% of the total daily exposure of 2,547 mg/kg body weight /day
Face cream	3.14%
EdT	39.26%
(Fine fragrance	39.26%; not used concurrently with EdT)
Fragrancing cream	37.96%
Antiperspirant	3.26%
Shampoo	0.27%
Bath products	0.0785%
Shower gel	0.3926%
Toilet Soap	0.47%
Hair Spray	0.314%
	100%

Using these percentages the daily exposure of 150 μg Methyleugenol for a typical 60 kg person is split up as follows:

Body lotion	22,26 μg/day (= 14.84% of 150 μg/day)
Face cream	4,71
EdT	58,89
(Fine fragrance	58,89)
Fragrancing cream	56,94
Antiperspirant	4,89
Shampoo	0,405
Bath products	0,11775
Shower gel	0,5889
Toilet Soap	0,705
Hair spray	0,471

Conversion via the amounts of products applied to skin per day results in the following maximum concentrations of ME in the finished product (%).

Explanation: The skin surface residue for body lotion per day is 5.68g/day, the amount of ME per day contributed via the application of a body lotion has been calculated 22,26 μg/day (see above); the percentage therefore is

$$\text{Body Lotion} \qquad \frac{22{,}26\ \mu g/day}{5.68\ g/day \times 10^6} \times 100\% = 0.00039\%$$

Face cream	0.000294	
EdT	**0.00785**	**rounded: 0.008**
Fine fragrance	**0.01963**	**rounded: 0.02**
Fragrancing cream	**0.00392**	**rounded: 0.004**
Antiperspirant	0.000978	
Shampoo	0.000506	
Bath products	0.002355	
Shower gel	0.0011	
Toilet soap	0.001468	
Hair spray	0.000471	

Body Lotion, face cream, antiperspirant and hair spray are summarized to result in 21.55% of the total exposure as **leave on products** with a limit of **0.0004**.

Rinse off products (shampoo, bath products, shower gel, toilet soap) contribute altogether 1.21% to the total exposure, with a limit of 0.00097 **rounded to 0.001**.
The same limit is applied to all household products (except those defined as non-skin contact products) on the basis that at these levels, incremental exposure from these products would not significantly increase the over-all per capita exposure to Methyleugenol.

CALCULATIONS FOR NON-SKIN CONTACT PRODUCT LEVEL
It is assumed that for non-skin contact products there will only be occasional and accidental (that means little or no) skin contact. The limit is therefore set at the maximum allowed for skin products i.e. 0.02%. To take account of inhalation from some classes of non-skin products (see calculation below for candles) this figure should be applied to the concentration in the fragrance compound.

<u>Exposure calculation for ME from candles:</u>

Limit of 0.02% ME in the fragrance oil used in the candle.

Assume a 5% fragrance load in the candle and a content of 0.02% ME
5% x 0.0002 = 0.001% ME

Assume a candle burn rate of 5 grams/hour during 4 hour exposure (per day) and also assume that all of the ME contained enters the atmosphere:
5g x 0.001% = 0.00005g ME
0.00005g x 4 hours = 0.0002 grams ME/day

Assume room size of 2,5 x 2,5 x 3m (18.75 cubic m)
0.2 mg/18.75 m^3 = 0.011 mg/m^3 = 11 µg/m^3 = 0.011 µg/l ME (per day)

Assume human respiratory volume 1000 litres/hr
1000 litres/hr x 4 hours = 4000 litres
0.011 µg/l x 4000 litres = 0.044 mg ME

Assume 10% lung deposition
0.044 mg ME x 10% = 0.0044 mg ME / 60kg person = 0.073 µg/kg ME exposure
This would result in a safety factor of around 14000.

6-Methyl-3,5-heptadien-2-one (Methyl heptadienone)

CAS N°: 1604-28-0 **Empirical formula:** $C_8H_{12}O$

Synonyms: 3,5-Heptadien-2-one, 6-methyl-
Methylheptadienone
2-Methylhepta-2,4-dien-6-one
6-Methylhepta-3,5-dien-2-one

History:

Initial reviews:	April 1989, April 1999	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2011
Next review date	2014	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1 See Note box (1)	0.002 %	Category 7	0.002 %
Category 2	0.002 %	Category 8	0.002 %
Category 3	0.002 %	Category 9	0.002 %
Category 4	0.002 %	Category 10	0.002 %
Category 5	0.002 %	Category 11	See Note box (2)
Category 6 See Note box (1)	0.100 %		

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be re-evaluated again.

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) (http://www.iofiorg.org/).

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

6-Methyl-3,5-heptadien-2-one (Methyl heptadienone)

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards).**

Critical effect: **Sensitization**

RIFM Summaries:

LLNA weighted mean EC3 values ($\mu g/cm^2$) [No. Studies]	Potency Classification Based on Animal Data[2]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – HMT (induction) ($\mu g/cm^2$)	LOEL[1] (induction) ($\mu g/cm^2$)	
> 1250 [1][4]	Weak	118	NA	1299	110

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1] Data derived from HRIPT or HMT
[2] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[3] WoE NESIL limited to two significant figures
[4] EC3 value from one LLNA, not the mean

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for 6-Methyl-3,5-heptadiene-2-one and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 110 mg/cm2. They recommend the limits for the 11 different product categories, which are the acceptable use levels of 6-Methyl-3,5-heptadiene-2-one in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 2008a. Local Lymph Node Assay. RIFM report number 55564, July 30. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2008b. Human repeated insult patch test. RIFM report number 55345, August 5. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2008c. Human repeated insult patch test. RIFM report number 55661, November 24a. (RIFM, Woodcliff Lake, NJ, USA).

Methyl heptine carbonate

CAS N°: 111-12-6 **Empirical formula:** $C_9H_{14}O_2$

Synonyms: Methyl heptyne carbonate
Methyl 2-octynoate
MHC
2-Octynoic acid, methyl ester
Folione

History:

Initial reviews:	October 1976, April 2000, April 2005 (39th Amendment, new format only)	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

For a description of the categories, refer to the QRA Informational Booklet.

Category 1	See Note box (1)	Category 7	0.008 %
Category 2	0.004	Category 8	0.01 %
Category 3	0.01 %	Category 9	0.01 %
Category 4	0.01 %	Category 10	0.01 %
Category 5	0.01 %	Category 11	Not Restricted (2)
Category 6	See Note box (1)	0.08 %	

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) http://www.iofiorg.org/.

Methyl heptine carbonate

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

When used in the same fragrance compound within a specific QRA category, the sum total of methyl heptine carbonate (MHC) and methyl octine carbonate (MOC) contributions must not exceed the maximum permitted level for MHC. At the same time, the contribution from methyl octine carbonate should always respect the maximum levels permitted in the respective categories as listed in the Standard for MOC.
If the same compound is intended for more than one IFRA QRA category, then the most restrictive limitations (based on foreseen use concentrations and maximum permitted level) will apply.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards)

Critical effect: Sensitization

RIFM Summaries:

EC3 value from one LLNA (not the mean) (µg/cm2)	**Potency Classification** Based on Animal Data[1]	**Human Data**			**WoE NESIL**[3] (µg/cm^2)
		NOEL – HRIPT (induction) (µg/cm^2)	**NOEL – HMT** (induction) (µg/cm^2)	**LOEL**[2] (induction) (µg/cm^2)	
< 125	Strong	118 [4]	NA	194	110

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[2] Data derived from HRIPT or HMT
[3] WoE NESIL limited to three significant figures
[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for methyl heptine carbonate and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 110 mg/cm2. They recommend the limits for the 11 different product categories, which are the acceptable use levels of methyl heptine carbonate in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

Methyl heptine carbonate

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 1964. Human repeated patch test on methyl-2-nonynoate and isoeugenol. Unpublished report from IFF, Inc., 30 April. Report number 1808. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1989. Human repeated insult patch test of methyl 2-octynoate. RIFM report number 12368, November 16. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1990. Repeated insult patch test of methyl 2-octynoate in human subjects. RIFM report number 12452, April 27. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2005. Methyl 2-octynoate diluted with vehicle 1:3 EtOH:DEP: Local Lymph Node Assay. RIFM report number 48753, January 28. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2006. Methyl 2-octynoate: Local Lymph Node Assay. RIFM report number 51627, April 6. (RIFM, Woodcliff Lake, NJ, USA).

p-Methylhydrocinnamic aldehyde

CAS N°: 5406-12-2

Empirical formula:

Synonyms: Benzenepropanal, 4-methyl
p-Methyldihydrocinnamaldehyde
p-Methylhydrocinnamaldehyde
3-(4-Methylphenyl)propanal
3-p-Tolylpropionaldehyde

History:

Initial reviews:	Nov. 1987, July 1994, January 2002, May 2007 (42nd Amendment)	
Current revision date:	N/A	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A

Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: See Note box

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:

p-Methylhydrocinnamic aldehyde

1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Reg. Tox & Pharm.*, 31, 166-181, 2000

Methyl ionone, mixed isomers

CAS N°: 1335-46-2
127-42-4
127-43-5
127-51-5
7779-30-8

Empirical formula: $C_{14}H_{22}O$

Synonyms:
1335-46-2 Methyl ionone, mixture of isomers
127-42-4 Methyl-alpha-ionone
alpha-Cetone
alpha-Cyclocitrylidenebutanone
alpha-Cyclocitrylidenemethyl ethyl ketone
Methyl-a-ionone
alpha-Methylionone
1-Penten-3-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, [R-(E)]-
(R-(E))-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)pent-1-en-3-one
127-43-5 Methyl-beta-ionone
Methyl-ß-ionone
beta-Methylionone
beta-Cetone
beta-Cyclocitrylidenebutanone
beta-Iraldeine
1-Penten-3-one, 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-
5-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-4-penten-3-one
1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)pent -1-en-3-one
127-51-5 alpha-iso methylionone
3-Buten-2-one, 3-methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-
3-Methyl-4-(2,6,6-trimethyl-2-cyclohexen-1-yl)-3-buten-2-one
alpha-Isomethyl ionone
gamma-Methylionone
Iraldeine gamma
Isoraldeine 95
7779-30-8 1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)pent-1-en-3-one
1-Penten-3-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-

History:

Initial reviews:	2007 (42nd Amendment)	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

Methyl ionone, mixed isomers

RESTRICTIONS:

Limits in the finished product:

For a description of the categories, refer to the QRA Informational Booklet.

Category 1 See Note box (1)	2.0 %	Category 7	5.3 %
Category 2	2.6 %	Category 8	2.0 %
Category 3	10.6 %	Category 9	5.0 %
Category 4	31.7 %	Category 10	2.5 %
Category 5	16.7 %	Category 11	See Note Box (2)
Category 6 See Note box (1)	50.7 %		

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) http://www.iofiorg.org/.

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

The above limits apply to methyl ionone isomers used individually or in combination.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards).**

Critical effect: Sensitization

RIFM Summaries:

EC3 value from one LLNA (not the mean) (µg/cm2) [No. Studies]	**Potency Classification** Based on Animal Data[1]	**Human Data**			**WoE NESIL**[3] (µg/cm^2)
		NOEL – HRIPT (induction) (µg/cm^2)	**NOEL – HMT** (induction) (µg/cm^2)	**LOEL**[2] (induction) (µg/cm^2)	
5450	Weak	70866 [4]	NA	NA	70000

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available

Methyl ionone, mixed isomers

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[2] Data derived from HRIPT or HMT
[3] WoE NESIL limited to three significant figures
[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Methyl ionone, mixed isomers and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 70000 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of Methyl ionone, mixed isomers in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 2004a. Repeated insult patch test with alpha-iso-methylionone. RIFM report number 47278, March 10. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2004b. Repeated insult patch test with alpha-iso-methylionone. RIFM report number 47279, March 10. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2005. alpha-iso-Methylionone diluted with vehicle 1:3 EtOH:DEP: Local Lymph Node Assay. RIFM report number 48749, January 26. (RIFM, Woodcliff Lake, NJ, USA).

Methyl methacrylate

CAS N°: 80-62-6 **Empirical formula:** $C_5H_8O_2$

Synonyms: Methyl 2-methacrylate, 2-(methoxycarbonyl)-1-propene
Methyl 2-methyl-2-propenoate
2-Propenoic acid, 2-methyl-, methyl ester
MMA

History:

Initial reviews:	N/A	
Current revision date:	N/A	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: See Note box

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or

Methyl methacrylate

2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Reg. Tox & Pharm.*, 31, 166-181, 2000

Methyl N-methylanthranilate

CAS N°: 85-91-6 **Empirical formula:** $C_9H_{11}NO_2$

Synonyms: Benzoic acid, 2-(methylamino)-, methyl ester
Dimethyl anthranilate
2-Methylamino methyl benzoate
N-Methylanthranilic acid, methyl ester
Methyl 2-(methylamino)benzoate
Methyl 2-methylaminobenzoate
Methyl *o*-methylaminobenzoate

History:

Initial reviews:	October 1978, April 2001, January 2002, May 2006 (40th Amendment)	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2010
Next review date	2014	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	0.1%	Rinse-off products:	No restriction
		Including household cleaning products	

Non skin contact products: No restriction

Note box:

The Standard is set due to the phototoxic effects of the material. The limit only applies to applications on skin, excluding rinse-off products.

If combinations of phototoxic fragrance ingredients are used, the use levels have to be reduced accordingly. The sum of the concentrations of all phototoxic ingredients, expressed in % of their recommended maximum level in the consumer product shall not exceed 100.

The material has been identified for having the potential of forming nitrosamines in nitrosating systems. Downstream users therefore have to be notified of the presence of the material and its potential to be able to consider adequate protective measures.

Fragrance material specifications: N/A

Methyl N-methylanthranilate

Contribution from other sources: See **Annex I**

Critical effect: **Phototoxicity and potential for nitrosamine formation**

RIFM Summaries:
A human phototoxicity study at 0.5% in 75% ethanol/25% diethyl phthalate (DEP) resulted in 0/26 reactions (RIFM, 2001). Another human phototoxicity study with concentrations of 0.1, 0.3, and 0.5% resulted in 0/29 reactions (RIFM, 1998). Several other phototoxicity studies showed phototoxic reactions at 1% and 5% (Kaidbey and Kligman, 1980; Letizia and Api, 2003; RIFM, 1999).
A human photosensitization study at 0.5% in 75% ethanol/25% DEP resulted in 0/26 reactions (RIFM, 2001). Another human photosensitization study at 5.0% resulted in no photoallergic reactions. However, 14/18 phototoxic reactions were observed (RIFM, 1978a).

A phototoxicity study at 50% in methanol and 100% on hairless mice produced reactions at both dose levels (RIFM, 1978b).

An *in vitro* phototoxicity assay using a human skin model (Skin2®) with concentrations of methyl N-methylanthranilate ranging from 0.05% to 25% in corn oil showed that the material was phototoxic at dose levels above 5% (Api, 1997).

REXPAN Rationale / Conclusion:

IFRA measures regarding potential nitrosamine formation noted - REXPAN April 2009.

References:

Api A.M. (1997). In vitro assessment of phototoxicity. In Vitro Toxicology: Journal of Molec. Cell. Toxicol., 10(3), 339-350.

Kaidbey K.H. and Kligman A.M. (1980). Identification of contact photosensitizers by human assay. In Current Concepts In Cutaneous Toxicity, Academic Press, New York, pages 55-68.

Letizia C.S. and Api A.M. (2003). Evaluation of the phototoxic and photoallergenic potential of methyl N-methyl anthranilate. The Toxicologist, 72(S1), 378-379.

Research Institute for Fragrance Materials, Inc. (1978a). Phototoxicity and contact photoallergy testing in human subjects. RIFM report number 1788, 18 January.

Research Institute for Fragrance Materials, Inc. (1978b). Phototoxicity and irritation studies of mice and pigs with fragrance materials. RIFM report number 2042, 13 April.

Research Institute for Fragrance Materials, Inc. (1998). Evaluation of phototoxicity of dimethyl anthranilate in humans. RIFM report number 34768, 8 December.

Methyl N-methylanthranilate

Research Institute for Fragrance Materials, Inc. (1999). Evaluation of phototoxicity of dimethyl anthranilate in humans. RIFM report number 34769, 20 July.

Research Institute for Fragrance Materials, Inc. (2001) Evaluation of human photoallergy by repeated insult patch test. RIFM report number 36789, 1 March.

Nitrosamine policy as contained in the EU Cosmetics Directive 76/768/EEC and its Amendments.

Methyl β-naphthyl ketone

CAS N°: 93-08-3 **Empirical formula:** $C_{12}H_{10}O$ / $C_{10}H_7\text{-}CO\text{-}CH_3$

Synonyms:
2-Acetonaphthone
beta-Acetylnaphthalene
Cetone d
Ethanone, 1-(2-naphthalenyl) (CAS)
beta-Methyl naphthyl ketone
beta-Naphthyl methyl ketone
Oranger crystals

History:

Initial reviews:	New Standard	
Current revision date:	October 2004	
Implementation date:	For new submissions*:	May 12, 2005
	For existing fragrance compounds*:	May 12, 2006
Next review date	2009	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	0.2%	Rinse-off products:	No restriction
		Including household cleaning products	

Non skin contact products: No restriction

Note box:

The Standard is set due to phototoxic effects of the material. The limit only applies to applications on skin, excluding rinse-off products.
If combinations of phototoxic fragrance ingredients are used, the use levels have to be reduced accordingly. The sum of the concentrations of all phototoxic ingredients, expressed in % of their recommended maximum level in the consumer product shall not exceed 100.

Fragrance material specifications: N/A

Methyl β-naphthyl ketone

Contribution from other sources: None known

Critical effect: **Phototoxicity**

RIFM Summaries:

Human Studies
A human phototoxicity study with methyl-b-naphthyl ketone (concentrations of 0.1, 1 and 10% in 3:1 DEP:EOH) was conducted. No reactions indicative of primary irritation were observed in this study. However, under irradiated conditions, methyl-b-naphthyl ketone at10% in 3:1 DEP:EtOH produced moderate erythema in 5 subjects. These responses were stronger than those seen for the irradiated blank patch, which only produced slight to mild erythema. Under the conditions of the study, methyl-b-naphthyl ketone at 10% in 3:1 DEP:EtOH showed evidence of phototoxicity. Erythema scores for methyl-b-naphthyl ketone at 0.1% and 1.0% in 3:1 DEP:EtOH were similar to those seen for the blank patch under irradiated conditions. These reactions were not indicative of phototoxic responses (RIFM, 2004).

Other Studies
Methyl -b-naphthyl ketone has been observed to absorb in the UV range of 290-400 nm and is positive in the Neutral Red Uptake Phototoxicity Assay (RIFM, 2002). However, it has been shown to be non-phototoxic in guinea pigs at concentrations up to 60% in 3:1 EtOH:DEP (RIFM, 2003).

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for methyl -b-naphthyl ketone and recommended a limit of 0.2%, based on a no-effect level for phototoxicity in humans of 1% (May 18, 2004).

References:

Research Institute for Fragrance Materials, Inc. (2002). Methyl beta-naphthyl ketone: Neutral red uptake phototoxicity assay in BALB/C 3T3 mouse fibroblasts. RIFM report number 40279, May 30. (RIFM, Woodcliff Lake, NJ, USA).

Research Institute for Fragrance Materials, Inc. (2003). Topical photoallergy screening testvof â-methyl naphthyl ketone in male albino hairless guinea pigs including primary irritation, phototoxicity and contact hypersensitivity evaluations. RIFM report number 44882, June 9. (RIFM, Woodcliff Lake, NJ, USA).

Research Institute for Fragrance Materials, Inc. (2004). Evaluation of phototoxicity of methyl â-naphthyl ketone in humans. RIFM report number 45136, March 16. (RIFM, Woodcliff Lake, NJ, USA).

3-Methyl-2(3)-nonenenitrile

CAS N°: 53153-66-5 **Empirical formula:** $C_{10}H_{17}N$

Synonyms: 2-Nonenenitrile, 3-methyl-
Citgrenile

History:

Initial reviews:	February 1980, May 1983, May 2007 (42nd Amendment)	
Current revision date:	N/A	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: See Note box

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

3-Methyl-2(3)-nonenenitrile

References:

Human Health Criteria Document, *Reg. Tox & Pharm.*, 31, 166-181, 2000

Methyl octine carbonate

CAS N°: 111-80-8 **Empirical formula:** $C_{10}H_{16}O_2$

Synonyms: MOC
Methyl octyne carbonate
Methyl 2-nonynoate
2-Nonynoic acid, methyl ester

History:

Initial reviews:	March 1988, April 2000	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1 See Note box (1)	0.001 %	Category 7	0.002 %
Category 2	0.001 %	Category 8	0.002 %
Category 3	0.002 %	Category 9	0.002 %
Category 4	0.002 %	Category 10	0.002 %
Category 5	0.002 %	Category 11	Not Restricted (2)
Category 6 See Note box (1)	0.02 %		

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be re-evaluated again.

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) (http://www.iofiorg.org/).

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a

Methyl octine carbonate

restriction of the concentration of this fragrance ingredient in the finished product.

When used in the same fragrance compound within a specific QRA category, the sum total of methyl octine carbonate (MOC) and methyl heptine carbonate (MHC) contributions must not exceed the maximum permitted level for MHC. At the same time, the contribution from methyl octine carbonate should always respect the maximum levels permitted as listed in the table above.

If the same compound is intended for more than one IFRA QRA category, then the most restrictive limitations (based on foreseen use concentrations and maximum permitted level) will apply.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards).**

Critical effect: **Sensitization**

RIFM Summaries:

LLNA weighted mean EC3 value from one LLNA (not the mean) ($\mu g/cm^2$)	**Potency Classification** Based on Animal Data[1]	**Human Data**			**WoE NESIL**[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	**NOEL – HMT** (induction) ($\mu g/cm^2$)	**LOEL**[2] (induction) ($\mu g/cm^2$)	
< 1250 Estimated 625	Strong	24[4]	NA	118	24

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[2] Data derived from HRIPT or HMT
[3] WoE NESIL limited to three significant figures
[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Methyl octine carbonate and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 24 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of Methyl octine carbonate in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

Methyl octine carbonate

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 1989a. Repeated insult patch test of methyl octine carbonate in human subjects. RIFM report number 27280, May 22. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1989b. Human repeated insult patch test of methyl 2-octynoate and methyl 2-nonynoate. RIFM report number 12367, November 16. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1990a. Repeated insult patch test of methyl octine carbonate and t-2-hexenal in human subjects. RIFM report number 27822, January 9. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1990b. Repeat insult patch test of methyl 2-nonynoate in human subjects. RIFM report number 12454, April 27. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1990c. Repeat insult patch test of methyl 2-octynoate and methyl 2-nonynoate in human subjects. RIFM report number 12456, April 27. (RIFM, Woodcliff Lake, NJ, USA).

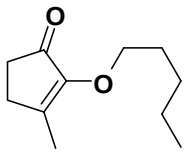
Ryan, C. A., Gerberick, G. F., Cruse, L. W., Basketter, D. A., Lea, L., Blaikie, L., Dearman, R. J., Warbrick, E. V., Kimber, I., 2000. Activity of human contact allergens in the murine local lymph node assay. *Contact Dermatitis*, 43(2), 95-102.

3-Methyl-2-(pentyloxy)cyclopent-2-en-1-one

CAS N°: 68922-13-4 **Empirical formula:** $C_{11}H_{18}O_2$

Synonyms: 2-Cyclopenten-1-one, 2-(pentyloxy)-3-methyl- Pentyloxy Cyclopentenone (trade name)

Structure:



History: Initial reviews: New Standard

Current revision date: June 20, 2011

Implementation date: For new submissions*: August 20, 2011

For existing fragrance compounds*: August 20, 2012

Next review date: 2016

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: RESTRICTED

RESTRICTIONS:

Limits in the finished product:			
Category 1 See Note box (1)	0.03 %	Category 7	0.08 %
Category 2	0.04 %	Category 8	1.11 %
Category 3	0.17 %	Category 9	5.00 %
Category 4	0.50 %	Category 10	2.50 %
Category 5	0.26 %	Category 11	See Note box (2)
Category 6 See Note box (1)	0.80 %		

Note box:

(1) See the IFRA Code of Practice (Appendix 8, Introduction to the IFRA Standards) regarding the Note on Oral Care Products and other products with the potential of ingestion.

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Indicative contribution from other sources: None known at the time of the publication of the Standard

---

Critical effect: Sensitization

3-Methyl-2-(pentyloxy)cyclopent-2-en-1-one

RIFM Summaries:

LLNA weighted mean EC3 values (µg/cm²) [no. studies]	Potency Classification Based on Animal Data[1]	Human Data[2]			WoE NESIL[4] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	NOEL – HMT (induction) (µg/cm²)	LOEL (induction) (µg/cm²)	
NA	NA	1181	NA	10%[3]	1100

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[2]Data derived from HRIPT or HMT.
[3]Conversion to µg/cm² was not possible due to absence of details
[4]WoE NESIL limited to two significant figures.

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for 3-Methyl-2-(pentyloxy)cyclopent-2-en-1-one and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 1100 µg/cm^2. They recommend the limits for the 11 different product categories, which are the acceptable use levels of 3-Methyl-2-(pentyloxy)cyclopent-2-en-1-one in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the publication by Api *et al*., 2008.

References:

Api AM, Basketter DA, Cadby PA, Cano M-F, Ellis G, Gerberick G, et al. Dermal Sensitization Quantitative Risk Assessment (QRA) For Fragrance Ingredients. *Regulatory Toxicology and Pharmacology* 2008;52(1): 3-23.

p-Methyltetrahydroquinoline

CAS N°: 91-61-2 **Empirical formula:** $C_{10}H_{13}N$

Synonyms: 6-Methyl-1,2,3,4-tetrahydroquinoline
Quinoline, 1,2,3,4-tetrahydro-6-methyl-
1,2,3,4-Tetrahydro-6-methylquinoline
Tetrahydro-*p*-methylquinoline

History:

Initial reviews:	New Standard	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2010
Next review date	2014	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	
Non skin contact products:	N/A		

Note box:

The material has been identified for having the potential of forming nitrosamines in nitrosating systems. Downstream users therefore have to be notified of the presence of the material and its potential to be able to consider adequate protective measures.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards**)

Critical effect: **Potential of nitrosamine formation**

REXPAN Rationale / Conclusion:

IFRA measures regarding potential nitrosamine formation noted - REXPAN April 2009.

References:

Nitrosamine policy as contained in the EU Cosmetics Directive 76/768/EEC and its Amendments.

Moskene (1,1,3,3,5-pentamethyl-4,6-dinitroindane)

CAS N°: 116-66-5 **Empirical formula:** $C_{14}H_{18}N_2O_4$

Synonyms: 1H-Indene, 2,3-dihydro-1,1,3,3,5-pentamethyl-4,6,-dinitro-
1,1,3,3,5-Pentamethyl-4,6-dinitroindane

History:

Initial reviews:	39th Amendment	
Current revision date:	N/A	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: See Note box

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

Moskene (1,1,3,3,5-pentamethyl-4,6-dinitroindane)

References:

Human Health Criteria Document, *Reg. Tox & Pharm.*, 31, 166-181, 2000

Musk ambrette

CAS N°: 83-66-9 **Empirical formula:** $C_{12}H_{16}N_2O_5$

Synonyms: Benzene, 1-(1,1-dimethylethyl)-2-methoxy-4-methyl-3,5-dinitro-
4-tert-Butyl-3-methoxy-2,6-dinitrotoluene
6-tert-Butyl-3-methyl-2,4-dinitroanisole
1-(1,1-Dimethylethyl)-2-methoxy-4-methyl-3,5-dinitrobenzene
2,6-Dinitro-3-methoxy-1-methyl-4-tert-butylbenzene
2,6-Dinitro-3-methoxy-4-tert-butyltoluene
2,4-Dinitro-3-methyl-6-tert-butylanisole

History:

Initial reviews:	June 1981, July 1994, December 1995	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	
Non skin contact products:	N/A		

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: **Photosensitization** and **Neurotoxicity**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

Musk ambrette

References:

Spencer, P.S., Bischoff-Fenton, M.C., Moreno, O.M., Opdyke D.L. and Ford, R.A. (1984), Toxicology and Applied Pharmacology 75, 571.

Musk Ketone

CAS N°: 81-14-1

Empirical formula: $C_{14}H_{18}N_2O_5$

Synonyms: 4'-*tert*-butyl-2',6'-dimethyl-3',5'-dinitroacetophenone

3,5-dinitro-2,6-dimethyl-4-*tert*-butyl-acetophenone

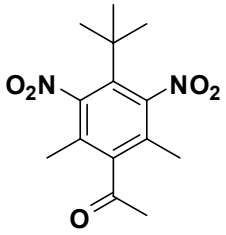
3,5-Dinitro-2,6-dimethyl-4-*tert*-butylacetophenone

1-(4-*tert*-Butyl-2,6-dimethyl-3,5-dinitrophenyl) ethanone

1-[4-(1,1-Dimethylethyl)-2,6-dimethyl-3,5-dinitrophenyl]ethanone

Ethanone, 1-[4-(1,1-dimethylethyl)-2,6-dimethyl-3,5-dinitrophenyl]-

Structure:



History:

Initial reviews:	New Standard	
Current revision date:	June 11, 2010	
Implementation date:	For new submissions*:	June 11, 2012
	For existing fragrance compounds*:	June 11, 2012
Next review date:	2015	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: SPECIFICATION

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A

Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Musk xylene (CAS 81-15-2), which has been prohibited for use in fragrance compounds for environmental reasons (vPvB), can be present in musk ketone as an impurity.

Fragrance material specifications:

Musk ketone should only be used if it contains less than 0.1% of musk xylene.

Indicative contribution from other sources: N/A

Critical effect: See note box

Musk Ketone

REXPAN Rationale / Conclusion:
IFRA policy on purity of musk ketone noted – REXPAN, February 2010.

References:

See Standard on musk xylene.

Musk tibetene (1-tert-butyl-2,6-dinitro-3,4,5-trimethylbenzene)

CAS N°: 145-39-1 **Empirical formula:** $C_{13}H_{18}N_2O_4$

Synonyms: Benzene, 1-(1,1-dimethylethyl)-3,4,5-trimethyl-2,6-dinitro-

---

History:

Initial reviews:	39th Amendment	
Current revision date:	N/A	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: See Note box

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Reg. Tox & Pharm.*, 31, 166-181, 2000

Musk xylene

CAS N°: 81-15-2 **Empirical formula:** $C_{12}H_{15}N_3O_6$

Synonyms: Benzene, 1-(1,1-dimethylethyl)-3,5-dimethyl-2,4,6-trinitro-
1-*tert*-Butyl-3,5-dimethyl-2,4,6-trinitrobenzene
Musk xylene
Musk xylol
2,4,6-Trinitro-1,3-methyl-5-*tert*-butylbenzene

History:			
	Initial reviews:	New Standard	
	Current revision date:	2009	
	Implementation date:	For new submissions*:	August 7, 2009
		For existing fragrance compounds*:	August 7, 2010
	Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:	
Risk Management Measures:	N/A
Note box:	
Fragrance material specifications:	N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards**)

Critical effect: **vPvB**

REXPAN Rationale / Conclusion:

Ongoing research on the fragrance ingredient musk xylene has provided evidence over time that it fulfills the criteria for being classified vPvB (Environmental half-life >180 days; BCF>5000).

Musk Xylene, as of October 8, 2008, has been identified by the European Chemicals Bureau as a material requiring authorization under REACH due to its properties as a vPvB

Based on its potential detrimental environmental impact the REXPAN has concluded that the material should not be used as a fragrance ingredient.

Musk xylene

References:

PBT draft Addendum to the final report (2005) of the Risk Assessment (PBT assessment), January 2008 (the Netherlands National Institute for Public health and Environment, RIVM).

ECHA (European Chemicals Agency, , Member State Committee, Substances of Very High Concern support document for identification of 5-tert-butyl-2,4,6-trinitro-m-xylene, Adopted on October 8, 2008 (http://echa.europa.eu/doc/candidate_list/svhc_supdoc_muskxylene_publication.pdf.)

Nitrobenzene

CAS N°: 98-95-3 **Empirical formula:** $C_6H_5NO_2$

Synonyms: Benzene, nitro
Nitrobenzol
Mirbane oil

History:

Initial reviews:	June 1974	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: **Acute toxicity and Skin toxicity**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Christensen, H.E., Toxic Substances List, National Institute for Occupational Safety and Health (1972), p. 369.

2,4-Nonadienal

CAS N°: 6750-03-4
(Including all geometric isomers)

Empirical formula: $C_9H_{14}O$

Synonyms: Nona-2,4-dienal

History:

Initial reviews:	New Standard	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2010
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A

Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: **Insufficient Data**

REXPAN Rationale / Conclusion:
The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

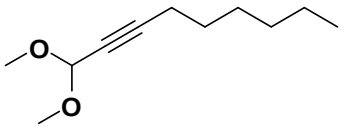
Human Health Criteria Document, *Regulatory Toxicology and Pharmacology*, 31, 166-181, 2000

2-Nonyn-1-al dimethyl acetal

CAS N°: 13257-44-8 **Empirical formula:** $C_{11}H_{20}O_2$

Synonyms: 1,1-Dimethoxynon-2-yne
2-Nonyn-1-al-Dimeth-Acetyl
2-Nonyne, 1,1-dimethoxy-
Parmavert

Structure:



History:	Initial reviews:	New Standard	
	Current revision date:	June 20, 2011	
	Implementation date:	For new submissions*:	August 20, 2011
		For existing fragrance compounds*:	August 20, 2012
	Next review date:	2016	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:			
Category 1 See Note box (1)	0.66 %	Category 7	1.74 %
Category 2	0.84 %	Category 8	2.00 %
Category 3	3.47 %	Category 9	5.00 %
Category 4	10.41 %	Category 10	2.50 %
Category 5	5.48 %	Category 11	See Note box (2)
Category 6 See Note box (1)	16.67 %		

Note box:
(1) See the IFRA Code of Practice (Appendix 8, Introduction to the IFRA Standards) regarding the Note on Oral Care Products and other products with the potential of ingestion.
(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Indicative contribution from other sources: None known at the time of the publication of the Standard

---

Critical effect: **Sensitization**

2-Nonyn-1-al dimethyl acetal

RIFM Summaries:

LLNA weighted mean EC3 values (µg/cm²) [no. studies]	Potency Classification Based on Animal Data[2]	Human Data[2]			WoE NESIL[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	NOEL – HMT (induction) (µg/cm²)	LOEL (induction) (µg/cm²)	
>5,000 [1]	Weak	23,622	NA	NA	23,000

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[2]Data derived from HRIPT or HMT.
[3]WoE NESIL limited to two significant figures.

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for 2-Nonyn-1-al dimethyl acetal and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 23,000 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of 2-Nonyn-1-al dimethyl acetal in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the publication by Api *et al*., 2008.

References:

Api AM, Basketter DA, Cadby PA, Cano M-F, Ellis G, Gerberick G, et al. Dermal Sensitization Quantitative Risk Assessment (QRA) For Fragrance Ingredients. *Regulatory Toxicology and Pharmacology* 2008;52(1): 3-23.

Nootkatone

CAS N°: 4674-50-4 **Empirical formula:** $C_{15}H_{22}O$

Synonyms: 5,6-Dimethyl-8-isopropenylbicyclo(4.4.0)dec-1-en-3-one
4a,5-Dimethyl-1,2,3,4,4a,5,6,7-octahydro-7-keto-3-isopropenylnaphthalene
4betaH,5alpha-Eremophila-1(10),11-dien-2-one
4betaH,5alpha-Eremorphila-1(10),11-dien-2-one
(4R-(4alpha,4a alpha,6beta))-4,4a,5,6,7,8-Hexahydro-4,4a-dimethyl-6-(1-methylvinyl)naphthalen-2(3H)-one
4,4a,5,6,7,8-Hexahydro-6-isopropenyl-4,4a-dimethyl-2(3H)-naphthalenone
2(3H)-Naphthalenone, 4,4a,5,6,7,8-hexahydro-4,4a-dimethyl-6-(1-methylethenyl)-,
(4R,4aS,6R)-

History:

Initial reviews:	October 1980	
Current revision date:	August 2005	
Implementation date:	For new submissions*:	Dec. 11, 2006
	For existing fragrance compounds*:	Dec. 11, 2007
Next review date	2009	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: SPECIFICATION

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	
Non skin contact products:	N/A		

Note box:

Fragrance material specifications:	Nootkatone used as a fragrance ingredient should be at least 98% pure, with a melting point of at least 32°C. Lower purity grades may not be used as a fragrance ingredient. Methods for the determination of purity of nootkatone are attached to this Standard.

Contribution from other sources: None to consider

Critical effect: Sensitization

Nootkatone

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the Standard on Nootkatone. After reviewing the critical effect data, the Panel concluded that only samples of Nootkatone that are at least 98% pure should be used. Lower purity grades may not be used as a fragrance ingredient. Sensitization was observed with the lower purity grades, but not with high purity material (>98% pure) samples of Nootkatone.

References:

Research Institute for Fragrance Materials, Inc., 1971. Sensitization and irritation study of nootkatone. Unpublished report from Givaudan, May 24, Report number 41820.

Research Institute for Fragrance Materials, Inc., 1977. Report on human maximization studies. RIFM report number 1702, June 6c.

Research Institute for Fragrance Materials, Inc., 1978. Report on human maximization studies. RIFM report number 1698, January 13a.

Research Institute for Fragrance Materials, Inc., 1979. Report on human maximization studies. RIFM report number 1775, September 11.

Research Institute for Fragrance Materials, Inc., 2005. Repeated insult patch test with nootkatone. Unpublished report from Bedoukian Research, Inc., May 11. Report number 46155.

Enclosure: Methods for purity determination of Nootkatone

Methods for purity determination of nootkatone

1) The purity of nootkatone could be determined by GLC determination, using the following parameters:
glass capillary column SP-2100, column temperature 75-220℃, programmed at 4℃/min.

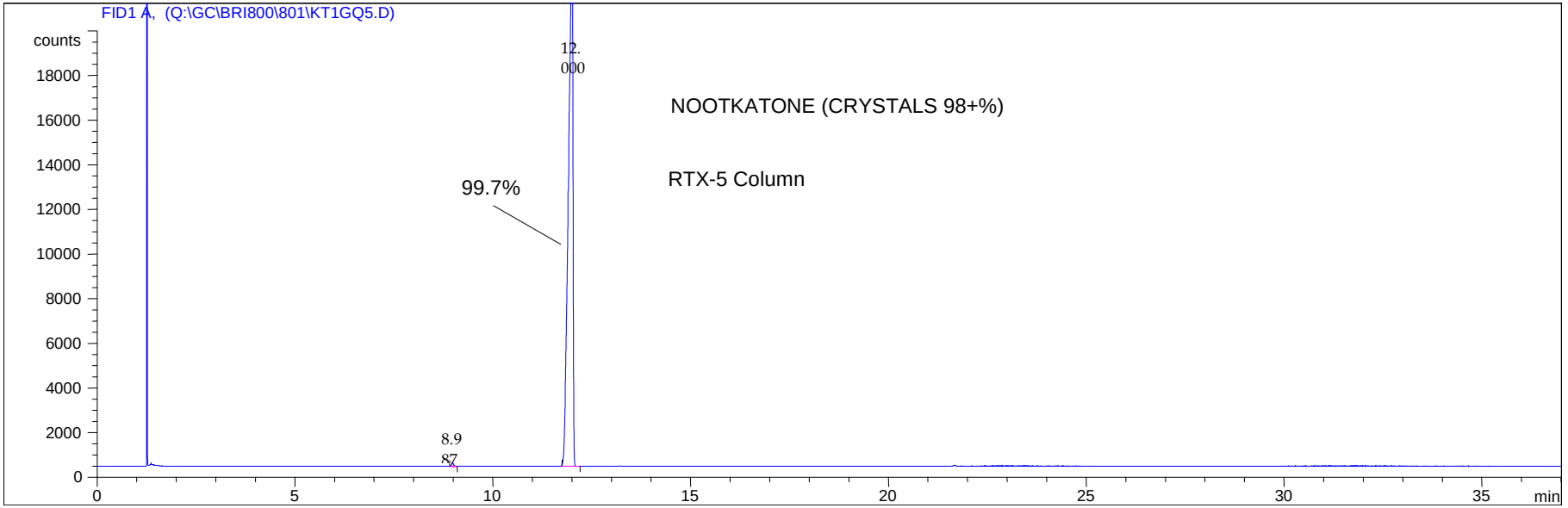
2) *Column type*: 30 meter RTX-5 capillary column (5% diphenyl-95% dimethyl polysiloxane), 0.25 mm ID, 0.25 micrometer film.

Analytical Conditions: FID Detector, Helium @ 25 psi head pressure used as carrier, Split ratio 150:1
Injector temperature= 250° C, Detector temperature= 300° C

Temperature program:

Initial oven temperature:	160° C
Initial time:	20 min.
Rate:	30°/min
Final oven:	220° C
Final time:	5 min.

Sample Preparation:
Sample injected by HP7373 Autosampler. Sample diluted 10% in acetone. Injection size is 0.1 ul.



Oakmoss extracts

CAS N°: 90028-68-5 = Evernia prunastri extract **Empirical formula:** N/A
9000-50-4 = oils, Oakmoss resinoid
68917-10-2 =oils, Oakmoss

Synonyms: Oakmoss absolute
Evernia absolute
Evernia prunastri, ext.
Mousse de Chêne absolute
Oakmoss absolute (*Evernia prunastri*)
Evernia prunastri (Oakmoss) extract

History:

Initial reviews:	April 1991, July 2001	
Current revision date:	2008	
Implementation date:	For new submissions*:	February 16, 2009
	For existing fragrance compounds*:	February 16, 2011
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED / SPECIFICATION**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1	See Note box (1)	Category 7	0.1 %
Category 2	0.03 %	Category 8	0.1 %
Category 3	0.1 %	Category 9	0.1 %
Category 4	0.1 %	Category 10	0.1 %
Category 5	0.1 %	Category 11	Not Restricted (2)
Category 6	See Note box (1)	0.5 %	

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.

In the presence of tree moss extracts, the level of oak moss in the respective category has to be reduced accordingly such that the total amount of both extracts does not exceed the maximum permitted level in each category as listed in the table above.
If the same compound is intended for more than one IFRA QRA category, then the most restrictive limitation (based on foreseen use concentrations and maximum

Oakmoss extracts

permitted level) will apply.

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) (http://www.iofiorg.org/).

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications:	Oak moss extracts used in fragrance compounds must not contain added tree moss, which is a source of resin acids. Traces of resin acids may be carried over to commercial qualities of oak moss in the manufacturing process. These traces must not exceed 0.1% (1000 ppm) dehydroabietic acid (DHA) in the extract. The concentration of resin acids in oak moss can be measured with an HPLC Reverse Phase – spectrofluorometry method. Further, levels of atranol and chloroatranol should each be below **100 ppm** in oak moss extracts.

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards).**

Critical effect: **Sensitization**

RIFM Summaries:

LLNA weighted mean EC3 values ($\mu g/cm^2$)	**Potency Classification** Based on Animal Data[1]	**Human Data**			**WoE NESIL**[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	**NOEL – HMT** (induction) ($\mu g/cm^2$)	**LOEL**[2] (induction) ($\mu g/cm^2$)	
970	Moderate	700[4]	1724[4]	1417	700

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[2] Data derived from HRIPT or HMT
[3] WoE NESIL limited to three significant figures

Oakmoss extracts

[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Oakmoss extracts and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 700 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of Oakmoss extracts in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 1973. Human Maximization Test. RIFM report number 1802, October 9a (RIFM, Woodcliff Lake, NJ, USA)

Research Institute for Fragrance materials, Inc. (1989). Human repeated insult patch test of oakmoss absolute. RIFM report number 12360, 31 October.

Research Institute for Fragrance Materials, Inc. (1989). Human repeated insult patch test of oakmoss absolute. RIFM report number 12361, 31 October.

Research Institute for Fragrance Materials, Inc. (1990). Human repeated insult patch test of oakmoss absolute. RIFM report number 12380, 1 March.

Research Institute for Fragrance Materials, Inc. (1990). Human repeated insult patch test on oakmoss absolute. RIFM report number 14118, 26 November.

RIFM (Research Institute for Fragrance Materials, Inc.), 2005. Local Lymph Node Assay. RIFM report number 50881, June 30 (RIFM, Woodcliff Lake, NJ, USA).

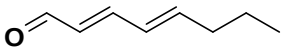
2,4-Octadienal

CAS N°: 30361-28-5
5577-44-6
(including all geometric isomers)

Empirical formula: $C_8H_{12}O$

Synonyms: Octa-2,4-dienal

Structure:



History:

Initial reviews:	New Standard	
Current revision date:	June 20, 2011	
Implementation date:	For new submissions*:	August 20, 2011
	For existing fragrance compounds*:	August 20, 2012
Next review date:	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A
Including household cleaning products

Non skin contact products: N/A

Note box:

Fragrance material specifications: N/A

Indicative contribution from other sources: None to consider

Critical effect: **Insufficient Data**

REXPAN Rationale / Conclusion:
The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) Presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) Adverse data on the material itself and/or
3) Adverse data for a structurally related material.

References:
Human Health Criteria Document, *Regulatory Toxicology and Pharmacology*, 31, 166-181, 2000

OTNE (1-(1,2,3,4,5,6,7,8 Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl) ethanone)

CAS N°: 54464-57-2 **Empirical formula:** $C_{16}H_{26}O$

Synonyms: 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-aphthalenyl)ethanone
1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthyl)ethan-1-one
Amberonne
Boisvelone
Isocyclemone E
Iso E super

History:

Initial reviews:	New Standard	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

For a description of the categories, refer to the QRA Informational Booklet.

Category 1 See Note box (1)	1.34 %	Category 7	3.6 %
Category 2	1.73 %	Category 8	2.0 %
Category 3	7.1 %	Category 9	5.0 %
Category 4	21.4 %	Category 10	2.5 %
Category 5	11.2 %	Category 11	Not Restricted (2)
Category 6 See Note box (1)	34.2 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) http://www.iofiorg.org/.

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

OTNE (1-(1,2,3,4,5,6,7,8 Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl) ethanone)

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards).**

Critical effect: Sensitization

RIFM Summaries:

EC3 value from one LLNA (not the mean) (µg/cm2)	**Potency Classification** Based on Animal Data[1]	**Human Data**			**WoE NESIL**[3] (µg/cm^2)
		NOEL – HRIPT (induction) (µg/cm^2)	**NOEL – HMT** (induction) (µg/cm^2)	**LOEL**[2] (induction) (µg/cm^2)	
6825	Weak	47 244 [4]	NA	NA	47 200

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[2] Data derived from HRIPT or HMT
[3] WoE NESIL limited to three significant figures
[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for OTNE and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 47200 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of OTNE in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 2004. Human Repeated Insult Patch Test with OTNE. RIFM report number 45124, June 28. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2005. Local Lymph Node Assay with OTNE. RIFM report number 51630, November 9. (RIFM, Woodcliff Lake, NJ, USA).

1-Octen-3-yl acetate

CAS N°: 2442-10-6

Empirical formula: $C_{10}H_{18}O_2$
CH_3-$[CH_2]_4$-CH(OOC-CH_3)-CH=CH_2

Synonyms:
3-Acetoxyoctene
Amyl crotonyl acetate
Amyl vinyl carbinyl acetate
1-Octen-3-ol, acetate
Octenyl acetate
beta-Octenyl acetate
n-Pentyl vinyl carbinol acetate

History:

Initial reviews:	July 1989, July 1994, May 2007 (42nd Amendment)	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1	See Note box (1)	Category 7	0.3 %
Category 2	0.1 %	Category 8	0.3 %
Category 3	0.3 %	Category 9	0.3 %
Category 4	0.3 %	Category 10	0.3 %
Category 5	0.3 %	Category 11	Not Restricted (2)
Category 6	See Note box (1)	2.5 %	

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry)

1-Octen-3-yl acetate

(http://www.iofiorg.org/).

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Contribution from other sources: See **Annex 1**

Critical effect: Sensitization

RIFM Summaries:

1-Octen-3-yl acetate - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values (µg/cm^2) [no. studies]	Potency Classification[2]	Human Data			WoE NESIL[3] (µg/cm^2)
		NOEL – HRIPT (induction) (µg/cm^2)	NOEL – MAX (induction) (µg/cm^2)	LOEL[1] (induction) (µg/cm^2)	
>7500 [1]	Extremely weak	3543	NA	6900	3500

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available
[1] Data derived from HRIPT or Human Max tests
[2] Gerberick *et al.*, 2001
[3] WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for 1-octen-3-yl acetate and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 3500 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of 1-octen-3-yl acetate in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161.

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

RIFM (Research Institute for Fragrance Materials, Inc.), 1974a. Report on human

maximization studies. Report to RIFM. RIFM report number 1779, June 06 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1974b. Report on human maximization studies. Report to RIFM. RIFM report number 1779, August 20 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1985. Report on human maximization studies. Report to RIFM. RIFM report number 1779, January 7a (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1988. Repeat insult patch test of 1-octen-3-yl acetate in human subjects. RIFM report number 8516, December 07 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2004. 1-Octen-3-yl acetate: Local Lymph Node Assay. Unpublished report from International Flavors and Fragrances, 13 December. Report number 47816 (RIFM, Woodcliff Lake, NJ, USA).

Opoponax

CAS N°:

History: Initial reviews: March 1978, July 1994

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:	
Skin contact:	0.6%
Non skin contact:	8%

Opoponax preparations, obtained from opoponax gums (the exudation from the bark of Commiphora erythraea var. glabrescens Engler) by solvent extraction or steam distillation, should not be used such that the level in consumer products exceeds 0.6%. This is equivalent to 3% in a fragrance compound used at 20% in the consumer product.

References:

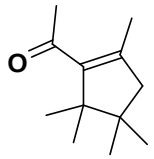
This recommendation is based on test results of RIFM with samples of resinoids, concretes, absolutes and oil of opoponax. Earlier samples showed limited sensitisation reactions when tested at 8% whereas tests on a larger number of more recent samples showed no sensitisation at 8% (private communication to IFRA).

1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl)ethan-1-one

CAS N°: 13144-88-2 **Empirical formula:** $C_{12}H_{20}O$

Synonyms: 2-Acetyl-1,3,3,4,4-pentamethyl-1-cyclopentene
Ethanone, 1-(2,4,4,5,5-pentamethyl-1-cyclopenten-1-yl)-
1-(2,4,4,5,5-Pentamethylcyclopent-1-en-1-yl)ethanone
Alpinone (trade name)

Structure:



History:

Initial reviews:	New Standard	
Current revision date:	June 20, 2011	
Implementation date:	For new submissions*:	August 20, 2011
	For existing fragrance compounds*:	August 20, 2012
Next review date:	2016	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: RESTRICTED

RESTRICTIONS:

Limits in the finished product:			
Category 1 See Note box (1)	0.03 %	Category 7	0.08 %
Category 2	0.04 %	Category 8	1.01 %
Category 3	0.15 %	Category 9	5.00 %
Category 4	0.45 %	Category 10	2.50 %
Category 5	0.24 %	Category 11	See Note box (2)
Category 6 See Note box (1)	0.72 %		

Note box:
(1) See the IFRA Code of Practice (Appendix 8, Introduction to the IFRA Standards) regarding the Note on Oral Care Products and other products with the potential of ingestion.
(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl)ethan-1-one

Indicative contribution from other sources: None known at the time of the publication of the Standard

---

Critical effect: Sensitization

RIFM Summaries:

LLNA weighted mean EC3 values (µg/cm²) [no. studies]	Potency Classification Based on Animal Data[1]	Human Data[2]			WoE NESIL[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	NOEL – HMT (induction) (µg/cm²)	LOEL (induction) (µg/cm²)	
3600 [1]	Weak	NA	NA	NA	1000

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[2]Data derived from HRIPT or HMT.
[3]WoE NESIL limited to two significant figures.

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for 1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl)ethan-1-one and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 1000 µg/cm², which is a default value based on the LLNA data. They recommend the limits for the 11 different product categories, which are the acceptable use levels of 1-(2,4,4,5,5-Pentamethyl-1-cyclopenten-1-yl)ethan-1-one in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the publication by Api *et al*., 2008.

References:

Api AM, Basketter DA, Cadby PA, Cano M-F, Ellis G, Gerberick G, et al. Dermal Sensitization Quantitative Risk Assessment (QRA) For Fragrance Ingredients. *Regulatory Toxicology and Pharmacology* 2008;52(1): 3-23.

2-Pentylidene cyclohexanone

CAS N°: 25677-40-1 **Empirical formula:** $C_{11}H_{18}O$

Synonyms: Cyclohexanone, 2-pentylidene-

History:

Initial reviews:	February 1979, May 1983
Current revision date:	September 2002
Implementation date:	For new submissions*:
	For existing fragrance compounds*:
Next review date	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Opdyke, D.L.J. and Letizia, C. (1982), Food and Chemical Toxicology, 20, 797.

Peru balsam crude

CAS N°: 8007-00-9 **Empirical formula:** N/A

Synonyms: Exudation of Myroxylon pereirae Klotsch

History:

Initial reviews:	October 1974, December 1991
Current revision date:	2007
Implementation date:	For new submissions*:
	For existing fragrance compounds*:
Next review date	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Restrictions on the use of Peru balsam oil, absolute and anhydrol are contained in a separate Standard (Peru balsam extracts and distillates).

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, January 2007.

References:

D.L. Opdyke (1974), Fd. Cosmet. Toxicol. 12, 951 and 953

Peru balsam extracts and distillates

CAS N°: 8007-00-9 **Empirical formula:** N/A

Synonyms: Balsam oil, Peru (*Myroxylon pereirae* Klotzsch)
Balsams, Peru
Myroxylon pereirae (Balsam Peru) oil
Myroxylon pereirae (Balsam Peru) resin
Myroxylon pereirae oil
Peru balsam absolute
Peru balsam anhydrol

History:

Initial reviews:	October 1974, December 1991, May 2007 (42nd Amendment)	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1	See Note box (1)	Category 7	0.07 %
Category 2	0.04 %	Category 8	0.4 %
Category 3	0.1 %	Category 9	0.4 %
Category 4	0.4 %	Category 10	0.4 %
Category 5	0.2 %	Category 11	Not Restricted (2)
Category 6	See Note box (1)	0.7 %	

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.

The use of Peru balsam crude is PROHIBITED in a separate Standard.

---

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in

Peru balsam extracts and distillates

compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) http://www.iofiorg.org/.

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Contribution from other sources: See **Annex 1**

Critical effect: Sensitization

RIFM Summaries:

Peru balsam - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values ($\mu g/cm^2$) [no. studies]	Potency Classification[2]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – MAX (induction) ($\mu g/cm^2$)	LOEL[1] (induction) ($\mu g/cm^2$)	
Balsam oil, Peru (Myroxylon pereirae Klotzsch)					
987	Moderate	950	NA	NA	950
Peru balsam absolute					
625	Moderate	NA	NA	NA	950
Peru balsam anhydrol					
NA	Moderate	NA	NA	NA	950

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available
[1] Data derived from HRIPT or Human Max tests
[2] Gerberick *et al.*, 2001
[3] WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Peru balsam extracts and distillates and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 950 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of Peru balsam extracts and distillates in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

Peru balsam extracts and distillates

References:

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161.

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

Peru balsam (myroxylon pereirae klotzch)
RIFM (Research Institute for Fragrance Materials, Inc.), 2004. Local Lymph Node Assay on Peru balsam (Myroxylon pereirae Klotzsch). RIFM report number 44372, February 16(RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2005. Repeated insult patch test with balsam, Peru (Myroxylon pereirae Klotzsch). RIFM report number 47380, January 20 (RIFM, Woodcliff Lake, NJ, USA).

Peru balsam absolute
RIFM (Research Institute for Fragrance Materials, Inc.), 2004. Local Lymph Node Assay on Peru balsam absolute. RIFM report number 44371, February 16 (RIFM, Woodcliff Lake, NJ, USA).

Phenylacetaldehyde

CAS N°: 122-78-1

Empirical formula: C_8H_8O
$C_6H_5\text{-}CH_2\text{-}CHO$

Synonyms:
Benzeneacetaldehyde
Benzylcarboxaldehyde
Hyacinthin
1-Oxo-2-phenylethane
Phenylacetic aldehyde
Phenyl Acetic Aldehyde (pure)
alpha-Tolualdehyde
alpha-Toluic aldehyde

History:

Initial reviews:	October 1975, February 1980	
Current revision date:	2006	
Implementation date:	For new submissions*:	June 11, 2007
	For existing fragrance compounds*:	June 11, 2008
Next review date	2011	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1	0.02 %	Category 7	0.04 %
Category 2	0.02 %	Category 8	0.6 %
Category 3	0.09 %	Category 9	3.0 %
Category 4	0.3 %	Category 10	2.5 %
Category 5	0.1 %	Category 11	See Note box
Category 6	0.4 %		

Note box:

Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

This Standard **cancels and replaces** the existing one on **phenylacetaldehyde**, which was based on the no longer supported 'quenching' phenomenon.

Fragrance material specifications: N/A

Phenylacetaldehyde

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **introduction to the IFRA Standards**)

Critical effect: Sensitization

RIFM Summaries:

Phenylacetaldehyde - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values ($\mu g/cm^2$) [no. studies]	Potency Classification[2]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – MAX (induction) ($\mu g/cm^2$)	LOEL[1] (induction) ($\mu g/cm^2$)	
962 [2]	Moderate	591	NA	1181	590

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; MAX = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available
[1] Data derived from HRIPT or Human Max tests
[2] Gerberick *et al.*, 2001
[3] WoE NESIL limited to two significant figures

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for phenylacetaldehyde and based on the weight of evidence established the No Expected Sensitization Induction Level (NESIL) as 590 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of phenylacetaldehyde in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of March 15, 2006.

References:

D.A.Basketter, Z.M.Wright, E.V.Warbrick, R.J.Dearman, I.Kimber, C.A.Ryan, G.F.Gerberick and I.R.White (2001). Human potency predictions for aldehydes using the local lymph node assay. Contact Dermatitis, 45(2), 89-94.

D.A.Basketter, N.Gilmour, R.J.Dearman, I.Kimber, C.A.Ryan and G.F. Gerberick (2003). Classification of skin sensitisation potency using the Local Lymph Node Assay. The Toxicologist, 72(S-1), 101.

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161

QRA Expert Group (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006,

Phenylacetaldehyde

http://www.rifm.org/pub/publications.asp.

Research Institute for Fragrance Materials, Inc (2003). Repeated insult patch test in human subjects with phenylacetaldehyde. RIFM report number 44245 (RIFM, Woodcliff Lake, NJ USA).

Research Institute for Fragrance Materials, Inc (2004). Repeated insult patch test in human subjects with phenylacetaldehyde. RIFM report number 45132 (RIFM, Woodcliff Lake, NJ USA).

Phenyl acetone (Methyl benzyl ketone)

CAS N°: 103-79-7 **Empirical formula:** $C_9H_{10}O$

Synonyms: Benzyl methyl ketone
Methyl benzyl ketone
2-Propanone, 1-phenyl

History:

Initial reviews:	N/A	
Current revision date:	N/A	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: See Note box

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

Phenyl acetone (Methyl benzyl ketone)

References:

Human Health Criteria Document, *Reg. Tox & Pharm*., 31, 166-181, 2000

Phenyl benzoate

CAS N°: 93-99-2 **Empirical formula:** $C_{13}H_{10}O_2$

Synonyms: Benzoic acid, phenyl ester

History:

Initial reviews:	N/A	
Current revision date:	N/A	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: See Note box

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

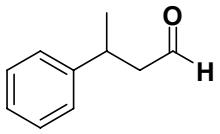
Human Health Criteria Document, *Reg. Tox & Pharm.*, 31, 166-181, 2000

3-Phenylbutanal

CAS N°: 16251-77-7 **Empirical formula:** $C_{10}H_{12}O$

Synonyms: Benzenepropanal, β-methyl-
3-Phenylbutanal
3-Phenylbutyraldehyde
3-Phenyl-3-methylpropanal
Trifernal (commercial name)

Structure:



History: Initial reviews: New Standard

Current revision date: June 11, 2010

Implementation date: For new submissions*: August 11, 2010

For existing fragrance compounds*: August 11, 2011

Next review date: 2015

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: RESTRICTED

RESTRICTIONS:

Limits in the finished product:			
Category 1 See Note box (1)	0.17%	Category 7	0.45%
Category 2	0.22%	Category 8	2.0%
Category 3	0.89%	Category 9	5.0%
Category 4	2.7%	Category 10	2.5%
Category 5	1.4%	Category 11	See Note box (2)
Category 6 See Note box (1)	4.3%		
Note box: (1) See the IFRA Code of Practice (Appendix 8, Introduction to the IFRA Standards) regarding the Note on Oral Care Products and other products with the potential of ingestion. (2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.			
Fragrance material specifications: N/A			

Indicative contribution from other sources: None known at the time of the publication of the Standard

---

Critical effect: Sensitization

3-Phenylbutanal

RIFM Summaries:

LLNA weighted mean EC3 values (µg/cm²) [no. studies]	Potency Classification Based on Animal Data[1]	Human Data[2]			WoE NESIL[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	NOEL – HMT (induction) (µg/cm²)	LOEL (induction) (µg/cm²)	
N/A	N/A	5906	N/A	12,500	5900

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[2]Data derived from HRIPT or HMT.
[3]WoE NESIL limited to two significant figures.

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for 3-phenylbutanal and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 5900 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of 3-phenylbutanal in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the publication by Api *et al*., 2008.

References:

Api AM, Basketter DA, Cadby PA, Cano M-F, Ellis G, Gerberick G, et al. Dermal Sensitization Quantitative Risk Assessment (QRA) For Fragrance Ingredients. *Regulatory Toxicology and Pharmacology* 2008;52(1): 3-23.

RIFM (Research Institute for Fragrance Materials, Inc.), 2009. Human repeated insult patch test. RIFM report number 57513, July 16. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1983. Human repeated insult patch test. Unpublished study from Firmenich, Inc., August 24. Report number 40514. (RIFM, Woodcliff Lake, NJ, USA).

2-Phenylpropionaldehyde

CAS N°: 93-53-8 **Empirical formula:** $C_9H_{10}O$

Synonyms: Benzeneacetaldehyde, α-methyl-
Hydratropaldehyde
Hydratropic aldehyde
α-Methylphenylacetaldehyde
α-Methyltolualdehyde
2-Phenylpropanal
α-Phenylpropionaldehyde

History:

Initial reviews:	New Standard	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2011
Next review date	2014	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1 See Note box (1)	0.01 %	Category 7	0.03 %
Category 2	0.01 %	Category 8	0.40 %
Category 3	0.06 %	Category 9	1.90 %
Category 4	0.17 %	Category 10	2.50 %
Category 5	0.09 %	Category 11	See Note box (2)
Category 6 See Note box (1)	0.28 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry - www.iofiorg.org)

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to negligible skin contact the concentration of a fragrance ingredient should not exceed the usual concentration of the fragrance compound in the finished product.

Fragrance material specifications: N/A

2-Phenylpropionaldehyde

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **introduction to the IFRA Standards**)

Critical effect: Sensitization

RIFM Summaries:

LLNA weighted mean EC3 values ($\mu g/cm^2$) [no. studies]	Potency Classification[2]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – MAX (induction) ($\mu g/cm^2$)	LOEL[1] (induction) ($\mu g/cm^2$)	
1575 [1][4]	Weak	388[5]	1380	1938	380[6]

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.
[1] Data derived from HRIPT or HMT.
[2] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[3] WoE NESIL limited to two significant figures.
[4] EC3 value from one LLNA, not the mean.
[5] HRIPT with 38 subjects only; study with 100 subjects not done because the material is used at a low volume (1-5 metric tons)
[6] WoE NESIL based on limited subject HRIPT which was lower than the default LLNA (1000 ug/cm2)

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for 2-Phenylpropionaldehyde and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 380 mg/cm2. They recommend the limits for the 11 different product categories, which are the acceptable use levels of 2-Phenylpropionaldehyde in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Patlewicz, G., Roberts, D.W., Walker, J.D., 2003. QSARs for the skin sensitization potential of aldehydes and related compounds. QSAR & Combinatorial Science, 22, 196-203.

RIFM (Research Institute for Fragrance Materials, Inc.), 1964. Human repeated insult patch test. Unpublished study from IFF Inc., 3 April. Report number 51926. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1971a. Human repeated insult patch test. Unpublished study from IFF Inc., 7 July. Report number 51925. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1971b. Maximization study with 2-phenylpropionaldehyde. RIFM report number 1805, April 2a. (RIFM, Woodcliff Lake, NJ, USA).

Pinacea derivatives

CAS N°:

History: Initial reviews: May 1976, July 1994

RECOMMENDATION: SPECIFICATION

RESTRICTIONS:

Limits in the finished product:	
Non skin contact products:	N/A

Critical effect: Sensitization

Essential oils (e.g. turpentine oil) and isolates (e.g. delta-3-carene) derived from the *Pinacea* family, including *Pinus* and *Abies* genera, should only be used when the level of peroxides is kept to the lowest practicable level, for instance by adding antioxidants at the time of production.
Such products should have a peroxide value of less than 10 millimoles peroxide per liter, determined according to the FMA method, which can be downloaded from the IFRA website (see Analytical Methods).

References:

This recommendation is based on the published literature, mentioning sensitizing properties when containing peroxides (Fd. Cosmet. Toxicol. 11, 1053 (1973); 16, 843 (1978);16, 853(1978).

This Guideline does not permit the use of colophony.

3-Propylidenephthalide

CAS N°: 17369-59-4 **Empirical formula:** $C_{11}H_{10}O_2$

Synonyms: 1(3H)-Isobenzofuranone, 3-propylidene-
Propylidene phthalide
3-Propylidenephthalide

History:

Initial reviews:	May 1977, July 1994 (28th Amendment)	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

For a description of the categories, refer to the QRA Informational Booklet.

Category 1 See Note box (1)	0.01 %	Category 7	0.01 %
Category 2	0.01 %	Category 8	0.01 %
Category 3	0.01 %	Category 9	0.01 %
Category 4	0.01 %	Category 10	0.01 %
Category 5	0.01 %	Category 11	Not Restricted (2)
Category 6 See Note box (1)	0.7 %		

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) http://www.iofiorg.org/.

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

3-Propylidenephthalide

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards).**

Critical effect: Sensitization

RIFM Summaries:

EC3 value from one LLNA (not the mean) (µg/cm2)	**Potency Classification** Based on Animal Data[1]	**Human Data**			**WoE NESIL**[3] (µg/cm^2)
		NOEL – HRIPT (induction) (µg/cm^2)	**NOEL – HMT** (induction) (µg/cm^2)	**LOEL**[2] (induction) (µg/cm^2)	
350	Moderate	945[4]	345[4]	2760	920

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[2] Data derived from HRIPT or HMT
[3] WoE NESIL limited to three significant figures
[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for 3-Propylidenephthalide and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 920 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of 3-Propylidenephthalide in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Gerberick, G.F., Ryan, C.A., Kern, P.S., Dearman, R.J., Kimber, I., Patlewicz, G.Y., Basketter, D.A., 2004. A chemical dataset for evaluation of alternative approaches to skinsensitization testing. *Contact Dermatitis* 50, 274-288.

RIFM (Research Institute for Fragrance Materials, Inc.), 1975. Human Maximization Test. RIFM report number 1799, June 16a (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1978. Human Maximization Test. RIFM report number 1787, May 1 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2007. Human Repeated Insult Patch Test. RIFM report number 53724, September 21a (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2008. Local Lymph Node Assay. DRAFT RIFM data, report 54427 (RIFM, Woodcliff Lake, NJ, USA).

Pseudoionone (2,6-Dimethylundeca-2,6,8-trien-10-one)

CAS N°: 141-10-6 **Empirical formula:** $C_{13}H_{20}O$

Synonyms: Citrylideneacetone
6,10-Dimethyl-3,5,9-undecatrien-2-one
3,5,9-Undecatrien-2-one, 6,10-dimethyl-

History:

Initial reviews:	February 1979, July 1987, April 1989
Current revision date:	September 2002
Implementation date:	For new submissions*:
	For existing fragrance compounds*:
Next review date	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED** / **SPECIFICATION**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	
Non skin contact products:	N/A		

Note box:

Pseudoionone should not be used as fragrance ingredient as such, but a level of up to 2% as an impurity in ionones is accepted.

Fragrance material specifications: See Note box

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards**)

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Opdyke D.L.J. (1975), Food and Cosmetics Toxicology 13, 549.

Ford R.A. et al. (1988), Food and Chemical Toxicology 26, 311.

Pseudo methylionones

CAS N°: 26651-96-7
72968-25-3
1117-41-5

Empirical formula: $C_{14}H_{22}O$

Synonyms: 2,6-Dimethyldodeca-2,6,8-trien-10-one
7,11-Dimethyl-4,6,10-dodecatrien-3-one
7,11-Dimethyldodeca-4,6,10-trien-3-one
4,6,10-Dodecatrien-3-one, 7,11-dimethyl-
3,6,10-Trimethylundeca-3,5,9-trien-2-one

History:

Initial reviews:	February 1979, October 1979, April 1989, September 2002, May 2006 (40th Amendment)	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2010
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	
Non skin contact products:	N/A		

Note box:

Pseudo methylionones should not be used as fragrance ingredients as such, but a level of up to 2% as an impurity in methylionones is accepted.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards**)

Critical effect: **Sensitization**

REXPAN Rationale / Conclusion:
IFRA ban noted – REXPAN, September 2002

Pseudo methylionones

References:

Opdyke, D.L.J. (1975), Food and Cosmetics Toxicology 13, 863.

Ford R.A. et al. (1988), Food and Chemical Toxicology 26, 305 and 413.

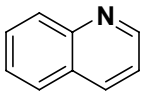
Quinoline

CAS N°: 91-22-5

Empirical formula: C_9H_7N

Synonyms: 1-Benzazine
2,3-Benzopyridine
Benzo(b)pyridine
Chinoleine
Leucoline
Quinoleine

Structure:



History:

Initial reviews:	New Standard	
Current revision date:	June 11, 2010	
Implementation date:	For new submissions*:	August 11, 2010
	For existing fragrance compounds*:	August 11, 2011
Next review date:	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material is considered as a carcinogenic / mutagenic agent and had only minor reported use in fragrances.
REXPAN agreed to the IFRA policy to ban the material for the given effects and not further elaborate on a risk management policy.

Fragrance material specifications: N/A

Indicative contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Carcinogenicity/Mutagenicity**

REXPAN Rationale / Conclusion:
IFRA ban noted – REXPAN, June 2010.

References:
Commission Directive 2009/2/EC (31st ATP to Directive 67/548/EEC)

Rose ketones

CAS N°: 23696-85-7
23726-93-4
43052-87-5
24720-09-0
23726-94-5
23726-92-3
23726-91-2
57378-68-4
71048-82-3
39872-57-6
70266-48-7
33673-71-1
35087-49-1
35044-68-9

Empirical formula: $C_{13}H_{20}O$

Synonyms:

23696-85-7 ($C_{13}H_{18}O$)
1-(2,6,6-Trimethylcyclohexa-1,3-dienyl)-2-buten-1-one
2-Buten-1-one, 1-(2,6,6-trimethyl-1,3-cyclohexadien-1-yl)
Damascenone, Floriffone

23726-93-4 ($C_{13}H_{18}O$)
(E)-1-(2,6,6-Trimethyl-1,3-cyclohexadien-1-yl)-2-buten-1-one
trans-1-(2,6,6-Trimethyl-1,3-cyclohexadien-1-yl)-2-buten-1-one
β-Damascenone

43052-87-5
α-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one
2-Buten-1-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-
α-Damascone, Dihydrofloriffone α

24720-09-0
(E)-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one
trans-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)but-2-en-1-one
2-Buten-1-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, (2E)-
trans-α-Damascone

23726-94-5
(Z)-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one
cis-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one
2-Buten-1-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, (Z)-
cis-α-Damascone

23726-92-3
1-(2,6,6-Trimethylcyclohex-1-en-1-yl)but-2-en-1-one
(Z)-β-1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-buten-1-one
(Z)-1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-buten-1-one
2-Buten-1-one, 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-, (2Z)-
cis-β-Damascone, Damasione

23726-91-2
(2E)-1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-buten-1-one
(E)-1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-buten-1-one

Rose ketones

1-(2,6,6-Trimethylcyclohex-1-en-1-yl)but-2-en-1-one
trans-β-Damascone, Dihydrofloriffone β

57378-68-4
δ-1-(2,6,6-Trimethyl-3-cyclohexen-1-yl)-2-buten-1-one 2-Buten-1-one, 1-(2,6,6-trimethyl-3-cyclohexen-1-yl)-
1-(2,6,6-Trimethyl-3-cyclohexen-1-yl)-2-buten-1-one
δ-Damascone, Dihydrofloriffone TD

71048-82-3
[1α(E),2β]-1-(2,6,6-Trimethyl-3-cyclohexen-1-yl)-2-buten-1-one
[1α(E),2β]-1-(2,6,6-Trimethylcyclohex-3-en-1-yl)but-2-en-1-one
trans,trans-δ-Damascone

39872-57-6
1-(2,4,4-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one
(E)-1-(2,4,4-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one
2-Buten-1-one, 1-(2,4,4-trimethyl-2-cyclohexen-1-yl)-, (2E)-
2-Buten-1-one, 1-(2,4,4-trimethyl-2-cyclohexen-1-yl)-, (E)-
Isodamascone (high α)

70266-48-7
1-(2,4,4-Trimethyl-1-cyclohexen-1-yl)-2-buten-1-one
2-Buten-1-one, 1-(2,4,4-trimethyl-1-cyclohexene-1-yl)
Isodamascone (standard quality)

33673-71-1
1-(2,4,4-Trimethylcyclohex-2-en-1-yl)but-2-en-1-one
1-(2,4,4-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one
2-Buten-1-one, 1-(2,4,4-trimethyl-2-cyclohexen-1-yl)-
Isodamascone (isomer unspecified)

35087-49-1
1-(2,2-Dimethyl-6-methylenecyclohexyl)but-2-en-1-one
2-Buten-1-one, 1-(2,2-dimethyl-6-methylenecyclohexyl)-
Damascone g-, γ-Damascone

35044-68-9
2-Buten-1-one, 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-
2,6,6-Trimethyl-1-(2-butenoyl)-1-cyclohexene
2,6,6-Trimethyl-1-crotonoyl-1-cyclohexene
1-(2,6,6-Trimethylcyclohexenyl)-2-buten-1-one
1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-buten-1-one
Damascone b-, β-Damascone

History:

Initial reviews:	December 1991, December 1995, July 2007 (42th Amendment), July 2008 (43th Amendment)	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2011

Rose ketones

Next review date 2014

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

For a description of the categories, refer to the QRA Informational Booklet.

Category 1 See Note box (1)	0.003 %	Category 7	0.008 %
Category 2	0.004 %	Category 8	0.02 %
Category 3	0.02 %	Category 9	0.02 %
Category 4	0.02 %	Category 10	0.02 %
Category 5	0.02 %	Category 11 Not Restricted (2)	
Category 6 See Note box (1)	0.07 %		

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be re-evaluated again. **The above limits apply to Rose Ketones used individually** or **in combination.**

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry - www.iofiorg.org)

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards)

Critical effect: **Sensitization**

RIFM Summaries:
See Enclosures

Rose ketones

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Rose Ketones and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 100 µg/cm2. They recommend the limits for the 11 different product categories, which are the acceptable use levels of Rose Ketones in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

Damascenone, 1-(2,6,6-Trimethylcyclohexa-1,3-dienyl)-2-buten-1-one (23696-85-7)
RIFM (Research Institute for Fragrance Materials, Inc.), 1978. Repeated insult patch test of 1-(2,6,6-trimethylcyclohexa-1,3-dienyl)-2-buten-1-one in human subjects. RIFM report number 15395, July 12 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2001. Murine local lymph node assay with 1-(2,6,6-trimethylcyclohexa-1,3-dienyl)-2-buten-1-one in mice. Unpublished report from Firmenich Incorporated, Report number 38813 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2002. 1-(2,6,6-Trimethylcyclohexa- 1,3-dienyl)-2-buten-1-one: local lymph node assay in mice. Unpublished report from Firmenich Incorporated, 22 October. Report number 41991 (RIFM, Woodcliff Lake, NJ, USA).

alpha-Damascone, alpha-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one (43052-87-5)
RIFM (Research Institute for Fragrance Materials, Inc.), 1979a. Evaluation of potential hazards of alpha-1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-2-buten-1-one by dermal contact in human subjects. Unpublished report from IFF Inc., 17 September. RIFM report number 15397. (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1979b. Repeated insult patch test of alpha-1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-2-buten-1-one in humans. Unpublished report from Firmenich Inc., 19 December. RIFM report number 153414. (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1985. Maximization study of alpha-1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-2-buten-1-one in humans. Unpublished report from Firmenich Inc., 29 July. RIFM report number 15416. (RIFM, Woodcliff Lake, NJ, USA).

trans-alpha–Damascone, (E)-1-(2,6,6-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one (24720-09-0)
RIFM (Research Institute for Fragrance Materials, Inc.), 2001. Murine local lymph node assay with 2-buten-1-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, (2E)- in mice. Unpublished report from Firmenich Incorporated, Report number 38814 (RIFM, Woodcliff Lake, NJ, USA).

Rose ketones

RIFM (Research Institute for Fragrance Materials, Inc.), 2001a. Repeated insult patch study of 2-buten-1-one, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-, (2E)- at 0.5% in diethyl phthalate (DEP). Unpublished report from Firmenich Incorporated, Report number 38815 (RIFM, Woodcliff Lake, NJ, USA).

cis-beta-Damascone, (Z)-ß-1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-buten-1-one (23726-92-3)
RIFM (Research Institute for Fragrance Materials, Inc.), 1979. Repeated insult patch test of beta-damascone in human subjects. Unpublished report from IFF, Inc., 19 February. RIFM report number 15394. (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1980. Repeat insult patch test with (Z)-b-1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-buten-1-one. Unpublished report from IFF, Inc., 17 June. Report number 47353. (RIFM, Woodcliff Lake, NJ, USA).

trans-beta-Damascone, (2E)-1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-2-buten-1-one (23726-91-2)
RIFM (Research Institute for Fragrance Materials, Inc.), 1979. Repeated insult patch test of (2E)-1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-buten-1-one in humans. Unpublished report from Firmenich, Inc., 19 December. Report number 15407. (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2001. Murine local lymph node assay with (2E)-1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2-buten-1-one. Unpublished report from Firmenich, Inc. Report number 38811. (RIFM, Woodcliff Lake, NJ, USA).

delta-Damascone, delta-1-(2,6,6-Trimethyl-3-cyclohexen-1-yl)-2-buten-1-one (57378-68-4)
RIFM (Research Institute for Fragrance Materials, Inc.), 1982. Evaluation of potential irritation and sensitization hazards of delta-damascone by dermal contact in humans. Unpublished report from International Flavors and Fragrances, 17 November. Report number 15399 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2002a. Murine local lymph node assay of delta-1-(2,6,6-trimethyl-3-cyclohexen-1-yl)-2-buten-1-one. Unpublished report from Firmenich Incorporated, 9 July. Report number 41992 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2002b. Murine local lymph node assay of delta-1-(2,6,6-trimethyl-3-cyclohexen-1-yl)-2-buten-1-one. Unpublished report from Firmenich Incorporated, 2 April. Report number 42139 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 2004. delta-1-(2,6,6-Trimethyl-3-cyclohexen-1-yl)-2-buten-1-one: Local Lymph Node Assay. Unpublished report from International Flavors and Fragrances, 13 December. Report number 47819 (RIFM, Woodcliff Lake, NJ, USA).

trans,trans-delta-Damascone, [1alpha(E),2beta]-1-(2,6,6-Trimethyl-3-cyclohexen-1-yl)-2-buten-1-one
(71048-82-3)
RIFM (Research Institute for Fragrance Materials, Inc.), 1978. Repeated insult patch test

Rose ketones

with [1.alpha.(E),2.beta.]-1-(2,6,6-trimethyl-3-cyclohexen-1-yl)-2-buten-1-one. Unpublished report from International Flavors and Fragrance, 11 August. Report number 50614 (RIFM, Woodcliff Lake, NJ, USA).

Isodamascone (high alpha), (E)-1-(2,4,4-Trimethyl-2-cyclohexen-1-yl)-2-buten-1-one (39872-57-6)
RIFM (Research Institute for Fragrance Materials, Inc.), 1994. Repeated insult patch test on isodamascone on human subjects. RIFM report number 25751, July 25 (RIFM, Woodcliff Lake, NJ, USA).
RIFM (Research Institute for Fragrance Materials, Inc.), 1995. Repeated insult patch test of isodamascone in human subjects. RIFM report number 25753, June 20 (RIFM, Woodcliff Lake, NJ, USA).

Isodamascone (standard quality), 1-(2,4,4-Trimethyl-1-cyclohexen-1-yl)-2-buten-1-One (70266-48-7)
RIFM (Research Institute for Fragrance Materials, Inc.), 1985. Repeated insult patch test with isodamascone. RIFM report number 41231, December 22 (RIFM, Woodcliff Lake, NJ, USA).

gamma-Damascone, 1-(2,2-Dimethyl-6-methylenecyclohexyl)but-2-en-1-one (35087-49-1)
RIFM (Research Institute for Fragrance Materials, Inc.), 2001. Murine local lymph node assay with 2-buten-1-one, 1-(2,2-dimethyl-6-methylenecyclohexyl)- in mice. Unpublished report from Firmenich Inc. RIFM report number 38812. (RIFM, Woodcliff Lake, NJ, USA).

Rue oil

CAS N°: 8014-29-7

Initial review: November 1974, October 1978, April 2001

RECOMMENDATION: RESTRICTED

RESTRICTIONS:

Limits in the finished product:	
Skin contact:	0.15% (excl. rinse-off prod.)
Non skin contact:	No limitation

For applications on areas of skin exposed to sunshine, excluding bath preparations, soaps and other products which are washed off the skin, Rue oil should not be used such that the level in the consumer product exceeds 0.15% (see remark on phototoxic ingredients in the introduction to the IFRA Code of Practice).

This recommendation is based on the fact that Rue oil is known to contain psoralens and on the no-effect level of 0.8% found in hairless mice (P.D. Forbes, F. Urbach, R.E. Davis (1977), Fd. Cosmet. Toxicol. 15 , 55-60 and communication from RIFM).

(35th Amendment to the IFRA Code of Practice)

Date of compliance for new submissions: April 17, 2001
Date of compliance for existing fragrance compounds: April 17, 2002

Website updated October 17, 2001

Safrole, Isosafrole, Dihydrosafrole

CAS N°: 94-59-7
120-58-1
94-58-6

Initial review: October 1976, July 1987

RECOMMENDATION: **PROHIBITED / RESTRICTED**

RESTRICTIONS:

Limits in the finished product:	
Skin contact:	0.01%
Non skin contact:	0.01%

Safrole as such should not be used as a fragrance ingredient; essential oils containing safrole should not be used at a level such that the total concentration of safrole exceeds 0.01% in consumer products. Examples of essential oils with a high safrole content are Sassafras oil (*Sassafras officinale* Nees& Eberm.), *Ocotea Cymbarum* oil (*Ocotea pretiosa* Metz) and certain qualities of Camphor oils.

The total concentration of safrole, isosafrole and dihydrosafrole should not exceed 0.01% in consumer products.

These recommendations are based on the conclusions of the Scientific Committee on Cosmetology of the EEC on safrole and on the similarity of the biological activity of these substances (Scientific Committee of Cosmetology of the EEC, opinion reached on September 2, 1980; Communication to the EEC Commission ENV/521/79 and IARC Monograph Vol. 10, 1976, 231-244).

Santolina oil

CAS N°: 84961-58-0 **Empirical formula:** N/A

Synonyms:

History:

Initial reviews:	May 2006 (40th Amendement)	
Current revision date:		
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material had been on the list of 'other materials' before, which for reasons of a unified Standard format for prohibited materials was disbanded.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: See Note box

REXPAN Rationale / Conclusion:

The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

References:

Human Health Criteria Document, *Reg. Tox & Pharm.*, 31, 166-181, 2000

Savin oil

CAS N°: 8024-00-8

Initial review: May 1980, June 1982

RECOMMENDATION: **PROHIBITED** / **SPECIFICATION**

RESTRICTIONS:

Limits in the finished product:	
Skin contact:	N/A
Non skin contact:	N/A

Savin oil should not be used as a fragrance ingredient if prepared from *Juniperus sabina* L. Only oils obtained from *Juniperus phoenicea* L. should be used.

In the absence of an international standard, the following specificiations for oils of *Juniperus phoenicea* L. are proposed:

Density d 20/20 0,864 - 0,873
Refraction n 20 D 1,4700 - 1,4720
Rotation alpha 20 D -1° - +4°
Acid value 0,4 - 1
Ester value 2,5 - 7
Ester value after acetylation 10 - 23
Solubility 0.5-6 vol. in alcohol 96%, beyond that opalescence on dilution

This recommendation is based on the high acute toxicity of oils from J. sabina L. (R.E. Gosselin, H.C. Hodge, R.P. Smith & M.N. Gleason (1976), Clinical Toxicology of Commercial Products, 4th ed., Section II, p. 153, Williams & Wilkins Co., Baltimore), and the low acute toxicity of oils from J. phoenicea L. (private communication to IFRA).

Sclareol

CAS N°: 515-03-7 **Empirical formula:** $C_{20}H_{36}O_2$

Synonyms: Labd-14-ene-8,13-diol
1-Naphthalenepropanol,decahydro-alpha-ethenyl-2-hydroxy-alpha,2,5,5,8apentamethyl-,
(1R-(1-alpha(R*),2-beta,4a-beta,8a-alpha))-

History:

Initial reviews:	February 1986	
Current revision date:	September 2004	
Implementation date:	For new submissions*:	November 12, 2005
	For existing fragrance compounds*:	November 12, 2006
Next review date	2009	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: SPECIFICATION

RESTRICTIONS:

Limits in the finished product:			
Skin contact products:			
Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	
Non skin contact products:	N/A		
Note box:			
Fragrance material specifications:	Sclareol used as a fragrance ingredient should have a minimum purity of 98%.		

Contribution from other sources: Contributions from other sources are known but not of relevance for this type of Standard.

Critical effect: Sensitization

REXPAN Rationale / Conclusion:

This recommendation is based on test results of RIFM with different qualities showing a sensitizing potential of samples with a lower purity and no sensitizing reactions for samples with a minimum purity of 98%.

Sclareol

References:

Research Institute for Fragrance Materials, Inc. (1975a). Repeated Insult Patch Test with Sclareol. RIFM report number 45024, June 17. (RIFM, Woodcliff Lake, NJ, USA).

Research Institute for Fragrance Materials, Inc. (1975b). Repeated Insult Patch Test with Sclareol. RIFM report number 45025, June 18. (RIFM, Woodcliff Lake, NJ, USA).

Research Institute for Fragrance Materials, Inc. (1979a). Report on Human Maximization Studies. RIFM report number 1697, April 20. (RIFM, Woodcliff Lake, NJ, USA).

Research Institute for Fragrance Materials, Inc. (1979b). Report on Human Maximization Studies. RIFM report number 1697, November 6. (RIFM, Woodcliff Lake, NJ, USA).

Research Institute for Fragrance Materials, Inc. (1981). Report on Human Maximization Studies. RIFM report number 1792, March 18. (RIFM, Woodcliff Lake, NJ, USA).

Research Institute for Fragrance Materials, Inc. (1986). Report on Human Maximization Studies. RIFM report number 3100, January 15. (RIFM, Woodcliff Lake, NJ, USA).

Styrax

CAS N°:

Initial review: November 1977, July 1994

RECOMMENDATION: **PROHIBITED / RESTRICTED**

RESTRICTIONS:

Limits in the finished product:	
Skin contact:	0.6% (extracts, distillates)
Non skin contact:	0.6% (extracts, distillates)

Crude gums of American and Asian styrax should not be used as fragrance ingredient. Only extracts or distillates (resinoids, absolutes and oils), prepared from exudations of *Liquidambar styraciflua* L. var. macrophylla or *Liquidambar orientalis* Mill., can be used and should not exceed a level of 0.6% in consumer products. This is equivalent to 3% in a fragrance compound used at 20% in the consumer product.

This recommendation is made in order to promote good manufacturing practice (GMP) for the use of styrax derivatives as fragrance ingredients. It is based on a wide variety of RIFM test data with gums, resinoids, absolutes and oils of American and Asian styrax (private communication to IFRA).

Tagetes oil and absolute

CAS N°: 91722-29-1
8016-84-0

Empirical formula: N/A

Synonyms: Tagetes absolute (*Tagetes patula* L.)
Tagetes patula absolute
Tagetes patula, ext.
Tagetes minuta absolute
Tagetes oil

History:

Initial reviews:	October 1986, April 2001 See IFRA Information Letter 637 rev.	
Current revision date:	January 2001	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date	2006	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	0.01%	Rinse-off products:	No restriction *Including household cleaning products*
Non skin contact products:	No restriction		

Note box:

The Standard is set due to the phototoxic effects of the material. The limit only applies to applications on skin, excluding rinse-off products.

If combinations of phototoxic fragrance ingredients are used, the use levels have to be reduced accordingly. The sum of the concentrations of all phototoxic ingredients, expressed in % of their recommended maximum level in the consumer product shall not exceed 100.

Fragrance material specifications: N/A

Tagetes oil and absolute

Contribution from other sources: None known

Critical effect: **Phototoxicity**

RIFM Summaries:

Tagetes oils and absolutes obtained from *Tagetes minuta L.* (syn. *Tagetes glandulifera Schrank* and *Tagetes patula L.*) were evaluated by RIFM (Letizia and Api, 2000). A noeffect level for phototoxicity of 0.05% was determined on humans using Egyptian *Tagete minuta* (RIFM, 1986a).

- At 0.003% in guinea pigs, no observable effects, 0/10 (RIFM, 1985a).
- At 0.01% in guinea pigs, phototoxicity observed, 8/10 (RIFM, 1985b).
- At 100% in mice, phototoxicity was observed, 6/6 (RIFM,1986b).
- At 1% in mice, phototoxicity was observed, 6/6 (RIFM, 1986c).
- At 0.1% in mice, phototoxicity was observed, 6/6 (RIFM, 1986c).
- At 0.01% in mice, phototoxicity was observed, 2/6 (RIFM, 1986c).

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for AHMI and recommended no change to the Standard (September 2001).

References:

Letizia C.S. and Api A.M (2000). A dermal safety evaluation of extracts from Tagetes plants used in fragrances. The Toxicologist, 54(1), 397.

Research Institute for Fragrance Materials, Inc. (1985a). Guinea Pig Phototoxicity Test. Unpublished report from Givaudan. Report number 3361, 17 December.

Research Institute for Fragrance Materials, Inc. (1985b). Guinea Pig Phototoxicity Test. Unpublished report from Givaudan. Report number 3362, 17 December.

Research Institute for Fragrance Materials, Inc. (1986a). Human Photosensitization Test. RIFM report number 1690, 21 November.

Research Institute for Fragrance Materials, Inc. (1986b). Mouse Phototoxicity Test. RIFM report number 3828, 25 June.

Research Institute for Fragrance Materials, Inc. (1986c). Mouse Phototoxicity Test. RIFM report number 4343, 31 July.

Tea leaf absolute

CAS N°: 84650-60-2 **Empirical formula:** N/A

Synonyms: Camellia sinensis leaf extract
Tea, ext.
Tea sinensis absolute
Thea chinensis ext.
Thea sinensis ext.

History: Initial reviews:
Current revision date: 2006
Implementation date: For new submissions*: June 11, 2007
For existing fragrance compounds*: June 11, 2008
Next review date 2011

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1	0.01 %	Category 7	0.04 %
Category 2	0.02 %	Category 8	0.5 %
Category 3	0.07 %	Category 9	2.4 %
Category 4	0.2 %	Category 10	2.5 %
Category 5	0.1 %	Category 11	See Note box (1)
Category 6	0.3 %		

Note box:

(1) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

(2) Prior to the introduction of this Standard, this material was listed under the so-called 'other materials' due to insufficient data supporting its use.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: **Sensitization**

Tea leaf absolute

RIFM Summaries:

Tea Leaf Absolute - Sensitization Potency Estimation Based on Weight of Evidence

LLNA weighted mean EC3 values ($\mu g/cm^2$) [no. studies]	Potency Classification[2]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – MAX (induction) ($\mu g/cm^2$)	LOEL[1] (induction) ($\mu g/cm^2$)	
>1250[1][4]	Moderate	480	NA	NA	480

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1] Data derived from HRIPT or HMT.
[2] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[3] WoE NESIL limited to two significant figures.
[4] Irritation was observed at higher concentrations; EC3 value not calculable

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for tea leaf absolute and based on the weight of evidence established the No Expected Sensitization Induction Level (NESIL) as 480 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of tea leaf absolute in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of March 15, 2006.

References:

Gerberick, GF. et. al. (2001) Contact allergenic potency: Correlation of human and local lymph node assay data. American Journal of Contact Dermatitis, 12(3), 156-161.

QRA Expert Group* (AM Api, DA Basketter, PA Cadby, M-F Cano, G Ellis, GF Gerberick, P Griem, PM McNamee, CA Ryan and R Safford), Dermal Sensitization Quantitative Risk Assessment (QRA) for Fragrance Ingredients, Technical Dossier, March 15, 2006, http://www.rifm.org/pub/publications.asp.

Research Institute for Fragrance Materials, Inc (1990). Delayed contact hypersensitivity study of tea leaf absolute in guinea pigs. RIFM report number 12409 (RIFM, Woodcliff Lake, NJ USA).

Research Institute for Fragrance Materials, Inc (2004). Repeated insult patch test of tea leaf absolute in human subjects. Unpublished report from Robertet Incorporated, Report number 44878 (RIFM, Woodcliff Lake, NJ USA).

Research Institute for Fragrance Materials, Inc (2005). Local Lymph Node Assay on tea leaf absolute. Unpublished report from Robertet Incorporated, Report number 47597 (RIFM, Woodcliff Lake, NJ USA).

1,2,3,4-Tetrahydro-4-methylquinoline

CAS N°: 19343-78-3 **Empirical formula:** $C_{10}H_{13}N$

Synonyms: 4-Methyl-1,2,3,4-tetrahydroquinoline
Quinoline, 1,2,3,4-tetrahydro-4-methyl-
1,2,3,4-Tetrahydrolepidine
1,2,3,4-Tetrahydro-4-methylquinoleine

History:

Initial reviews:	New Standard	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2010
Next review date	2014	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

The material has been identified for having the potential of forming nitrosamines in nitrosating systems. Downstream users therefore have to be notified of the presence of the material and its potential to be able to consider adequate protective measures.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards**)

Critical effect: **Potential of nitrosamine formation**

REXPAN Rationale / Conclusion:

IFRA measures regarding potential nitrosamine formation noted - REXPAN April 2009.

References:

Nitrosamine policy as contained in the EU Cosmetics Directive 76/768/EEC and its Amendments.

Toluene

CAS N°: 108-88-3 **Empirical formula:** C_7H_8

Synonyms: Toluol
Methylbenzol
Methylbenzene

History:

Initial reviews:		
Current revision date:	October 2003	
Implementation date:	For new submissions*:	May 6, 2004
	For existing fragrance compounds*:	May 6, 2005
Next review date		

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:			
Skin contact products:			
Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	
Non skin contact products:	N/A		
Note box:			
The material should not be used as fragrance ingredient for any application.			
Fragrance material specifications:	The level of toluene has to be kept as low as practicable and should never exceed **100 ppm** in the fragrance compound.		

Contribution from other sources: N/A

Critical effect: **Liver toxicity**

REXPAN Rationale / Conclusion:

IFRA ban noted - REXPAN, October 15, 2003

References:

1) Cosmetic Ingredient Review, Journal of the American College of Toxicology JACT 6 (1) 1987.

2) IARC (International Agency for Research on Cancer) Monographs Vol 47, p .79 (1989); Vol 71 p. 829 (1999)

Treemoss extracts

CAS N°: 90028-67-4 = Evernia furfuracea
68648-41-9 = oils, Treemoss
68917-40-8 = oils, Treemoss resinoid

Empirical formula: N/A

Synonyms: Treemoss absolute (Pseudevernia furfuracea)
Treemoss (Usnea furfuracea)
Treemoss Colourless
Pseudevernia furfuracea extract
Cedar moss

History:

Initial reviews:	1991, 2001	
Current revision date:	2008	
Implementation date:	For new submissions*:	February 16, 2009
	For existing fragrance compounds*:	February 16, 2011
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: RESTRICTED / SPECIFICATION

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Informational Booklet.

Category 1 See Note box (1)	0.02 %	Category 7	0.1 %
Category 2	0.03 %	Category 8	0.1 %
Category 3	0.1 %	Category 9	0.1 %
Category 4	0.1 %	Category 10	0.1 %
Category 5	0.1 %	Category 11 Not Restricted (2)	
Category 6 See Note box (1)	0.5 %		

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.

In the presence of oak moss extracts, the level of tree moss in the respective category has to be reduced accordingly such that the total amount of both extracts does not exceed the maximum permitted level in each category as listed in the table above.

If the same compound is intended for more than one IFRA QRA category, then the most restrictive limitation (based on foreseen use concentrations and maximum

Treemoss extracts

permitted level) will apply.

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry) http://www.iofiorg.org/.

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications:	Tree moss extracts shall not contain more than 0.8% of dehydroabietic acid (DHA) as a marker of 2% of total resin acids. The concentration of DHA (about 40% of the total resin acids) in tree moss can be measured with an HPLC reverse Phase - spectrofluorometry method. Further, levels of atranol and chloroatranol should each be below **100 ppm** in tree moss extracts.

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards)

Critical effect: Sensitization

RIFM Summaries:

EC3 value from one LLNA (not the mean) (µg/cm2)	**Potency Classification** Based on Animal Data[1]	**Human Data**			**WoE NESIL**[3] (µg/cm^2)
		NOEL – HRIPT (induction) (µg/cm^2)	**NOEL – HMT** (induction) (µg/cm^2)	**LOEL**[2] (induction) (µg/cm^2)	
> 5000	Moderate	700 [4]	6896[4]	1417	700

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test;
LOEL = lowest observed effect level; NA = Not Available

[1] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
[2] Data derived from HRIPT or HMT
[3] WoE NESIL limited to three significant figures
[4] MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Treemoss extracts and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 700 µg/cm². They recommend the limits for the 11 different product

Treemoss extracts

categories, which are the acceptable use levels of Treemoss extracts in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 1974. Human Maximization Test. RIFM report number 1779, September 12 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1990a. Human Repeated Insult Patch Test. RIFM report number 12382, March 1 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1990b. Human Repeated Insult Patch Test. RIFM report number 14120, November 26 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1990c. Human Repeated Insult Patch Test. RIFM report number 14118, November 26 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2004. Local Lymph Node Assay. RIFM report number 44368, March 25 (RIFM, Woodcliff Lake, NJ, USA).

2,6,6-Trimethylcyclohexa-1,3-dienyl methanal (Safranal)

CAS N°: 116-26-7

Initial review: December 1998

RECOMMENDATION: RESTRICTED

RESTRICTIONS:

Limits in the finished product:	
Skin contact:	0.005%
Non skin contact:	0.05%

2,6,6-Trimethylcyclohexa-1,3-dienyl methanal (Safranal) should not be used such that the level in consumer products exceeds 0.005 %. This is equivalent to 0.025% in a fragrance compound used at 20% in the consumer product.

For use in consumer products for which no skin contact is foreseeable under normal conditions of use, e.g. closed system air freshners, toilet blocks but not rinse off products and household cleaning products, the level in the consumer product should not exceed 0.05%.

This recommendation is based on test results showing sensitization reaction when tested at 0.1% and no sensitization reaction when tested at 0.05% in a Human Repeated Insult Patch Test (private communication to IFRA).

2,4-Undecadienal

CAS N°: 13162-46-4
(Including all geometric isomers)

Empirical formula: $C_{11}H_{18}O$

Synonyms: N/A

History:

Initial reviews:	New Standard	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2010
Next review date	N/A	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products:	N/A	Rinse-off products:	N/A
		Including household cleaning products	
Non skin contact products:	N/A		

Note box:

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the **Introduction to the IFRA Standards**)

Critical effect: **Insufficient Data**

REXPAN Rationale / Conclusion:
The material has been reviewed by the RIFM Expert Panel with the conclusion that it should not be used as or in fragrance ingredients until additional data is available and considered sufficient to support its safe use.
This conclusion is based on:
1) presence of structural alerts as defined in the Human Health Criteria Document (Ford et al., 2000) and/or
2) adverse data on the material itself and/or
3) adverse data for a structurally related material

2,4-Undecadienal

References:

Human Health Criteria Document, *Regulatory Toxicology and Pharmacology*, 31, 166-181, 2000

Verbena absolute (Lippia citriodora Kunth.)

CAS N°: 8024-12-2
85116-63-8

Empirical formula: N/A

Synonyms: Lippia citriodora absolute
Verbena absolute
Aloysia triphylla absolute
Lippia triphylla absolute
Verbena triphylla absolute
Zappania citrodora absolute

History:

Initial reviews:	November 1987	
Current revision date:	June 11, 2010	
Implementation date:	For new submissions*:	August 11, 2010
	For existing fragrance compounds*:	August 11, 2011
Next review date:	2015	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: RESTRICTED

RESTRICTIONS:

Limits in the finished product:			
Category 1 See Note box (1)	0.05%	Category 7	0.12%
Category 2	0.06%	Category 8	0.2%
Category 3	0.2%	Category 9	0.2%
Category 4	0.2%	Category 10	0.2%
Category 5	0.2%	Category 11	See Note box (2)
Category 6 See Note box (1)	1.2%		

Note box:

For this material, for pragmatic reasons, restrictive levels allowed by the QRA for certain categories but actually being higher than those already in place before applying the QRA, will temporarily not be implemented until the end of a 5 year monitoring phase. At the end of the 5 years the position will be reevaluated again.

(1) See the IFRA Code of Practice (Appendix 8, Introduction to the IFRA Standards) regarding the Note on Oral Care Products and other products with the potential of ingestion.
(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Verbena absolute (Lippia citriodora Kunth.)

Indicative contribution from other sources: N/A

Critical effect: Sensitization

RIFM Summaries:

LLNA weighted EC3 values (µg/cm²) [no. studies]	Potency Classification Based on Animal Data[1]	Human Data[2]			WoE NESIL[3] (µg/cm²)
		NOEL – HRIPT (induction) (µg/cm²)	NOEL – HMT (induction) (µg/cm²)	LOEL (induction) (µg/cm²)	
4500 [1][4]	Weak	1600	1380	8280[5]	1600

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1]Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[2]Data derived from HRIPT or HMT.
[3]WoE NESIL limited to two significant figures.
[4]EC3 value from one LLNA, not the mean.
[5]LOEL from human maximization test, not a human repeated insult patch test.

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for verbena absolute and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 1600 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of verbena absolute in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the publication by Api *et al*., 2008.

References:

Api AM, Basketter DA, Cadby PA, Cano M-F, Ellis G, Gerberick GF, et al. Dermal Sensitization Quantitative Risk Assessment (QRA) For Fragrance Ingredients. *Regulatory Toxicology and Pharmacology* 2008;52(1): 3-23.

RIFM (Research Institute for Fragrance Materials, Inc.), 1979. Maximization study with verbena absolute. RIFM report number 1697, October 24a. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2009. Cutaneous tolerance and sensitizing potential of verbena. Unpublished study from Robertet, September 23. Report number 58178. (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2009. Local Lymph Node Assay. Unpublished study from Robertet, January 23. Report number 54268. (RIFM, Woodcliff Lake, NJ, USA).

Verbena oil

CAS N°: 8024-12-2 **Empirical formula:** N/A

Synonyms: Lippia citriodora oils

History:

Initial reviews:	December 1981	
Current revision date:	September 2002	
Implementation date:	For new submissions*:	N/A
	For existing fragrance compounds*:	N/A
Next review date		

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **PROHIBITED**

RESTRICTIONS:

Limits in the finished product:

Skin contact products:

Leave-on products: N/A Rinse-off products: N/A

Including household cleaning products

Non skin contact products: N/A

Note box:

Verbena oil from *Lippia citriodora* Kunth should not be used as a fragrance ingredient, based on its sensitizing and phototoxic potential. Commercial compositions of the verbena type should meet the requirements of the IFRA Standards.

Fragrance material specifications: N/A

Contribution from other sources: None to consider (see also the note on contributions from other sources in the Introduction to the IFRA Standards).

Critical effect: **Sensitization** and **Phototoxicity**

REXPAN Rationale / Conclusion:

IFRA ban noted – REXPAN, September 2002.

References:

Private communication to IFRA.

Vetiveryl acetate

CAS N°: 117-98-6
62563-80-8
68917-34-0
73246-97-6
84082-84-8

Empirical formula: $C_{17}H_{26}O_2$

Synonyms: 6-Azulenol, 1,2,3,3a,4,5,6,8a-octahydro-4,8-dimethyl-2-(methylethylidene)-, acetate
6-Azulenol, 1,2,3,3a,4,5,6,8a-octahydro-4,8-dimethyl-2-(1-methylethylidene)-, acetate
2-Isopropylidene-4,8-dimethyl-1,2,3,3a,4,5,6,8a-octahydroazulen-6-yl acetate
Vetivert acetate, Vetivert acetate (Haiti), Vetyvenyl acetate
Vetiverol, acetate

History:

Initial reviews:	New Standard	
Current revision date:	2009	
Implementation date:	For new submissions*:	August 7, 2009
	For existing fragrance compounds*:	August 7, 2011
Next review date	2014	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED / SPECIFICATION**

RESTRICTIONS:

Limits in the finished product:
For a description of the categories, refer to the QRA Information Booklet.

Category 1 - See Note box (1)	0.07 %	Category 7	0.17 %
Category 2	0.08 %	Category 8	2.00 %
Category 3	0.35 %	Category 9	5.00 %
Category 4	1.04 %	Category 10	2.50 %
Category 5	0.55 %	Category 11	See Note box (2)
Category 6 - See Note box (1)	1.67 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry - www.iofiorg.org)

Vetiveryl acetate

(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to negligible skin contact the concentration of a fragrance ingredient should not exceed the usual concentration of the fragrance compound in the finished product.	
Fragrance material specifications:	Acetylated vetiver oil (Vetiveryl acetate) should only be used as a fragrance ingredient if produced by methods that lead to a reduction in allergenic materials, like the ones outlined below (acetylation methods using acetic anhydride): • without catalyst, at a temperature not exceeding 120°C. • with ortho phosphoric acid at room temperature. • with sodium acetate in toluene at reflux temperature. The first two products can be used in their crude form after the usual procedures, but may be further purified. In the last case, distillation is necessary. Another method accepted is an enzymatic acetylation process. This recommendation is based on test results of RIFM with samples prepared according to different acetylation methods (private communication to IFRA).

Contribution from other sources: None to consider (see also note on contributions from other sources in the **Introduction to the IFRA Standards**)

Critical effect: Sensitization

RIFM Summaries:

LLNA weighted mean EC3 values ($\mu g/cm^2$) [no. studies]	Potency Classification[2]	Human Data			WoE NESIL[3] ($\mu g/cm^2$)
		NOEL – HRIPT (induction) ($\mu g/cm^2$)	NOEL – MAX (induction) ($\mu g/cm^2$)	LOEL[1] (induction) ($\mu g/cm^2$)	
2910 [4]	Weak	2362	NA	NA	2300

All data in this Table are available from RIFM and are listed in the RIFM Database.
NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available.

[1] Data derived from HRIPT or HMT.
[2] Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003.
[3] WoE NESIL limited to two significant figures.

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Vetiveryl acetate and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 2300 mg/cm2. They recommend the limits for the 11 different product categories, which are the acceptable use levels of Vetiveryl acetate in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

Vetiveryl acetate

References:

Jones, L., Foxenberg, R., Lalko, J., Letizia, C., Api, A, 2008. Sensitization potential of vetiveryl acetate evaluated using the Local Lymph Node Assay. The Toxicologist, 102, 298.

RIFM (Research Institute for Fragrance Materials, Inc.), 2008. Local Lymph Node Assay. RIFM report number 55336, July 29. (RIFM, Woodcliff Lake, NJ, USA).

Ylang Ylang extracts

CAS N°: 8006-81-3
68606-83-7
83863-30-3

Empirical formula: N/A

Synonyms: Cananga odorata (Lamark) (Hooker et Thompson) (Anonaceae)
Cananga odorata extract
Cananga odorata flower oil
Cananga odorata oil
Cananga oil
Ylang ylang oil (Cananga odorata Hook. f. and Thomas)
Ylang ylang oil extra
Ylang ylang oil I
Ylang ylang oil II
Ylang ylang oil III
Ylang ylang, Cananga odorata, ext.

History:

Initial reviews:	New Standard	
Current revision date:	2008	
Implementation date:	For new submissions*:	August 16, 2008
	For existing fragrance compounds*:	August 16, 2010
Next review date	2013	

* This date applies to the supply of fragrance compounds (formulas) only, not to the finished products in the marketplace.

RECOMMENDATION: **RESTRICTED**

RESTRICTIONS:

Limits in the finished product:

Category 1 See Note box (1)	0.05 %	Category 7	0.1 %
Category 2	0.06 %	Category 8	1.8 %
Category 3	0.27 %	Category 9	5.0 %
Category 4	0.8 %	Category 10	2.5 %
Category 5	0.4 %	Category 11	Not Restricted (2)
Category 6 See Note box (1)	1.3 %		

Note box:

(1) IFRA would recommend that any material used to impart perfume or flavour in products
intended for human ingestion should consist of ingredients that are in compliance with appropriate regulations for foods and food flavourings in the countries of planned distribution and, where these are lacking, with the recommendations laid down in the Code of Practice of IOFI (International Organisation of the Flavor Industry)

Ylang Ylang extracts

http://www.iofiorg.org/.
(2) Category 11 includes all non-skin contact or incidental skin contact products. Due to the negligible skin contact from these types of products there is no justification for a restriction of the concentration of this fragrance ingredient in the finished product.

Fragrance material specifications: N/A

Contribution from other sources: N/A

Critical effect: **Sensitization**

RIFM Summaries:

LLNA weighted mean EC3 values (µg/cm^2) [no. studies]	Potency Classification Based on Animal Data[2]	Human Data			WoE NESIL[3] (µg/cm^2)
		NOEL – HRIPT (induction) (µg/cm^2)	NOEL – HMT (induction) (µg/cm^2)	LOEL[1] (induction) (µg/cm^2)	
1700	Moderate	1772[4]	6897[4]	7752	1770

NOEL = No observed effect level; HRIPT = Human Repeat Insult Patch Test; HMT = Human Maximization Test; LOEL = lowest observed effect level; NA = Not Available
1 Based on animal data using classification defined in ECETOC, Technical Report No. 87, 2003
2 Data derived from HRIPT or HMT
3 WoE NESIL limited to three significant figures
4 MT-NOEL = Maximum Tested No Effect Level. No sensitization was observed in human predictive studies. Doses reported reflect the highest concentration tested, not necessarily the highest achievable NOEL

REXPAN Rationale / Conclusion:

The RIFM Expert Panel reviewed the critical effect data for Ylang Ylang Extracts and, based on the weight of evidence, established the No Expected Sensitization Induction Level (NESIL) as 230 µg/cm². They recommend the limits for the 11 different product categories, which are the acceptable use levels of Ylang Ylang Extracts in the various product categories. These were derived from the application of the exposure-based quantitative risk assessment approach for fragrance ingredients, which is detailed in the QRA Expert Group Technical Dossier of June 22, 2006.

References:

RIFM (Research Institute for Fragrance Materials, Inc.), 1971a. Human Maximization Test. RIFM report number 1805, April 20 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1971b. Human Repeated Insult Patch Test. RIFM report number 7906, April 13 and August 23 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1972a. Human Maximization Test. RIFM report number 1804, February 18 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1972b. Human Repeated Insult Patch Test. RIFM report number 14033, March 21 (RIFM, Woodcliff Lake, NJ, USA).

Ylang Ylang extracts

RIFM (Research Institute for Fragrance Materials, Inc.), 1975. Human Maximization Test. RIFM report number 1798, March 28 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 1979. Human Maximization Test. RIFM report number 1697, July 6a (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2007a. Human Repeated Insult Patch Test. RIFM report number 52898, May 15 (RIFM, Woodcliff Lake, NJ, USA).

RIFM (Research Institute for Fragrance Materials, Inc.), 2007b. Local Lymph Node Assay. RIFM report number 52903, April 24 (RIFM, Woodcliff Lake, NJ, USA).

International Fragrance Association (IFRA)

Avenue des Arts, 6, B-1210 Brussels, Belgium
Tel:+32 2 214 2067 - Fax:+32 2 214 2069

www.ifraorg.org