Who is IFRA?

Set up in 1973

Global trade association network to represent the fragrance industry & promote the safe use and benefits of fragrances

Members are associations and companies (Drom, Firmenich, Givaudan, I.F.F., Robertet, Symrise, Takasago)

Organizational structure in 4 regions (Asia-Pacific, North America, South-America and Europe/Middle East)

90% of the worldwide market (in volume)
IFRA

North America
Canada
USA

Latin America
Argentina
Brazil
Chile
Colombia
Mexico

EMEA
Europe – Middle East - Africa
France
Germany
Italy
Netherlands
Spain
South Africa
Switzerland
Turkey
UK

Asia-Pacific
Australia
China
Indonesia
Japan
Singapore
South Korea
What we do

Global safety program

IFRA Code of Practice

IFRA Standards

Compliance program – capacity building

Issue management and advocacy
IFRA Standards

Establishment of usage standards for fragrance ingredients: voluntary initiative

Based on safety assessments carried out by the Research Institute for Fragrance Materials (RIFM) and reviewed by the industry’s panel

Member companies have to comply with the Standards
Experts advising the industry for risk assessment

Dr. I. Glenn Sipes, PhD
Prof. Peter Calow, PhD
Prof. Donald V. Belsito, MD
Prof. Allison D. Fryer, PhD
Dr. Terry Schultz
Dr. Daniel C. Liebler, PhD

Prof. Magnus Bruze, MD
Prof. Dr. Wolfgang Dekant

Prof. Maria L. Z. Dagli, DVM, PhD

Dr. Yoshiki Miyachi, MD, PhD
IFRA Code of Practice

- Currently **191 IFRA Standards for fragrance ingredients**
- Latest Amendment (48th) notified June 10, 2015
- 77 Standards prohibiting the use of certain fragrance ingredients
- 100 Standards restrict the use of particular fragrance ingredients in fragrance compounds
- 14 raw materials: special purity criteria (when toxicity results from an impurity - e.g. limitation of sensitizing (hydro)-peroxides of Linalool or Limonene)
- Some Standards do not only cover individual materials but groups (Rose Ketones) and some materials can have more than one type of rules applying (restriction and purity criteria for Oak and Tree moss).
- Next regular Amendment to be notified in 2017
Overview of the IFRA Standards available in the website

All the information related to the IFRA Standards is available at http://www.ifraorg.org/en-us/standards#.VjyAjCtZiuw
Overview of the IFRA Standards available in the website

1) QRA Restriction Standards

<table>
<thead>
<tr>
<th>Material</th>
<th>CAS Number</th>
<th>Amendment</th>
<th>Category 1</th>
<th>Category 2</th>
<th>Category 3</th>
<th>Category 4</th>
<th>Category 5</th>
<th>Category 6</th>
<th>Category 7</th>
<th>Cat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic, anhydride, reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene</td>
<td>144020-22-4, 28371-99-5</td>
<td>48</td>
<td>0.16</td>
<td>0.20</td>
<td>0.83</td>
<td>2.49</td>
<td>1.31</td>
<td>3.99</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>Acetylated Vetiver oil</td>
<td>117-98-6</td>
<td>48</td>
<td>0.07</td>
<td>0.08</td>
<td>0.35</td>
<td>1.04</td>
<td>0.55</td>
<td>1.67</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Alчисленate</td>
<td>7493-74-5</td>
<td>44</td>
<td>0.02</td>
<td>0.03</td>
<td>0.11</td>
<td>0.32</td>
<td>0.17</td>
<td>0.51</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>α-Amyl cinnamic alcohol</td>
<td>101-85-9</td>
<td>42</td>
<td>0.10</td>
<td>0.10</td>
<td>0.50</td>
<td>1.60</td>
<td>0.80</td>
<td>2.50</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>α-Amyl cinnamic aldehyde</td>
<td>122-40-7</td>
<td>47</td>
<td>0.70</td>
<td>0.90</td>
<td>3.60</td>
<td>10.70</td>
<td>5.60</td>
<td>17.10</td>
<td>1.80</td>
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<tr>
<td>Anisyl alcohol</td>
<td>105-13-5</td>
<td>48</td>
<td>0.04</td>
<td>0.06</td>
<td>0.23</td>
<td>0.68</td>
<td>0.36</td>
<td>1.09</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>Benzaldehyde</td>
<td>100-52-7</td>
<td>47</td>
<td>0.02</td>
<td>0.02</td>
<td>0.09</td>
<td>0.27</td>
<td>0.14</td>
<td>0.43</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>100-51-6</td>
<td>42</td>
<td>0.20</td>
<td>0.20</td>
<td>0.90</td>
<td>2.70</td>
<td>1.40</td>
<td>4.30</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Benzyl benzoate</td>
<td>120-51-4</td>
<td>42</td>
<td>1.70</td>
<td>2.20</td>
<td>8.90</td>
<td>26.70</td>
<td>14.00</td>
<td>42.80</td>
<td>4.50</td>
<td></td>
</tr>
<tr>
<td>Benzyl cinnamate</td>
<td>103-41-3</td>
<td>42</td>
<td>0.10</td>
<td>0.20</td>
<td>0.70</td>
<td>2.10</td>
<td>1.10</td>
<td>3.40</td>
<td>0.40</td>
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</tr>
<tr>
<td>Benzyl salicylate</td>
<td>118-58-1</td>
<td>42</td>
<td>0.50</td>
<td>0.70</td>
<td>2.70</td>
<td>8.00</td>
<td>4.20</td>
<td>12.80</td>
<td>1.30</td>
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<tr>
<td>α-Butylicinnalamaldehyde</td>
<td>7492-44-6</td>
<td>46</td>
<td>0.03</td>
<td>0.04</td>
<td>0.15</td>
<td>0.45</td>
<td>0.24</td>
<td>0.72</td>
<td>0.08</td>
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</tr>
<tr>
<td>3-(m-tert-Butylphenyl)-2-methylpropionialdehyde (m-BMHCA)</td>
<td>62518-65-4</td>
<td>48</td>
<td>0.12</td>
<td>0.15</td>
<td>0.62</td>
<td>1.86</td>
<td>0.98</td>
<td>2.97</td>
<td>0.31</td>
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</tr>
<tr>
<td>p-tert-Butyldihydrocinnalamaldehyde (Bourgeois)</td>
<td>18127-01-0</td>
<td>43</td>
<td>0.03</td>
<td>0.04</td>
<td>0.20</td>
<td>0.50</td>
<td>0.30</td>
<td>0.80</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>p-tert-Butyl-α-methylhydrocinnalamaldehyde (BMHCA)</td>
<td>80-54-6</td>
<td>47</td>
<td>0.10</td>
<td>0.20</td>
<td>0.60</td>
<td>1.90</td>
<td>1.00</td>
<td>3.00</td>
<td>0.30</td>
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</tr>
<tr>
<td>Carvone</td>
<td>99-49-0</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
### Overview of the IFRA Standards available in the website

#### 2) Non-QRA Restriction Standards

**IFRA non QRA Restricted Standards - 48th Amendment to the Code of Practice**

<table>
<thead>
<tr>
<th>Material</th>
<th>CAS Number</th>
<th>Amendment</th>
<th>Skin contact products</th>
<th>Non skin contact products</th>
<th>Note box</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-Abiet-1,2,3,6-tetraol, crude</td>
<td>1523-25-0</td>
<td>48</td>
<td>2</td>
<td>No Restriction</td>
<td></td>
</tr>
<tr>
<td>Angelica root oil</td>
<td>8016-64-3</td>
<td>48</td>
<td>0.8</td>
<td>No Restriction</td>
<td></td>
</tr>
<tr>
<td>Bergamot oil expressed</td>
<td>39090-57-9</td>
<td>48</td>
<td>0.4</td>
<td>No Restriction</td>
<td></td>
</tr>
<tr>
<td>Black orange peel expressed</td>
<td>6899-54-8</td>
<td>48</td>
<td>0.15</td>
<td>No Restriction</td>
<td></td>
</tr>
<tr>
<td>Citrus oils and other functional containing essential oils (Bergamot)</td>
<td>-</td>
<td>48</td>
<td>0.0025</td>
<td>No Restriction</td>
<td></td>
</tr>
<tr>
<td>Cumin oil</td>
<td>8014-10-0</td>
<td>48</td>
<td>0.4</td>
<td>No Restriction</td>
<td></td>
</tr>
<tr>
<td>Grapefruit oil expressed</td>
<td>8076-20-4</td>
<td>48</td>
<td>4</td>
<td>No Restriction</td>
<td></td>
</tr>
<tr>
<td>Lemon oil expressed</td>
<td>8008-56-6</td>
<td>48</td>
<td>2</td>
<td>No Restriction</td>
<td></td>
</tr>
<tr>
<td>Lime oil expressed</td>
<td>8008-20-0</td>
<td>48</td>
<td>0.7</td>
<td>No Restriction</td>
<td></td>
</tr>
<tr>
<td>Methyl salicylate</td>
<td>95-52-9</td>
<td>48</td>
<td>0.1</td>
<td>No Restriction</td>
<td></td>
</tr>
<tr>
<td>Methyl farnesit locone</td>
<td>95-58-3</td>
<td>48</td>
<td>0.2</td>
<td>No Restriction</td>
<td></td>
</tr>
<tr>
<td>Peat oil</td>
<td>3614-29-7</td>
<td>48</td>
<td>0.15</td>
<td>No Restriction</td>
<td></td>
</tr>
<tr>
<td>Tangerine oil absolute</td>
<td>9722-25-1</td>
<td>48</td>
<td>0.01</td>
<td>No Restriction</td>
<td></td>
</tr>
</tbody>
</table>

**Limits in the finished product (%)**

<table>
<thead>
<tr>
<th>Material</th>
<th>CAS Number</th>
<th>Amendment</th>
<th>Fine Fragrance</th>
<th>Eau de Toilette</th>
<th>Fragrancing cream</th>
<th>Other Leave on</th>
<th>Rinse off</th>
<th>Non-skin, incidental skin contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruital</td>
<td>165-95-1</td>
<td>47</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Lily sylage</td>
<td>140-07-0</td>
<td>48</td>
<td>0.2</td>
<td>0.3</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Petrol, sylage</td>
<td>52-72-2</td>
<td>48</td>
<td>0.02</td>
<td>0.003</td>
<td>0.004</td>
<td>0.004</td>
<td>0.001</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Restriction Details**

<table>
<thead>
<tr>
<th>Restriction Standards</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>(QRA cat)</td>
<td></td>
</tr>
<tr>
<td>(non QRA)</td>
<td></td>
</tr>
<tr>
<td>Specification Stds</td>
<td></td>
</tr>
<tr>
<td>Prohibition Stds</td>
<td></td>
</tr>
</tbody>
</table>
### Overview of the IFRA Standards available in the website

#### 3) Specification Standards

<table>
<thead>
<tr>
<th>Material</th>
<th>CAS Number</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allyl Esters</td>
<td>N/A</td>
<td>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.</td>
</tr>
<tr>
<td>Allyl phenoxyacetate</td>
<td>7493-74-5</td>
<td>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.</td>
</tr>
<tr>
<td>Birch wood pyrolysate</td>
<td>8001-88-5</td>
<td>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. Limit content of polynuclear aromatic hydrocarbons (PAH) resulting from the use of rectified oils according to Good Manufacturing Practice. Benzopyrene and 1,2-Benzanthracene are to be used as markers for PAH. If used alone or in combination with rectified Cade oil, rectified Styrax oil or rectified Opoponax oil, the total concentration of both of the markers should not exceed 1 ppb in the final product.</td>
</tr>
<tr>
<td></td>
<td>84012-15-7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>85940-29-0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>68917-50-0</td>
<td></td>
</tr>
<tr>
<td>Cade oil (Juniperus oxycedrus L.)</td>
<td>8013-10-3</td>
<td>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. Limit content of polynuclear aromatic hydrocarbons (PAH) resulting from the use of rectified oils according to Good Manufacturing Practice.</td>
</tr>
<tr>
<td></td>
<td>90046-02-9</td>
<td></td>
</tr>
</tbody>
</table>
### Overview of the IFRA Standards available in the website

#### 4) Prohibition Standards

<table>
<thead>
<tr>
<th>Material</th>
<th>CAS Number</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetyl ethyl tetramethyl tetralin (AETT, Versalide)</td>
<td>88-29-9</td>
<td></td>
</tr>
<tr>
<td>Acetyl isovaleryl (5-Methyl-2,3-hexanedione)</td>
<td>13706-86-0</td>
<td></td>
</tr>
<tr>
<td>Alantroot oil (Elecampane oil)</td>
<td>97676-35-2</td>
<td></td>
</tr>
<tr>
<td>Allyl heptine carbonate</td>
<td>73157-43-4</td>
<td></td>
</tr>
<tr>
<td>Allyl isothiocyanate</td>
<td>57-06-7</td>
<td></td>
</tr>
<tr>
<td>Amylcyclopentenone</td>
<td>25564-22-1</td>
<td></td>
</tr>
<tr>
<td>Anisylidene acetone (4-(p-methoxyphenyl)-3-butene-2-one)</td>
<td>943-88-4</td>
<td>The total level of cis- and trans-asarone resulting from natural presence in essential oils (e.g. calamus oil) should not exceeds 0,01% in the finished product.</td>
</tr>
<tr>
<td>cis-and trans-Asarone ((E)-and(Z)-2,4,5-Trimethoxypropen-1-yl benzene)</td>
<td>2883-98-9</td>
<td>The total level of cis- and trans-asarone resulting from natural presence in essential oils (e.g. calamus oil) should not exceeds 0,01% in the finished product.</td>
</tr>
<tr>
<td></td>
<td>5273-86-9</td>
<td></td>
</tr>
<tr>
<td>Benzene</td>
<td>71-43-2</td>
<td>The level of benzene has to be kept as low as practicable and should never exceed 1ppm in the fragrance compound.</td>
</tr>
<tr>
<td>Benzyl cyanide</td>
<td>140-29-4</td>
<td>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 authorized as long as the level of benzyl cyanide in the finished product does not exceed 100ppm.</td>
</tr>
<tr>
<td>Benzyldiene acetone (4-Phenyl-3-buten-2-one)</td>
<td>122-57-6</td>
<td>The rectified (purified) birch tar oils can be used insofar the below requirement is respected:</td>
</tr>
</tbody>
</table>
## Annex I
including the new IFRA-RIFM Nomenclature for NCS

### Annex I to the IFRA Standards - 48th Amendment

A compound under its conditions of use. However, if reliable analysis has shown that the level of the limited substance in a specific fragrance material is not the same as the indicative level given in this Annex, then the analyzed level can be used.

The list is intended to be as comprehensive as possible but still remains illustrative only and cannot be regarded as exhaustive.

### Part I

**Part I** is an alphabetical list of the materials that have a standard and for which contributions from other sources need to be taken into account, listing the sources with indicative values.

<table>
<thead>
<tr>
<th>CAS No.</th>
<th>Principle Name</th>
<th>Level (%)</th>
<th>Essential oil Category</th>
<th>RIFM ID</th>
<th>Principle/Main CAS/RIFM DATABASE</th>
<th>ALTERNATIVE/EINECS CAS NO</th>
<th>Principle Name</th>
<th>Botanical/Binomial name</th>
</tr>
</thead>
<tbody>
<tr>
<td>2442-10-6</td>
<td>1-Octen-3-yl acetate</td>
<td>0,2</td>
<td>F2.1</td>
<td>190</td>
<td>8022-15-9</td>
<td>91722-69-9</td>
<td>Lavandin absolute</td>
<td>Lavandula officinalis x Lavandula latifolia</td>
</tr>
<tr>
<td>2442-10-6</td>
<td>0,2</td>
<td>F2.7</td>
<td>190</td>
<td>8022-15-9</td>
<td>91722-69-9</td>
<td>Lavandin concrete</td>
<td>Lavandula officinalis x Lavandula latifolia</td>
<td></td>
</tr>
<tr>
<td>2442-10-6</td>
<td>0,3</td>
<td>F2.12</td>
<td>5333</td>
<td>8022-15-9</td>
<td>93455-97-1</td>
<td>Lavandin grosso oil</td>
<td>Lavandula x intermedia grosso</td>
<td></td>
</tr>
<tr>
<td>2442-10-6</td>
<td>0,7</td>
<td>F2.1</td>
<td>169</td>
<td>8000-28-0</td>
<td>84776-65-8; 90063-37-9; 97722-12-8</td>
<td>Lavender absolute</td>
<td>Lavandula angustifolia Mill.</td>
<td></td>
</tr>
<tr>
<td>2442-10-6</td>
<td>0,5</td>
<td>F2.1</td>
<td>169</td>
<td>8000-28-0</td>
<td>84776-65-8 and 90063-37-9</td>
<td>Lavender concrete</td>
<td>Lavandula angustifolia Mill.</td>
<td></td>
</tr>
<tr>
<td>2442-10-6</td>
<td>0,9</td>
<td>F2.12</td>
<td>169</td>
<td>8000-28-0</td>
<td>84776-65-8; 90063-37-9; 97722-12-8</td>
<td>Lavender oil</td>
<td>Lavandula officinalis Chaix</td>
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</tr>
<tr>
<td>2442-10-6</td>
<td>0,5</td>
<td>E2.12</td>
<td>83</td>
<td>68917-15-7</td>
<td>85085-49-0</td>
<td>Mentha citrata oil</td>
<td>Mentha citrata Ehrhart</td>
<td></td>
</tr>
<tr>
<td>2442-10-6</td>
<td>0,06</td>
<td>E2.12</td>
<td>771</td>
<td>8068-79-5</td>
<td>84696-51-5</td>
<td>Spearmint oil</td>
<td>Mentha spicata L.</td>
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</tr>
<tr>
<td>2442-10-6</td>
<td>0,06</td>
<td>E2.13</td>
<td>771</td>
<td>98561-44-5</td>
<td></td>
<td>Spearmint, Mentha spicata crispa, extract</td>
<td>Mentha spicata L. spicata</td>
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</tr>
<tr>
<td>1504-74-1</td>
<td>o-Methoxycinnamaldehyde</td>
<td>2</td>
<td>C2.13</td>
<td>327</td>
<td>8007-80-5</td>
<td>84961-46-6</td>
<td>Cassia bark extract</td>
<td>Cinnamomum cassia Blume</td>
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<tr>
<td>1504-74-1</td>
<td>4</td>
<td>E2.12</td>
<td>327</td>
<td>8007-80-5</td>
<td>84961-46-6</td>
<td>Cassia oil</td>
<td>Cinnamomum cassia Blume</td>
<td></td>
</tr>
<tr>
<td>17369-59-4</td>
<td>3-Propyldienephthalide</td>
<td>0,1</td>
<td>A2.12</td>
<td>813</td>
<td>8016-31-7</td>
<td>84837-06-9</td>
<td>Lovage root oil</td>
<td>Levisticum officinale Koch</td>
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<tr>
<td>2883-98-9</td>
<td>trans-Asarone/alpha-Asarone</td>
<td>4</td>
<td>A2.12</td>
<td>576</td>
<td>8015-79-0</td>
<td></td>
<td>Calamus oil</td>
<td>Acorus calamus L.</td>
</tr>
<tr>
<td>2883-98-9</td>
<td>0,1</td>
<td>E2.1</td>
<td>776</td>
<td>8024-12-2</td>
<td>85115-63-8</td>
<td>Verbena absolute</td>
<td>Aloysia citrodora Palau</td>
<td></td>
</tr>
<tr>
<td>5273-86-9</td>
<td>cis-Asarone/beta-Asarone</td>
<td>70</td>
<td>A2.12</td>
<td>576</td>
<td>8015-79-0</td>
<td></td>
<td>Calamus oil</td>
<td>Acorus calamus L.</td>
</tr>
</tbody>
</table>

02 June 2016

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IFRA Standards - recognition

IFRA Standards are the only globally recognized risk management system for fragrance ingredients with high appreciation by customers and regulatory authorities.

- An IFRA Certificate is required for product notifications in Argentina and Brazil.
- The ASEAN Cosmetics Directive Guidelines for Safety Assessment contain a requirement for proving IFRA compliance.
- The Cosmetic Products Group Standard in New Zealand requires compliance with IFRA Standards.
- China has included IFRA Standards up to the 43rd Amendment in a Chinese standard (GB/T 22731-2008) and is currently working on an update.
- Most of the IFRA banned as well as a number of restricted materials have been included into Annex II of the EU Cosmetics Directive (IL 748, 2006, IL 802, 2008)
for more information please consult our website: www.ifraorg.org
Fragrance ingredients
What are we talking about?

Some are hazardous and some are not. Some are sensitizers, a few are potent, most are weak sensitizers. Some may cause allergy (and actually do). Some have other toxicological properties and some are not hazardous at all.

All are managed via industry’s safety assessment process.
Rose oil – at the heart of perfumery
Rose oil – at the heart of perfumery

Methyleugenol – classified CMR – possible carcinogen to humans
So, Fragrances can be...
but sometimes...
Focus on (Skin) allergens and the current situation in Europe
Citrus oils
key fragrance ingredients
Citrus oils
key fragrance ingredients

$R (d)$-limonene  $S (l)$-limonene

Low sensitizing potential

Primary oxidation products
- limonene-1-hydroperoxide
- limonene-2-hydroperoxide

Secondary oxidation products
- carvone
- limonene epoxide
- limonene alcohols

Strong sensitizers

Structures kindly provided by A.T. Karlberg
Mechanism of allergic contact eczema

**Induction**

Chemical (hapten) contacts skin, penetrates into the epidermis and reacts with protein(s), disturbing the status quo and so releasing danger signals.

Activated Langerhans cells (LC) migrate to the local lymph node, differentiating as they go to get ready to interact with T cells.

Mature LC presents hapten to T cells for 12h to 24h.

**Elicitation**

Subsequent sufficient skin contact with chemical activates effector T cells and leads to eczema.

Systemic recirculation of memory/effector of skin homing T lymphocytes no earlier than one week after initial skin exposure to chemical.

This clonal expansion is the LLNA endpoint.

**Inflammation**

Clonal expansion of hapten specific T cells driven by multiple ligand-receptor interactions in the presence of a recognised hapten.
Contact-allergy diagnosis

Most of the dermatologist regard patch testing as the golden standard in diagnosis of contact allergy (CA) and allergic contact dermatitis (ACD).

Photos kindly provided by Prof. A Goossens K.U.Leuven
**FM 1 and FM2**

- **FM1** (introduced as a 'screening tool' by Larsen in 1977); mixture of 8 fragrance ingredients (each 1%) plus plus emulsifier Sorbitan Sesquioleate. Solvent Petrolatum.

  - alpha-Amyl cinnamic aldehyde
  - Eugenol
  - Oak moss
  - Geraniol
  - aldehyde
  - Isoeugenol
  - Hydroxycitronellal
  - Cinnamic alcohol
  - Cinnamic


  - Citral 1%
  - Citronellol 0.5%
  - Farnesol 2.5%
  - Coumarin 2.5%
  - alpha-Hexylcinnamic aldehyde 5%
  - HMPCC (Lyral) 2.5%

- 42% of the patients reacting to FMII do also react to FMI

- Fragrance (as a mixture) is the second most common cause for contact allergy (following Nickel)
Fragrance allergens: clinical data

- Fragrance Mix I
- Fragrance Mix I
- Turpentine

Percentage in selected years:
- 1997: 10.2%
- 1999: 11.3%
- 2001: 12.5%
- 2003: 7.2%
- 2005: 7.8%
Fragrance allergens: clinical data

% positive Reaktionen


4.3 4.8 4.6 4.5 4.9 4.4 4.7 5.0 4.5 4.0
Dermal sensitization is a threshold phenomenon.

Thresholds for induction can be determined with a high level of reliability (contrary to elicitation thresholds).

2006 the fragrance industry started to apply the Quantitative Risk Assessment (QRA) approach to address sensitizing ingredients.

The output of a QRA for a dermal sensitizer is aimed to provide a level at which the sensitizer can be used in consumer products that will not cause induction of skin sensitization (for the majority of the population).
The QRA in a nutshell

**AEL - Acceptable Exposure Level**

**WoE NESIL ÷ SAF = AEL**

**Weight of Evidence**

**NESIL**

Which pre-clinical and/or clinical data are available

- Human data (historical) (HRIPT NOEL in µg/cm²)
- Local Lymph Node Assay (EC3 in µg/cm²)
- Guinea-pig data

Based on weight of evidence value expressed in µg/cm²

**Sensitization Assessment Factor**

Considerations for calculation of SAF:

- For the product type the SAF is:
  - Inter-individual = 10
  - Matrix Effects = 1-10
  - Use considerations = 1-10

Overall SAF is the multiple of the three defined areas

**Exposure**

Calculation for daily exposure to the contact allergen in the product type:

\[ \text{Exposure} = \left(\frac{\text{Amount of contact allergen in product (µg/g product)} \times \text{Amount product applied (g)}}{\text{Retention Factor / Surface area exposed (cm²)}} \right) \]

Calculated consumer exposure level (CEL) expressed in µg/cm²/day

Comparison of Acceptable Exposure Level (AEL) to calculated Consumer Exposure Level (CEL)

**AEL ≥ CEL to be acceptable**

Published in Regulatory, Toxicology & Pharmacology, Special Issue Oct. 2008, Api et al.
**QRA Dermal Sensitization**

*Citral in hydroalcoholics for unshaved skin*

---

- **Citral Level - log μg/cm²**

- **AEL > CEL**
  - Acceptable

- **1.7% - 37 μg/cm² CEL**
  - Unacceptable

- **0.64% - 14 μg/cm² AEL**

- **1400 μg/cm² WoE NESIL**

---

Survey information:
- **0.6% - 13 μg/cm² CEL**
- **1.7% - 37 μg/cm² CEL**

---

**SAF = 100 AEL < CEL**

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SCCS Opinion 2012

• Recommendations in the SCCS Opinion on fragrance allergens (SCCS/1459/11) adopted in June 2012 to:

  • Ban Atranol, Chloroatranol (impurities in Moss extracts) and HICC
  
  • Restrict 11 key fragrance ingredients (to 100 ppm based on elicitation (Cinnamic aldehyde, Cinnamic alcohol, Citral, Coumarin, Eugenol*, Farnesol*, Geraniol*, Hydroxycitronellal, Isoeugenol*, Limonene (oxidised), Linalool* (oxidised)) *incl. esters

  • Inform the consumer about up to 127 fragrance allergens

• Conclusions mainly based on elicitation (patch test) data and a categorization system defined by the SCCS.

• The market impact of the literal transposition of the proposed measures was estimated to affect more than 90% of the products in certain product categories (like fine fragrances).
IDEA – International Dialogue on the Evaluation of Allergens

Move the issue of dealing with allergens to a new dimension by building a multi-stakeholder dialogue.

Aim to agree on the fundamental concepts that form the basis of assessing and managing the risk of contact allergy and allergic contact dermatitis among consumers of cosmetics and other perfumed products.

IDEA was developed and is conducted in partnership with the EU Commission.

Official endorsement by Commissioner Tonio Borg 03/13.
Multi-stakeholder approach to allow an open exchange on different points of view on the same topic

MC Escher
1898 - 1972
IDEA Project

• IDEA consists of a series of workshops/expert meetings stimulating a dialogue to reach consensus on improving existing or developing new methodologies.

• Every year a public Annual Review takes place under the auspices of DG SANCO. It provides the opportunity to present an overview of the achievements made with the project over the year and an outlook into the next year in presence of stakeholders, the Commission and the SCCS.

• The work plan related to risk assessment that is the basis for IDEA covers:

  1. The definition of fragrance allergens / fragrance allergens of specific concern

      ▶ The study of pre- and pro-haptens (oxidation / hydrolysis)

      ▶ The refinement of the dermal sensitization QRA (Quantitative Risk Assessment) methodology
Participants in the workshops

- IDEA management team
- European Commission
- Scientific committees
- Independent experts
- Industry experts
- Industry observers

Participants are invited based on expertise and knowledge regarding the topic of the WS.

The list of participants is overseen by the Supervisory Group and DG Sanco.
IDEA Management

• **Supervisory Group** (currently 5 members) with no vested interests in industry activities: Prof. Jim Bridges (Chair), Prof. Helmut Greim, Dr. Alain Khaiat, Dr. Christin Mowad, Dr. Ian White

• SG to
  • monitor the process and ensure the scientific integrity and full transparency of the overall project.
  • validate the program and participant lists
  • nominate a Rapporteur of a WS and write a report.
  • adopt the report of the Rapporteur and the proposed action program.

• A vital role in the functioning of the WSs is with the moderator (Hans Bender)
Our priorities for 2016

• WG meeting on feasibility of prospective study to 'validate' the QRA (prove its effectiveness)

• Integration of Alternatives to Animal Testing into the QRA

• Structure activity predictions and TTC (for sensitization)

• Development of a robust protocol for pre and pro haptens to be incorporated in a subsequent QRA3
FYI and to answer further questions
### EC’s Regulatory proposal for Risk Management - Where are we?

<table>
<thead>
<tr>
<th>SCCS Recommendations</th>
<th>Regulatory proposal of 2014 for public consultation</th>
</tr>
</thead>
<tbody>
<tr>
<td>129 allergens to be labelled on pack when above 10/100 ppm in finished product</td>
<td>90 allergens declared on pack when above 10/100 ppm in finished product</td>
</tr>
<tr>
<td>11 substances to be restricted at 100ppm in finished products</td>
<td>11 substances managed through QRA (or peroxide threshold)</td>
</tr>
<tr>
<td>Ban of HICC and (chloro)atranol.</td>
<td>No HICC or (chloro)atranol above ‘traces’ – regulatory process just started</td>
</tr>
</tbody>
</table>
Why limitations?
Why not just ban a material?

• Induction of contact allergy is a threshold phenomenon – so if you have safe use levels – why not use them?
• Perfumers are artists and taking materials away is like reducing the palette of colours of a painter

Sorry Mr. Tizian, No more red!
Why limitations? Why not just ban a material?

- Oak moss is a major constituent of the ‘Chypre’ concept, which is characterized by the contrast between a fresh citrus accord and Oak moss.

- The term goes back to Francois Coty (1874 – 1934), who in 1917 created a perfume of the same name from fragrance materials that came predominantly from the Mediterranean region. ‘Kypre’ is the Corsican word for Chene (the French word for Oak) and Francois Coty was from Corsica.

- The perfume Chypre for the first time allowed a prominent role for Oak moss extracts.

- Numerous classic male and female perfumes, some of which may be counted cultural heritage, since then are based on the ‘Chypre’ concept.
Why limitations? Why not just ban a material?
Thank you very much for your attention

Dr. Matthias Vey, IFRA Scientific Director
Email: mvey@ifraorg.org