EU regulatory update on botanical substances and preparations in animal nutrition

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Classification of botanical substances and preparations in feed (Reg. (EC) No 1831/2003)

• Feed material
  – Nutritional purposes
  – Minor processing (crushed dried herbs and spices)

• Feed additive
  – Sensory additives: flavouring compounds
  – Zootechnical additive (FRESTA® F)

• Premixture of feed additives
  – Mixture of flavouring compounds
  – Mixtures of different additives (commercial products)
Botanically defined feed flavourings (BDF)
(by FEFANA – FFAC)

Type of Botanical

- EO (Essential oil)
- EX (Extract)
- Ti (Tincture)
- O (Oleoresin)
- R (Remains: absolute, distillate, concentrate and terpenes)

Distribution of BDF

- Total BDF: 246
  - Essential oil: 35%
  - Oleoresin: 30%
  - Extract: 23%
  - Tincture: 7%
  - Remains: 5%

Based on the specifications of the International Organization of Standardization

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From plant to feeding though

- **Plant**
  - Farming / wild harvesting
  - Basic processing of plants on farm (e.g. distillation)

- **Botanical**
  - Analytics
  - Identity
  - Development of specifications
  - Quality control
  - Standardisation
  - Fractioning

- **Feed Flavouring**
  - Blending of flavouring compounds
  - Coating
  - Spray on carrier material

- **Compound Feed**
  - Mixing of feed materials with additives
  - Processing (e.g. pelletizing)

- **Animal Feeding**
  - Feeding compound feed
Application of botanicals as feed additive

Plant → Botanical → Feed Flavouring

Manufacturer of botanicals → FFAC members/Applicant
Market and trade channels

- Manufacturer of essential oils and other botanical extracts produce botanicals for different markets.
- The market distribution of essential oils and other botanical extracts differs between the botanicals.
- The predominant user of botanicals is the food industry. Less than 10% of the overall botanical production is used in the feed industry.

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EFSA evaluation of botanicals

Preparatory work to streamline the evaluation process

- EFSA guidance: Safety assessment of botanical compounds and preparations
- Compendium of botanicals
- QPS concept
Safety assessment of botanical compounds and preparations (EFSA guidance, EFSA Journal 2009; 7(9):1249)

**Level A**

Assessment of existing data related to the preparation

- Sufficient data available for safety assessment
- Use levels ≤ history of safe use levels
- Consideration of exposure to substances of concern (TTC, NOAEL, safety margin)

**Level B**

Evaluation of additional data related to the preparation

- Toxicity studies required according to OECD guidelines
“...The purpose of the Compendium is to assist risk assessors responsible for the evaluation of specific ingredients in food supplements, in more easily identifying the compound(s) of concern on which to focus the assessment.

...without any judgment on whether they are suitable or not suitable for food applications in Europe; it has no legal or regulatory force pertaining to the legal classification of products or substances.”
The Compendium comprises around 900 botanical entries, identifying for each of them the scientific name, the most common synonyms, the plant part containing compound(s) of concern, the chemical(s) of concern, specific remarks and references of relevance for a safety assessment.

• **Annex A**: Botanicals for which not enough information on possible substances of concern or adverse effects could be found, or for which the information present could not be verified

• **Annex B**: Botanicals for which data are available but the Scientific Committee could not identify substances of concern, or other reasons for the inclusion in the compendium
QPS approach for botanicals (EFSA Journal 2014;12(3):3593)

Generic assessment system allowing for priority setting among botanicals to be evaluated

• The EFSA guidance for the safety assessment of botanicals foresees that botanicals for which an adequate body of knowledge exists could benefit from a “presumption of safety” without any need for further testing
• The applicability for botanical species of a Qualified Presumption of Safety (QPS) approach, similar to that developed for the assessment of selected microorganisms referred to EFSA and added to the food chain was considered
• The use of botanicals and botanical preparations in animal feed is excluded from consideration at this stage
Methodology for QPS assessment (EFSA Journal 2014;12(3):3593)
Methodology for QPS assessment (EFSA Journal 2014;12(3):3593)

Step 1: Definition of the botanical due to variation in composition
- Plant species/subspecies
- Plant origin/environmental conditions
- Plant parts
- Plant processing
## Composition of Rosemary oil of different origin

<table>
<thead>
<tr>
<th>Composition %</th>
<th>Rosemary oil</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spanish type</td>
<td>Moroccan type</td>
<td></td>
</tr>
<tr>
<td>a-pinene</td>
<td>18 - 26</td>
<td>9 - 14</td>
<td></td>
</tr>
<tr>
<td>camphene</td>
<td>8 - 12</td>
<td>2.5 - 6.0</td>
<td></td>
</tr>
<tr>
<td>b-pinene</td>
<td>2.0 - 6.0</td>
<td>4.0 - 9.0</td>
<td></td>
</tr>
<tr>
<td>b-myrcene</td>
<td>1.5 - 5.0</td>
<td>1.0 - 2.0</td>
<td></td>
</tr>
<tr>
<td>limonene</td>
<td>2.5 - 5.0</td>
<td>1.5 - 4.0</td>
<td></td>
</tr>
<tr>
<td>cineole</td>
<td>16 - 25</td>
<td>38 - 55</td>
<td></td>
</tr>
<tr>
<td>p-cymene</td>
<td>1.0 - 2.2</td>
<td>0.8 - 2.5</td>
<td></td>
</tr>
<tr>
<td>camphor</td>
<td>13 - 21</td>
<td>5.0 - 15</td>
<td></td>
</tr>
<tr>
<td>bornyl acetate</td>
<td>0.5 - 2.5</td>
<td>0.1 - 1.5</td>
<td></td>
</tr>
<tr>
<td>a-terpineol</td>
<td>1.0 - 3.5</td>
<td>1.0 - 2.6</td>
<td></td>
</tr>
<tr>
<td>borneol</td>
<td>2.0 - 4.5</td>
<td>1.5 - 5.0</td>
<td></td>
</tr>
<tr>
<td>verbenone</td>
<td>0.7 - 2.5</td>
<td>&lt; 0.4</td>
<td></td>
</tr>
</tbody>
</table>

### Definition of the botanical
- Variation in chemical composition is huge
- Availability of information on full composition is limited
- Are analytical methods available?
- Description of plant extracts in scientific trials is limited
Methodology for QPS assessment (EFSA Journal 2014;12(3):3593)

Step 2: Evaluation of available data (compositional/toxicological/use)
  - 99% characterisation
  - Quantify active substances
  - History of use
QPS approach for botanicals

• Reiterative applications of the assessment scheme to related botanicals or different botanical preparations obtained from the same plant variety can allow a QPS status to be derived for specific botanical groupings.

• The particularity of botanicals makes the possibility of establishing QPS status at high taxonomic levels quite limited.

• Still, the structured safety assessment scheme provides a practical method of implementing the Level A of the 2009 EFSA Guidance

• the QPS approach, while possible, offers only limited advantages over the existing procedure and may not be cost-effective in the short term

Bernard Bottex, Scientific Committee and Emerging Risks Unit
EFSA workshop: Barcelona, 6 May 2015
Substances of concern


“A discussion took place regarding the presence of substances with genotoxic-carcinogenic properties, like estragole and methyl-eugenol, in feed additives. These substances are components of essential oils of botanical origin, like star anise oil and clove oil. The Panel stated that the intentional addition of such substances to the food chain via feed additives is not acceptable. This applies independently from the origin of the substances (chemical synthesis or botanical origin).”
Botanicals containing substances of concern - examples

<table>
<thead>
<tr>
<th>Plant</th>
<th>Additive</th>
<th>Substance</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocimum basilicum</td>
<td>Basil oil</td>
<td>Estragole</td>
<td>10 – 90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methyl eugenol</td>
<td>0 – 2.5</td>
</tr>
<tr>
<td>Pimpinella anisum</td>
<td>Anise oil</td>
<td>Estragole</td>
<td>0 – 10</td>
</tr>
<tr>
<td>Illicium verum</td>
<td>Anise star tincture</td>
<td>Estragole</td>
<td>0 – 6</td>
</tr>
<tr>
<td>Foeniculum vulgare</td>
<td>Fennel tincture</td>
<td>Estragole</td>
<td>0 – 7</td>
</tr>
<tr>
<td>Artemisia dracunculus</td>
<td>Tarragon oil</td>
<td>Estragole</td>
<td>70 – 90</td>
</tr>
<tr>
<td>Laurus nobilis</td>
<td>Laurel leaves extract/oleoresin</td>
<td>Methyl eugenol</td>
<td>0 – 3</td>
</tr>
<tr>
<td>Cananga odorata</td>
<td>Ylang-ylang oil</td>
<td>Methyl eugenol</td>
<td>0 – 2</td>
</tr>
<tr>
<td>Pimenta racemosa</td>
<td>Bay oil</td>
<td>Methyl eugenol</td>
<td>1 – 3</td>
</tr>
<tr>
<td>Pimenta dioica</td>
<td>Allspice oil</td>
<td>Methyl eugenol</td>
<td>2 – 10</td>
</tr>
</tbody>
</table>

~ 30% of botanicals are affected
### Substances of concern – restriction in food


<table>
<thead>
<tr>
<th>Substance</th>
<th>Restriction in food</th>
<th>max. level (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyleugenol</td>
<td>Dairy products</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Meat products</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Fish products</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Soups and sauces</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Ready-to-eat savouries</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Non-alcoholic beverages</td>
<td>1</td>
</tr>
</tbody>
</table>

No maximum use levels defined for feed
Threshold of Toxicological Concern concept
(EFSA Journal 2012;10(7):2750)

<table>
<thead>
<tr>
<th>Cramer class</th>
<th>Max. safe feed use (mg/kg feed)</th>
<th>Max. intended use of botanical (mg/kg feed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1.0</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4%</td>
</tr>
<tr>
<td>II</td>
<td>0.3</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.2%</td>
</tr>
<tr>
<td>III</td>
<td>0.05</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Andrew Chesson, WG on Botanical Feed Flavourings
EFSA workshop: Barcelona, 6 May 2015
Safety evaluation – key issues to be solved

- “Substances of concern” occurring in botanical flavourings enter the feed chain in lower dosages if compared to food
- Considerations of the PlantLIBRA project: toxicity of botanicals is not the arithmetical sum of the toxicity of its ingredients
- Target animal safety
  - Short life time of food producing animals
  - Metabolic pathways at low dosages
- Consumer safety
  - exposure calculation should consider metabolism by animals
  - Crucial parameter for safety evaluation should be the presence of residues in animal tissues.
Industry activities

• Provide additional data on the identity of the botanical
  – Additional resources required
  – Support of manufactures?
  – Support from research institutes for identity?

• Clean-up the list of botanicals that will supported by FFAC
  – Amount of substances
  – Target animal species
  – Use level
EFSA workshop - Barcelona, 6 May 2015

Key issues for the assessment of botanical flavourings

http://www.efsa.europa.eu/en/events/event/150506a
Impact on the industry
Outlook – to be discussed....

- How many botanical substances will be authorized as feed additives?
- Who will provide additional resources to characterize botanicals (research institutes, EU-funding....)
- How will the authorisation procedure effect future product development and research activities?
- ...

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Thank you!

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