Safety Assessment of Botanicals and Botanical Preparations
Overview of EFSA’s activities

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Guidance document for the safety assessment of botanicals and botanical preparations intended for use as ingredients in food supplements

- Data requirements for the assessment (technical, exposure, toxicological data)
- Science-based framework for the assessment (tiered approach)
  - Level A: safety presumed based on available knowledge
  - Level B: evaluation of additional data
Toolkit for assessing the safety of botanicals

ESCO Report
Examples how to apply the EFSA safety assessment approach

<table>
<thead>
<tr>
<th>Botanical</th>
<th>Preparation</th>
<th>Possible safety issue</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Citrus aurantium</em> L. ssp. <em>aurantium</em> L.</td>
<td>Hydroalcoholic extract of dried peel</td>
<td>Misidentification / adulteration</td>
</tr>
<tr>
<td><em>Camellia sinensis</em> (L.) O. Kuntze</td>
<td>Dried green tea extract</td>
<td>Liver toxicity</td>
</tr>
<tr>
<td><em>Ocimum tenuiflorum</em> L.</td>
<td>Dry leaves extract</td>
<td>Reproduction toxicity</td>
</tr>
<tr>
<td><em>Foeniculum vulgare</em> Mill. ssp. <em>vulgare</em> var. <em>vulgare</em></td>
<td>Dried fruits (water extracts)</td>
<td>Genotoxic carcinogen</td>
</tr>
<tr>
<td><em>Linum usitatissimum</em> L.</td>
<td>Dried ripe seeds</td>
<td>Phytoestrogens</td>
</tr>
<tr>
<td><em>Triticum aestivum</em> L.</td>
<td>Wheat Bran</td>
<td>Low concern – presumption of safety</td>
</tr>
</tbody>
</table>
Compendium of botanicals reported to contain naturally occurring substances of possible concern for human health when used in food and food supplements

The compendium is a hazard database; it does not bring any judgment whether these botanicals are safe or not safe for food applications.

The compendium has no legal status and may not be used as support or evidence in any disagreement or dispute pertaining to the legal classification of products or substances.
• 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
Compendium Version 3

- Convert the compendium in a database format, searchable on the EFSA website and compatible with the EFSA chemical hazard database

- Expand the existing compendium
  - 700 botanical species still pending for review for possible inclusion in the compendium
  - 300 “exotic” plant species to be inserted
  - Provide information on toxic/adverse effects in a systematic manner

- Timeframe: mid 2015 for part 1, then regular information upload until end of 2016
QPS approach for botanicals

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.
What is QPS?

QPS is based on four principle considerations:

• **Taxonomy** – definition of the taxonomic unit (species/genus) for which QPS status is sought

• **Body of knowledge** – whether there is sufficient knowledge concerning the group of botanicals to reach a decision on their safety

• **Toxicity** – whether the taxonomic unit contains naturally occurring substances of concern. If so, whether sufficient is known about their toxicity to identify a dose under which such substance(s) could be concluded as being of no concern

• **End use** – the presence of a substance of concern in a given botanical does not necessarily mean that this substance will also be present in the botanical preparation and, if present, that it is at a dosage causing a health concern
Step 1: Defining the botanical species, part(s) of plant and preparation(s) of interest

Crucial step given the variation in composition that may exist:
- Between different subspecies/varieties of a botanical species
- Between botanicals grown under different environmental conditions
- Between different parts of the same botanical
- Between preparations made using different manufacturing processes

Step 2: Evaluating the compositional/toxicological/use data

- Define all biologically active substances, including their actual levels
- Define the percentage of the material that has been characterised, and the percentage of the preparation that remains unidentified
- History of use should also be considered as part of the body of knowledge
Step 3 – Evaluating the compositional/toxicological data

Adequate chemical characterisation
no reported adverse effect

Suitable for QPS without qualification

Step 4:
Iteration with other species, plant parts and/or preparations of interest
Step 3 – Evaluating the compositional/toxicological data

- Substances of concern
- Substances with known structure but unknown toxicity profile
- Adequate chemical characterisation no reported adverse effect

Validated In-silico / Read across approaches

Yes

No

Excluded from QPS approach
Step 3 – Evaluating the compositional/toxicological data

Substances of concern

Non-thresholded substances
- Genotoxicity and carcinogenicity data
  - Yes
    - Exposure below relevant TTC
      - Yes
        - Suitable for QPS with qualification
      - No
        - Excluded from QPS approach
  - No

Thresholded substances
- No established health-based guidance value
  - Yes
    - Toxicity data and/or history of safe use at specific exposure levels
      - Yes
        - Suitable for QPS with qualification
      - No
        - Excluded from QPS approach
  - No

Established health-based guidance value

Step 4: Iteration with other species, plant parts and/or preparations of interest
Step 3 – Evaluating the compositional/toxicological data

1. **Uncharacterised substances**
   - Reported adverse effect(s)
   - no substance of concern identified

2. **History of safe use at traditional exposure levels**
   - **No**
   - Excluded from QPS approach
   - **Yes**
   - Suitable for QPS with qualification

**Step 4:**
Iteration with other species, plant parts and/or preparations of interest
Step 4 – iterative process

When positive conclusions on safety have been reached, either with qualifications or not, it may be relevant to repeat the process in an iterative way to other species/plant parts/preparations.

Step 4 should therefore include a consideration about whether there are similar preparations from other subspecies/varieties/species for which the assessment could be relevant and if the safety evaluation could be extended to other preparations from other species/varieties, thus extending the number of botanical preparations for which the QPS status would hold.

The grouping should preferably include plants relevant for food consumption and with a history of safe 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
Safety assessment of alkenylbenzenes 
(estragole, methyleugenol, safrole)

- Present in a lot of plants
- Weak genotoxic carcinogenic compounds
- Margin of Exposure quite low for certain population groups

Thank you!