Part 5
Safety Requirements for functional foods

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Safety and Health Claims in Europe
Foods are regulated under **food law** in the EU.

Food law is only **partially harmonised** in the EU.

Foods are therefore subject to:

1. **a. EU horizontal rules applicable to foods in general**
2. **b. EU vertical rules applicable to specific food categories**
3. **National specific rules of Member States**
4. **Mutual recognition**
Example: food supplements

**Harmonisation on:**
- Definition
- Vitamin & mineral sources
- Labelling & warning statements
- Food supplement notification

**Still National Rules on:**
- Other ingredients
- Botanicals
- Maximum limits for vitamins/minerals
- Modalities of the notification

Uniform application in all MS

Subject to Mutual Recognition

All other aspects of Food Law

Classification issues
Different attitudes
  Botanicals considered ‘medicinal by function’
  Traditional emphasis on food supplements or medicinal products

Variety of risk management measures
  Lists
    Negative lists
    Positive lists
  Conditions of use
    Restrictions
    Maximum levels
  Labelling requirements
  Notification / Registration
  Guidance / …
## Starflower (Borago officinalis L.)

<table>
<thead>
<tr>
<th>Specific Plant parts permitted:</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Seeds &amp; oil</td>
</tr>
<tr>
<td>** Seeds (incl. seed by-products) &amp; flowers only</td>
</tr>
</tbody>
</table>

### National Measures

<table>
<thead>
<tr>
<th>Country</th>
<th>Food</th>
<th>Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estonia*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyprus</td>
<td></td>
<td>case by case</td>
</tr>
<tr>
<td>Belgium**</td>
<td></td>
<td>&lt;1 µg/kg pyrrolizidine alkaloids</td>
</tr>
<tr>
<td>Hungary**</td>
<td></td>
<td>&lt;0.001 mg/kg pyrrolizidine alkaloids</td>
</tr>
<tr>
<td>Czech Republic</td>
<td></td>
<td>not permitted</td>
</tr>
<tr>
<td>Ireland</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Netherlands</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### SAFETY

- Hungary**: <0.001 mg/kg pyrrolizidine alkaloids
**St John’s Wort (Hypericum perforatum L.)**

<table>
<thead>
<tr>
<th>Country</th>
<th>SAFETY</th>
<th>National Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands</td>
<td>case by case</td>
<td></td>
</tr>
<tr>
<td>Cyprus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Czech Republic</td>
<td>max 300 mg</td>
<td></td>
</tr>
<tr>
<td>Belgium (+warning statement*)</td>
<td>&lt; 700 µg Hypericin</td>
<td></td>
</tr>
<tr>
<td>Italy (+warning statement**)</td>
<td>&lt; 0.7 mg Hypericin and max 100 mg fresh flower</td>
<td></td>
</tr>
<tr>
<td>Denmark (+optional warning***)</td>
<td>aerial parts &lt;0.1 mg Hypericin</td>
<td></td>
</tr>
<tr>
<td>Estonia</td>
<td>not permitted</td>
<td></td>
</tr>
<tr>
<td>Hungary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Inform your doctor and/or pharmacist if you are taking medication simultaneously’
**’If using medicines, consult your doctor prior to using this product because hypericum extract can interfere on their metabolism also inhibiting their activity. The extract of hypericum is contraindicated during pedriatic age and adolescence’
***May cause photosensitisation
Basic Principles

Safety under company responsibility

In EU for ingredients: No pre-marketing authorisation needed unless

- Food Improvements Agent (additives, enzymes, favourings)
- Nutritional substances
- Novel food (Regulation 258/97)

Novel food

Any food or food ingredient

Not used to a significant degree as food before 15 May 1997

An belonging to one of the following categories:
Scope

Foods and food ingredients with a **new or intentionally modified primary molecular structure**

Foods and food ingredients **consisting of or isolated from microorganisms, fungi or algae**

Foods and food ingredients **consisting of or isolated from plants and food ingredients isolated from animals**, except for foods and food ingredients obtained by traditional propagating or breeding practices and having a history of safe food use

Foods and food ingredients **to which has been applied a production process not currently used**, where that process gives rise to significant changes in the composition or structure of the foods or food ingredients which affect their nutritional value, metabolism or level of undesirable substances
Current legislation (Reg 258/97)

Application to Member State (and Commission) → 3 months → Initial Assessment → 60 days → Reasoned objection or additional assessment required? →

- NO → Centralised procedure → EFSA opinion → 12-24 months → Decision
- YES → Centralised procedure → No EFSA opinion → 6-18 months → Decision

New legislation (Reg 2015/2283)

Application to Commission

Request to EFSA → 9 months → Can be extended → EFSA opinion → 7 months → Commission implementing act proposal → 6-18 months → Decision via examination procedure

NO request to EFSA → 7 months → Decision
Experience and issues

Outcome since 1997

- Full procedure: about 150 applications
- Notification procedure: about 270 applications

Inefficient procedure

- Systematic objections of Member States on national assessments
- Long duration (2-3 years)
- Notification procedures turned into an authorisation procedure

Lack of clarity

- Consumption to a significant degree
  - Guidance published
- Substantial Equivalence
  - Guidance published
## History of use: Significant use prior to 1997

**EC Guidance**

### Table 3: Evidence of a history of consumption

<table>
<thead>
<tr>
<th>Type of Evidence</th>
<th>Type of evidence</th>
<th>Possible Weighting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comprehensive Sales Information</td>
<td>Invoices etc detailing sale of food, including evidence of large quantities of sale in the EU</td>
<td>Very Good Evidence, if purpose (food use) is indicated</td>
</tr>
<tr>
<td>Sales Information</td>
<td>Invoices etc detailing sale of food</td>
<td>Good Evidence, if purpose (food use) is indicated</td>
</tr>
<tr>
<td>Government Import/Export Information</td>
<td>Official documents</td>
<td>Supporting Evidence, if purpose (food use) is indicated</td>
</tr>
<tr>
<td>Sales Information</td>
<td>Catalogues, Sales Brochures</td>
<td>Supporting Evidence, if purpose (food use) is indicated</td>
</tr>
<tr>
<td>Listed in recognised catalogues/documents</td>
<td></td>
<td>Supporting Evidence</td>
</tr>
<tr>
<td>Expert knowledge</td>
<td>Personal Testimonies</td>
<td>Supporting Evidence</td>
</tr>
<tr>
<td>Supporting Information</td>
<td>Magazine articles, Recipe Books etc.</td>
<td>Supporting Evidence</td>
</tr>
<tr>
<td>Other</td>
<td>Please Specify</td>
<td></td>
</tr>
</tbody>
</table>
How to Assess Novel Food Status

Novel Food catalogue
Non exhaustive / living database

Provides orientation only and does not necessarily reflect the legal status of these ingredients in the Member States => National rules may apply

Also consider the manufacturing process

Have a good rationale at hand
New legislation published on 11 December 2015: Reg 2015/2283

Key elements

Broadening of the definition to more categories not used before May 1997

- Increased potential to challenge new products
- Retroactive application
- Proof of marketing prior to 15 May 1997 crucial but difficult
- Transition period involving the submission of an application

Centralised procedure involving EFSA

- Not necessarily shorter and less complex

Simplified procedure for foods from third countries

- Only applicable to food from primary production
- In reality most likely not simpler

Generic decisions

- Not applicant linked but protection of proprietary data is possible
Novel Foods: data requirements

EFSA guidance (under discussion): Main principles for toxicological testing

1. Data on the source or the novel food itself to provide information on critical substances, potential hazards or precautions, based on a comprehensive literature review of human studies reporting on relevant safety outcomes, also including studies with compounds of the novel food or similar foods.

2. A rationale for the target population, proposed uses and use levels, precautions and restrictions of use should be provided with cross-referencing to safety relevant data.

=> The data requested may be pertinent for the intended use of the product as FSMP. This may already lead to discussions on the FSMP status during the novel foods process.

3. For single substances, data on toxicokinetics (absorption, distribution, metabolism, and excretion (ADME)) are essential as basis to development the appropriate toxicity testing strategy.

4. The tiered toxicological data approach proposed in EFSA’s additives guidance applies.
Novel Foods: data requirements

Toxicokinetic data

In summary:

Tier 1: Establish whether there is absorption of the compound or its breakdown products.
   If yes => Tier 2.

Tier 2: Studies to define distribution, metabolism and excretion and other basic toxicokinetic parameters following a single dose.
   Toxicokinetic studies (OECD TG 417) should provide data on systemic exposure to the compound and definition of basic single dose toxicokinetic parameters (T1/2, AUC, bioavailability, Cmax and Tmax) together with in vivo assessment of its absorption, distribution, metabolism and excretion including identification and quantification of metabolites, preferably determined at a range of dose levels.
   If indications of limited or slow excretion or potential for bioaccumulation => Tier 3.

Tier 3: Studies to define toxicokinetic parameters following repeated administration.
   The following data should be considered:
   – Tier 3 toxicokinetic studies with repeated doses in experimental animals, normally this would involve studies to steady-state which would be approximately five terminal half lives.
   – Additional data to help predict the absorption, distribution, metabolism and excretion of a
Novel Foods: data requirements

Genotoxicity data

In summary:

Tier 1: The absolute minimum to be carried out.
Tier 1 consists of the following two in vitro tests:
- A bacterial reverse mutation assay (OECD TG 471), and
- An in vitro mammalian cell micronucleus test (OECD TG 487).
Any deviation should be justified.
If positive or inconclusive => Tier 2 to determine if the hazard is expressed in vivo.

Tier 2: Tests to be conducted in succession: if negative result, the next test must be carried out.
The following tests are considered as suitable in vivo tests:
- An in vivo micronucleus test (OECD TG 474).
- An in vivo Comet assay (no OECD TG at present (see hptt://cometassay.com).
- A transgenic rodent assay (OECD TG 488).
If Tier 2 is positive it is usually assumed that the compound is a somatic cell genotoxin and will be potentially carcinogenic and also mutagenic in germ cells. Such compounds are not considered acceptable as food.
Novel Foods: data requirements

Subchronic, chronic and carcinogenic toxicity testing

In summary:

Tier 1: A subchronic toxicity study, conducted for a period of at least 90 days (OECD TG 408) in rodents, modified to include assessment of additional parameter described in the more recent guideline on repeated-dose 28-day oral toxicity study in rodents (OECD TG 407).

This to allow for the identification of chemicals with the potential to cause neurotoxic, immunological or reproductive organ effects or endocrine-mediated effects, which may warrant further investigation.

The results from the repeated dose 90-day oral toxicity can be used to identify a BMDL or a NOAEL.

Tier 2: Chronic toxicity study to reveal effects not evident in subchronic studies, or to confirm effects observed in subchronic studies at the same or perhaps lower doses.

– A stand-alone study in rats, using the relevant OECD TG 452 and OECD TG 451.
– Alternatively, the use of a combined protocol to study chronic toxicity and carcinogenicity in the same experiment will often be appropriate, in accordance with OECD TG 453.

Carcinogenicity study in a second species would only be triggered by the results in the preferred species (equivocal results or species specific findings) or by observations from specialised studies to investigate the mode of action or mechanism of toxicity or
Novel Foods: data requirements

The results from the toxicokinetic, genotoxicity and subchronic, chronic and carcinogenic toxicity testing may also indicate if further testing is required.

Reproductive and developmental toxicity testing:

Tier 1: Outcome of subchronic toxicity testing.

Tier 2: Tier 2 testing for reproductive and developmental toxicity comprises:
- A prenatal developmental toxicity study (OECD TG 414) in the rabbit and
- An Extended One-Generation Reproduction Toxicity Study (EOGRTS) (OECD TG 443).

Carcinogenicity study in a second species would only be triggered by the results in the preferred species (equivocal results or species specific findings) or by observations from specialised studies to investigate the mode of action or mechanism of toxicity or carcinogenicity observed.

Tier 3: Is triggered by results in Tier 2 studies and might comprise of additional studies for e.g. endocrine, developmental neurotoxicity (OECD TG 426), and mode of action studies which could include both guideline studies and experimental studies designed on a case-by-case basis.
Safety is interfering with Health Claims approvals

Novel Foods and Claims Assessment can run in parallel
Claims decisions are delayed because of discussions in relation to safety

E.g. Caffeine
15 Jan 2015: EFSA opinion
EC is now proposing to accept all but one health claim for caffeine

E.g. Hydroxy-anthracene derivates
Positive EFSA opinion
But concerns about the use, interactions, contra-indications, etc
Introduced in the Article 8 procedure of Reg 1925/2006

E.g. Monacolin K
Positive EFSA opinion
But opinions from several national food safety authorities
The Case of China
Key Government Authorities

China Food and Drug Administration (CFDA)
- General administration and market surveillance of food, health food, and drug
- Setting health food regulations
- Pre-market approvals

National Health & Family Planning Commission (NHFPC)
- Setting science-based food safety standards
- Evaluation and approval of novel food ingredients / additives

General Administration of Quality Supervision, Inspection, and Quarantine (AQSIQ)
- Inspection of imported/exported products to make sure they meet regulatory requirements
Key Legislations Pertaining to Health Foods

Current

Food Safety Law 2009

Administration on Health Food Registration (2005)

National Food Safety Standards (GB Standards)
  GB16740-2014 Health Foods
  Horizontal standards e.g. contaminants, additives, etc.
  Other commodity standards

➡️

Food Safety Law 2015
  To be effective 1 Oct 2015

New regulatory framework for health foods 2016
  Regulation on Health Food Registration and Notification
  Regulation on Health Food Functional Claims and Raw Materials Catalogues
  Regulation on Health Food Labelling
  To be effective mid 2016
Definition of Health Food

Legal Definition:

- Foods with specific health functions or to supplement vitamins and minerals
- For specific populations
- Not intended for diseases treatment
- Does not cause actual or chronic harms

Subcategories:

**Nutrient Supplements**
- products aimed to supply vitamins and minerals and not energy, thus to replenish dietary insufficiency and reduce the risk of chronic degenerative diseases. Most vitamins and minerals supplements fall under this category.

**Health Food with Functional Claims**
- foods that have specific health benefits, which are given by the active ingredients in the products.
- The use of functional ingredients in health foods should be in compliance with several regulatory documents including permitted / banned substances.
Health Food with Claims

27 permitted health food claims

Antioxidant
Clears throat
Helps in reducing blood pressure
Improves growth
Protects against harmful radiation
Improves skin oil content
Reduces blood lipid level
Improves anaemic condition
Lower blood sugar level
Improves memory
Improves sleep
Improves hypoxia tolerance
Increasing bone density
Promote lactation
Promotes lead elimination
Protects the liver against chemical damage
Relieves eye fatigue
Relieves fatigue
Slimming
Strengthens immunity
Improves skin moisture
Eradicates acne
Eradicates freckles
Promotes digestion
Relieves constipation
Regulates intestinal flora
Helps in the protection of gastrointestinal mucosal membrane

Max 2 claims on each product
Proposal to reduce the list to 18 claims
Regulations on Health Food Ingredients

List of substances that can be used in both medicines and foods
   E.g. ginger, cinnamon

List of substances that can only be used in health foods
   E.g. turmeric

List of substances that are banned for use in food and health foods
   E.g. Chinese yew, croton

Lists of permitted fungus / pre- and pro- biotics / nucleic acids / wildlife species, etc. in health foods
Health Food Registration Process

Pre-registration Studies (by designated laboratories)
- safety
- stability
- efficacy
- toxicology

Submit Application to CFDA

Technical Evaluation
- by CFDA Health Food Evaluation Committee

CFDA Approval & Issue Certificate

Lengthy process, ~2 years
Health Food Registration Process

Step 1: Pre-registration studies

- Technical studies and assessment must be conducted in designated Chinese laboratories

- Imported products: although published overseas clinical and animal studies may be used as supporting documents, local studies at the Chinese Center for Disease Control and Prevention (CDC) are still mandatory.

- Documents / material to be provided by the company include product formula, finished product specification, raw material specifications, 3 batches of finished product samples, active ingredient reference standards, test methods and method validation reports. Each of the laboratories/institutions will specify the quantity of samples and reference standard required.

- Studies: Toxicology study, stability study, active ingredient analysis, test for absence of stimulant (for claims on slimming and anti-fatigue), hygiene tests, and efficacy study.

Step 2: Submit Application
More focus on food safety
  - Stricter rules, heavier punishments
  - More science-based
  - More focus on ingredient safety

Simplified pre-market requirements
  Registration for
    - Products that use new ingredients outside the Health Food Ingredients Catalogue
    - Products that are imported for the first time into China
  Notification for
    - Products that use ingredients from the Health Food Ingredients Catalogue
    - Products that are imported for the first time into China but belong to nutritional supplements such as vitamins and minerals
    - Products that are already notified and require update of information

More focus on post-market surveillance
  - More inspection programmes
Novel Foods

2013: Regulation No. 23

Novel food authorisation required for the following foods which do not have a history of consumption in China:

- Animals, plants and microorganisms;
- Extracts/parts of animals, plants and microorganisms;
- Food components of which the original structure had been changed;
- Other newly developed food ingredients.

Under National Health & Family Planning Commission (NHFPC)

Approval within 95 days (in reality 1-2 years)

Does in principle not apply to Health Foods
General Conclusions
Conclusions

Doing research in view of a health claim means:

- Knowing the target country
- Knowing the procedures and responsible authorities
- Knowing the requirements
- Knowing the legal status of the ingredient
- Knowing product entry procedures
- Knowing practices, e.g. on borderline and product classification
- Knowing dos and don’ts
- Know how strong your scientific substantiation is