Part 3
Scientific Requirements for functional foods

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Appropriate scientific standard

The requirements for scientific substantiation are high

PASSCLAIM based?
Alignment between EFSA and FDA
Consideration of totality of the data (Codex)?
Grading is not applied

PASSCLAIM
PROCESS FOR THE ASSESSMENT OF SCIENTIFIC SUPPORT
FOR CLAIMS ON FOODS

Consensus on Criteria

Authors:

Substantiation of Health Claims

Systematic review of the scientific evidence:

- Identify the proposed relationship between food and health effect
- Identify appropriate valid measurements for the food and health effect
- Identify and categorise all the relevant scientific data
- Assess the quality of and interpret each relevant scientific study
- Evaluate the totality of the available relevant scientific data
- Weigh the evidence across studies
- Determine if, and under what circumstances, the claim is substantiated
By taking into account the totality of the relevant scientific data and by weighing the evidence, demonstrate the extent to which:

- the claimed effect is beneficial for human health
- a cause and effect relationship is established between consumption of the food or food constituent and the claimed effect in humans
- the quantity of the food and pattern of consumption required could reasonably be achieved as part of a balanced diet
- the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended

Codex specifically recognises the value of observational evidence such as epidemiological studies.
Scientific Assessment as applied by EFSA
The EFSA approach is based on human intervention studies to assess measurable improvements in validated markers or end points of beneficial physiological functions in healthy subjects.

With a strong focus on reduction of (risk) factors linked to disease states, e.g., cholesterol, blood pressure, dental caries, …

This view is shared by FDA and other assessment bodies.
Why did cranberry fail?

“helps reduce the risk of urinary tract infection in women by inhibiting the adhesion of certain bacteria in the urinary tract”

EFSA does not accept:
- In vitro studies
- Studies in neurogenic bladder patients
- Flaws in study design
- Meta-analysis
- French Food Safety Agency previous positive opinion
Why did cranberry fail?

EFSA highlights flaws in study designs:
- small number of subjects
- lack of control groups
- short duration of the studies
- high drop-out rate
- lack of statistical power
- lack of adequate randomization
- intervention matrices (e.g. capsules) differing from the foods specified in the application
Why did WSTE succeed?

Water Soluble Tomato Extract:

- Clearly defined substance

  Derived from ripe tomatoes, and intended for use in fruit juices, fruit flavoured drinks and yoghurt drinks
  Manufacturing process, chemical specification of the constituents, batch-to-batch reproducibility

- Cause-effect relationship

  Ex vivo tests to assess the percent inhibition in platelet aggregation in response to different platelet agonists
  Acute effect testing (3h post consumption)
  Chronic effect
  Dose-effect

  No increased inhibition at higher doses
Why did Lutein fail?

Submission as Article 13 claim

Considered as generally accepted and well understood by the consumer

Supported by an opinion by AFSSA

- Lutein helps to protect the retina and lens from oxidation
- Lutein is one (of the) constituent(s) of the retina and the lens

323 references included

The industry assessment report indicated:

The Nature of Evidence is extensive, detailed and includes authoritative body, text books, reviews and numerous studies.

It should in theory be supportive of the proposed Level of Grading of 5.
EFSA opinion:

The generally consistent epidemiological evidence indicating a possible role for lutein in vision was not supported by the weight of evidence from the human intervention studies.

While it is established that lutein can increase macular pigment density in most but not all healthy subjects, it has not been established that such increases in macular density is related to vision.

the evidence provided is insufficient to establish a cause and effect relationship between the consumption of lutein and maintenance of normal vision.

Why did Lutein fail?
Observations:

EFSA choose ‘maintenance of vision’, while the claim related to ‘protection of the retina against oxidative damage’

Because “Normal vision is a function of the eye which can be assessed by established methods”?

EFSA did not consider the AFSSA review?

EFSA was quite selective in some data it considered as pertinent

Much of the data were excluded from the totality of the evidence?

E.g. EFSA considered a study with bilberry extract rather than lutein as pertinent ???
Why did Lutein fail?

Fundamental issues:

**Appropriate markers / end points?**
- Vision? Macular pigment optical density MPOD?

**Limitations of RCTs?**
- How to demonstrate maintenance/improvement of visual function in healthy subjects?
- Is this practically feasible (long term study – thousands of subjects – statistical power)?
- How can a correlation between MPOD levels and visual function be established?

**Alternative assessment of the totality of the evidence?**
- Including experimental and epidemiological data?
- Studies in Age-related Macular Degeneration (AMD)?
- By the key experts in the field
The (limited) value of observational evidence
Soy protein has been shown to lower/reduce blood cholesterol; blood cholesterol lowering may reduce the risk of (coronary) heart disease.

32 RCTs
- Most RCTs were not designed to test the effects of soy protein
  - Conflicting evidence on the effect of soy-isoflavones on LDL cholesterol
  - Key studies do not give significant differences

10 meta-analyses: inappropriate study selection

8 observational studies not considered

1 review on possible mechanisms
  - Not corroborated with available scientific evidence
Protein-rich component from soybeans with limited quantities of other macronutrients and micronutrients has been shown to lower/reduce blood cholesterol; blood cholesterol lowering may reduce the risk of (coronary) heart disease.

23 RCTs with the food as characterised
4 inadequate methodology or insufficient reporting
19 methodological limitations in the statistical analyses performed
When only primary analysis are considered: no significant effects in 14
6 RCTs with whole soy foods not accepted because different matrix
8 observational studies not even considered
1 animal and 2 in vitro studies: No extrapolation accepted
11 published meta-analyses and 1 unpublished systematic review
Most considered interventions with soy-isoflavones or soy protein
Why did Glucosamine fail?

Article 13 submission: Joint health

Data provided:

11 human intervention studies, 3 meta-analyses, 21 reviews and background papers, 2 animal studies, 1 in vitro study, 1 short report, and 1 case report

All studies conducted in patients with osteoarthritis (OA)

The evidence provided does not establish that patients with OA are representative of the general population with regard to the status of joint tissues, or that results obtained in studies on subjects with OA relating to the treatment of symptoms of this disease (e.g. erosion of articular cartilage, reduced mobility of joints) can be extrapolated to the maintenance of normal joints in the general population.

The evidence provided in the animal and in vitro studies submitted does not predict the occurrence of an effect of glucosamine intake on the maintenance of normal joints in humans.
Will Vitamin D succeed?

Article 14 submission: **Risk of falling** (risk factor for bone fractures)

Data provided:
- 7 RCTs, 5 observational studies and 4 meta-analyses

Assessment of the data
- 5 RCTs showed a significant reduction in the risk of falling.
- 1 other RCT was unable to demonstrate an effect.
- The results from the observational studies provided are inconsistent and residual confounding cannot be excluded.
- Although plausible, the relationship between vitamin D intake or vitamin D status and muscle strength, physical performance and balance in the elderly is yet to be established.

But
- The available data do not provide information about the lowest effective dose of vitamin D needed to obtain the claimed effect.

In the end, the claim was approved
- Vitamin D helps to reduce the risk of falling associated with postural instability and muscle weakness. Falling is a risk factor for bone fractures among men and women 60 years of age and older.
Why did Melatonin succeed?

Art. 13: Alleviation of subjective feelings of jet lag

Assessment of the data

The conclusions of the Cochrane review indicate that melatonin is effective in alleviating the subjective symptoms of jet lag.

Art. 13: Reduction of sleep onset latency

Assessment of the data

A meta-analysis of controlled human intervention studies in normal sleepers indicated a statistically significant reduction of sleep onset latency following melatonin consumption, and that these results were supported by two meta-analyses of controlled human intervention studies, one in subjects with primary sleep disorders and one in healthy subjects combined with subjects with insomnia.

But

Melatonin is considered as a medicinal substance by the majority of Member States.

In the end, both claims were approved, but cannot be used in all Member States.
Why did LGG Fail?

Lactobacillus rhamnosus GG, ATCC53103 and maintenance of defence against pathogenic gastrointestinal microorganisms.

7 studies on development of gastrointestinal infections
  2 refused because of methodological limitations
  4 did not show an effect of LGG consumption
  Only 1 study supported the effect

2 studies on immune responses after oral (viral) vaccination
  Both did not support an effect on the stimulation of protective immune response

17 studies, 2 meta-analysis and 1 consensus opinion on the treatment of acute diarrhoea
  Acute diarrhoea due to a viral GI infection in infants not representative

4 studies and 2 meta-analysis on diarrhoea during antibiotic use
  Diarrhoea during antibiotic use is not representative for the general population

1 study on eradication of vancomycin resistant enterococci
  Methodological limitation
Science is a continuum

- Conclusive
- Convincing
- Probable
- Possible
- Insufficient
- No evidence

Strength and consistency of scientific evidence

- Scientific Consensus
  - Authoritative statement
- Significant Scientific Agreement
- Emerging Evidence
  - Indicative but not conclusive
  - Support from totality of evidence available
- Need to weigh and grade the evidence
Qualified Health Claims

Framework for strength and consistency of the totality of the evidence in nutrition science

<table>
<thead>
<tr>
<th>Qualification</th>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONVINCING</td>
<td>A</td>
<td>Significant scientific agreement (STRONG)</td>
</tr>
<tr>
<td>PROBABLE</td>
<td>B</td>
<td>Good to moderate level of scientific agreement (MODERATE)</td>
</tr>
<tr>
<td>POSSIBLE</td>
<td>C</td>
<td>Low level of scientific agreement (WEAK)</td>
</tr>
<tr>
<td>INSUFFICIENT</td>
<td>D</td>
<td>Very low level of scientific agreement</td>
</tr>
</tbody>
</table>

Most of the state-of-the-art nutrition evidence falls within the probable/possible categories

WCRF (2007); USFDA (2003); FOSHU (2003) WHO (2004); CODEX (2008); Menté et al. (2009)
Qualified Health Claims

- Example: WHO Report Series

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Decreased risk</th>
<th>No relationship</th>
<th>Increased risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Convincing</td>
<td>Regular physical activity</td>
<td>High dietary intake of NSP (dietary fibre)⁵</td>
<td>Sedentary lifestyles</td>
</tr>
<tr>
<td>Probable</td>
<td>Home and school environments that support healthy food choices for children⁴</td>
<td>Breastfeeding</td>
<td></td>
</tr>
<tr>
<td>Possible</td>
<td>Low glycaemic index foods</td>
<td>Protein content of the diet</td>
<td></td>
</tr>
<tr>
<td>Insufficient</td>
<td>Increased eating frequency</td>
<td></td>
<td></td>
</tr>
</tbody>
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⁴ Definition of evidence: the totality of the evidence was taken into account. The World Cancer Research Fund schema was taken as the starting point but was modified in the following manner: randomized controlled trials were given prominence as the highest ranking study design (randomized controlled trials were not a major source of cancer evidence); associated evidence and expert opinion was also taken into account in relation to environmental determinants (direct trials were usually not available).

⁵ Specific amounts will depend on the analytical methodologies used to measure fibre.

⁶ Energy-dense and micronutrient-poor foods tend to be processed foods that are high in fat and/or sugars. Low energy-dense (or energy-dilute) foods, such as fruit, legumes, vegetables and whole grain cereals, are high in dietary fibre and water.

⁷ Associated evidence and expert opinion included.
Substantiation of Health Claims

EFSA approach

Characterise the food or food component
Characterise the claimed effect and judge if it is beneficial
Assess if there is a cause and effect relationship
Assess the quantity of the food
Assess the population group
Assess the wording of the claim

Evidence Based Medicine / Significant Scientific Agreement
Substantiation of Health Claims

US FDA

Define the substance/disease relationship

Collect and submit all relevant studies

Classify, and rate, each study as to type of study

Rate each study for quality

Rate the strength of the total body of evidence

Report the "rank"

Possibility for food groups

Totality of the evidence

Rating of the evidence

Qualified language possible
Outcome Of Claims assessments

Because of the approach taken by EFSA in the EU:

Only claims accepted for:

- **Vitamins, minerals, essential fatty acids**
  - Because of essentiality and deficiency disease symptoms

Limited number of outcomes:

- **Cholesterol lowering, blood pressure, blood glucose**
  - Because these markers are validated

Substances with pharmacological activity (melatonin, monacolin K)

- Because effects can be assessed in RCT’s

Whole categories of health effects rejected

- Probiotics
- Anti-oxidants
- Botanicals
- Joint health

...
Important limitations of the significant scientific agreement approach

- Improvement of normal function is difficult to assess
  - Balancing on the border of (ab)normaility

- Prevention/health maintenance exceedingly difficult to “prove”

- Normal functions are influenced by dietary and life-style factors

- Compliance of food interventions and study control in the natural setting is difficult

- Majority of research that comprises substantiation for claims on foods/food components
  - Not conducted by the food/supplement industries
  - Not intended to meet the regulatory requirements for claims

- New methodologies take time to be validated

- Industry loses interest in investing in innovation
Claims legislation is a learning process

1990: Health Claims (= Reduction of disease risk)
   Authorisation – Significant Scientific Agreement
   Totality of the Evidence + Grade ‘convincing’

1994: Structure/Function claims (supplements)
   Notification + disclaimer - No authorisation

1997: Authoritative Health Claims
   Authorisation – Authoritative Statements
   General agreement – Grade ‘convincing’

2003: Qualified Health Claims
   Authorisation – Qualified wording
   Totality of the evidence
   Ranking – Grade ‘probable – possible’
Learning Process

1991: Foods for Special Health Use (FOSHU)
Beneficial effects on the physiological functions of the human body, maintain or promote health and improve health-related conditions
FOSHU Authorisation

2001: Foods with Nutrient Function Claims
Standardised list – No product authorisation

2005: Standardised FOSHU
• No detailed review of safety and efficacy

2005: FOSHU for disease risk reduction

2005: Qualified’ FOSHU claims
• Qualified wording: insufficient scientific evidence, but still certain efficacy

2015: Foods with functional claims
• Notification
2003: Health Functional Foods
A product intended to be used to enhance and/or preserve the human health that contains one or more of the functional food/constituents, manufactured or processed in a form of tablet, capsule, powder, granule, liquid or pill, etc. with ingredients or components, that possess the functionality useful for human body

General Health Functional Foods
Standardized list - No product authorization

Product-Specific Health Functional Foods
Reduction of disease risk claims
Ingredient based Authorization

Other function claims
Ingredient based Authorisation + Qualified wording
Three levels of grading: ‘convincing’, ‘probable’ and ‘insufficient’

2008: Extended to regular foods
Learning Process

2006: Function claims
  Authorisation - List
  General agreement – Grade ‘convincing’

2006: Reduction of disease risk claims
  Authorisation – Conclusive standard
  General agreement – Grade ‘convincing’
  No consideration of totality of the evidence
  No acceptance of the grades ‘probable – possible’

2010: 50% of claims put on hold

2012: Challenges before the Court of Justice
  So far all cases have supported the legislation

2013: Discussions on how to cover botanicals
Botanicals

27 September 2010: EC Announcement

Botanical claims removed from the process

Because of the likelihood that all opinions would be negative
Because tradition of use is recognised for medicinal herbal medicinal products
1548 botanical claims awaiting assessment by EFSA

2012: Discussion document for Member States

Two options proposed to solve the situation of botanicals
- Apply the legislation as foreseen
- Develop a new system based on tradition of use

2015: Announcement to do a formal impact assessment under the REFIT programme
What can we learn from the EFSA assessments?

Key reasons for rejections

- Insufficient characterisation of substance or claim
- Inappropriate scientific data
  - No pertinent studies
  - Studies based on human observational evidence, animal and in vitro research, etc
- Flaws in study design or statistics
  - Number of subjects
  - Study duration
- Studies not showing a significant result
- Inappropriate target population
- Inappropriate quantity of the food
What can we learn from the EFSA assessments?

EFSA investigates:

If **characterisation** of the food or food component is sufficient
- The substance for which the claim is made must be the same as that for which the evidence is provided
- Control authorities must be able to determine that the substance for which the claim is made is the same as that for which the claim is authorized

If the claimed effect is **beneficial to health**
- In terms of the validity of end-point used
- In terms of the size of the effect
- In terms of benefit for specific EU population groups
- For Reduction of Disease Risk Claims the effect must relate to a **risk factor**

If there is a **cause-effect relationship** between consumption of the food or food component and the claimed effect
- With particular focus on whether the evidence has been obtained in the same population group the claim is intended for
- With particular focus on the intake required to obtain the claimed effect
What can we learn from the EFSA assessments?

The evidence proposed

- Are human intervention studies available with appropriate outcome measure(s) in relation to the claimed effect?
- Validated end-points, biomarkers or outcome variables?
- Are studies representative for proposed target group?
- Are the conditions of use of the studies in line with those of the claim (quantity and/or pattern of consumption)?
- Is a rationale available to explain how evidence of human observational and animal/in vitro studies support the claimed effect in humans (and match trial results)?
- Can a mechanisms or mode of action be proposed?
- Does the proposed wording reflect the scientific evidence?
What can we learn from the EFSA assessments?

The Study design – Do a Gap-Match analysis

Population
  Representative
  Randomisation – Double blinding

Duration
  Sustained effects

Control of confounding variables and potential bias
  Diet / Medication / Physical activity / …

Statistics !!!
  Power calculation
  Primary and secondary outcomes
  Treatment of drop-outs / missing data
  Intention to treat analysis
  No post-hoc or unplanned analyses
Companies tend to be overoptimistic about the quality of their data !!!
Scientific substantiation

EU

EFSA Guidance on Art 14 - Art 13.5 submission
Reg 353/2008 of 18/04/2008: implementing rules for applications for authorisation of health claims
Various EFSA Guidance documents:

FDA

Guidelines on Significant Scientific Agreement Standard:
http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm073332.htm

Guidelines on authoritative statement-based health claims:
http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/ucm056975.htm

Guide on interim procedures for qualified health claims and on the ranking of the strength of evidence supporting a qualified claim:
EFSA clarification
See www.efsa.europa.eu

Gut and immune function
   Finalised April 2011 – Revised version published on 18 January 2016

Antioxidants, oxidative damage and cardiovascular health
   Finalised November 2011

Bone, joints and oral health
   Finalised April 2012

Appetite ratings, weight management and blood glucose concentrations
   Finalised February 2012

Neurological and psychological function
   Finalised June 2012

Physical performance
   Finalised September 2012
Specific guidance papers describe:

- The **claimed effects** that are considered beneficial and those that are not
- **Outcome parameters** that are considered appropriate and those that are not
- **Methods of analysis** that are acceptable and those that are not

**Limitations:**

Guidance is drawn from *experience* so far and only addresses fields of health where experience has been gathered.

Many calls for more *clarification and specific examples* from the consultation have not been followed.

Only one guidance was subject of a *technical meeting*