Evaluation criteria for health claims

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EFSA NDA Panel member

Evaluation criteria of health claim applications in Europe

- **Issues addressed by NDA Panel**
  - Characterisation of food/constituent
  - Definition of the health claim
  - Relevance of the claimed effect to human health
  - Establishment of a cause-effect relationship
- **Lessons from published opinions on health claims**
- **Main challenges in research oriented to claims**

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Evaluation criteria of health claim applications in Europe

The extent to which:

1. The food/constituent is **characterised** in the context of the claim

2. The **claimed effect is defined**

3. The claim effect is a **beneficial physiological** effect

4. A **cause and effect relationship is established** between the consumption of the food/constituent and the claimed effect.

Evaluation criteria of health claim applications in Europe

Characterization of food/constituent

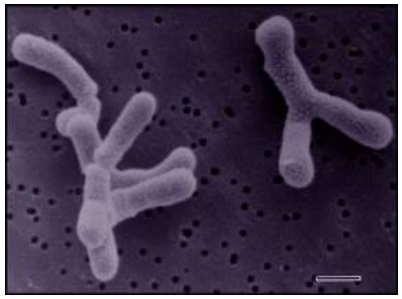
- Food (category) or food constituent (e.g. nutrient or other constituent) or combination.

- The food/constituent should be sufficiently defined and characterised in relation to the claim effect

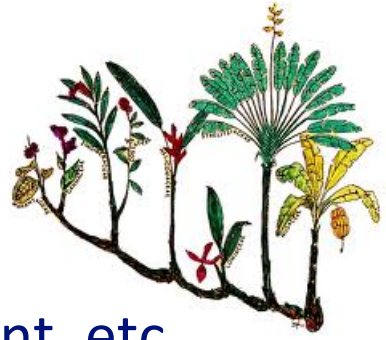
- The purposes of characterisation are to confirm the identity and to establish that the studies provided for substantiation of the health claim were performed with the food/constituent.

Evaluation criteria of health claim applications in Europe

Characterization of food/constituent



- **Microorganisms**
  - Identification of genus, species and strain:
    - Phenotypic
    - Genotypic methods



- **Botanical products**
  - Scientific name of the plant, part of the plant, etc.
  - Quantification/standardization of active principle

Evaluation criteria of health claim applications in Europe

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Evaluation criteria of health claim applications in Europe

Definition of the health claim

- Health claims should be **specific** and the effect **measurable.**
- **Non defined**: “gut health”, “digestive health”, “intestinal microbiota”, “probiotic”, “immune system”, etc.
- **Defined health claims**: “intestinal regularity/transit”, “contributes to immune defences against gastrointestinal pathogens”

Scientific literature

Non-defined terms and concepts have been widely used

Drug Discov Today. 2003 Aug 1;8(15):692-700.

Using **probiotics** and **prebiotics** to improve **gut health.**

Tuohy KM, Probert HM, Smejkal CW, Gibson GR.

Food Microbial Sciences Unit, School of Food Biosciences, University of Reading, PO Box 226, Whiteknights, Reading RG6 6AP, UK. k.m.tuohy@reading.ac.uk

Abstract

Recent molecular-based investigations have confirmed the species diversity and metabolic complexity of the human gut microbiota. It is also increasingly clear that the human gut microbiota plays a crucial role in host health, both as a source of infection and environmental insult and, conversely, in protection against disease and maintenance of gut function. Although little is known about the health impact of the dominant groups of gut bacteria it is generally accepted that bifidobacteria and lactobacilli are important components of what might be termed the beneficial gut microbiota. The microbiota management tools of **probiotics**, **prebiotics** and synbiotics have been developed and, indeed, commercialized over the past few decades with the expressed purpose of increasing numbers of bifidobacteria and/or lactobacilli within the gastrointestinal tract.

Nutr Rev. 2002 Oct;60(10 Pt 1):326-34.

Immune-stimulating and **gut health**-promoting properties of short-chain fructo-oligosaccharides.

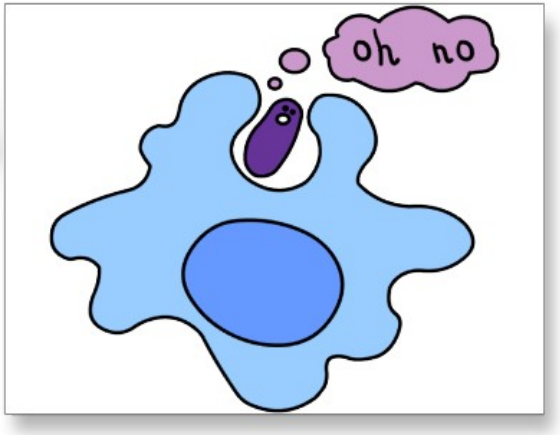
Bornet FR, Brouns F.

NUTRI-HEALTH SA, Rueil-Malmaison, France.

Abstract

Short-chain fructo-oligosaccharides are a group of linear fructose oligomers with a degree of polymerization ranging from one up to five (oligosaccharides). Recent observations in animal models demonstrate that **prebiotics** and **probiotics** may exert beneficial effects on **gut health** by enhancing gut-associated lymphoid tissue responses either directly or indirectly through the production of short-chain fatty acids and the enhanced growth of lactic bacteria such as bifidobacteria and lactobacilli. Demonstration of the potential health benefits of short-chain fructooligosaccharides on colon cancer risk is an active field of research in animal and human nutrition.

Publicity messages about health benefits



Evaluation criteria of health claim applications in Europe

Definition of the health claim

- Health claims should be **specific** and the effect **measurable.**

- **Non defined**: “gut health”, “digestive health”, “intestinal microbiota”, “probiotic”, “immune system”, etc.

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Evaluation criteria of health claim applications in Europe

The extent to which:

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Evaluation criteria of health claim applications in Europe

Which effects are considered beneficial?

- Contributing to defence against gastrointestinal **pathogens or reducing the presence of** gastrointestinal **pathogens**

- Contributing to **normal bowel function** in terms of intestinal regularity/transit.

- Contributing to **normal immune function** in the context of reducing infections, etc.

Evaluation criteria of health claim applications in Europe

Which effects are considered beneficial?

- Contribution to a "**beneficial" or "healthy microbiota**" or to **increases in lactobacilli or bifidobacteria, is not considered beneficial *per se*.**

- Contribution to stimulation of immunity/immune system is not considered beneficial *per se*,

- **Reduction in inflammation** is not considered beneficial *per se*, might be in certain circumstances.

Evaluation criteria of health claim applications in Europe

What is a healthy microbiota?

160 bacterial species are largely shared by all individuals and a minimal gut microbiome has already been defined based on functional genes (Quin et al. 2010. Nature 464:4, 59. MetaHIT project).

What is an unhealthy microbiota?

Evaluation criteria of health claim applications in Europe

What is a healthy microbiota?

NATURE | ARTICLE

Enterotypes of the human gut microbiome

Manimozhiyan Arumugam, Jeroen Raes, Eric Pelletier, Denis Le Paslier, Takuji Yamada, Daniel R. Mende, Gabriel R. Fernandes, Julien Tap, Thomas Bruls, Jean-Michel Batto, Marcelo Bertalan, Natalia Borruel, Francesc Casellas, Leyden Fernandez, Laurent Gautier, Torben Hansen, Masahira Hattori, Tetsuya Hayashi, Michiel Kleerebezem, Ken Kurokawa, Marion Leclerc, Florence Levenez, Chaysavanh Manichanh, H. Bjørn Nielsen, Trine Nielsen + *et al.*

Affiliations | Contributions | Corresponding authors

Nature **473**, 174–180 (12 May 2011) | doi:10.1038/nature09944

3 enterotypes driven by species composition not nation or continent specific, **but relations to physiological features (BMI, age, etc.) are still unclear**

Evaluation criteria of health claim applications in Europe

Which effects are considered beneficial?

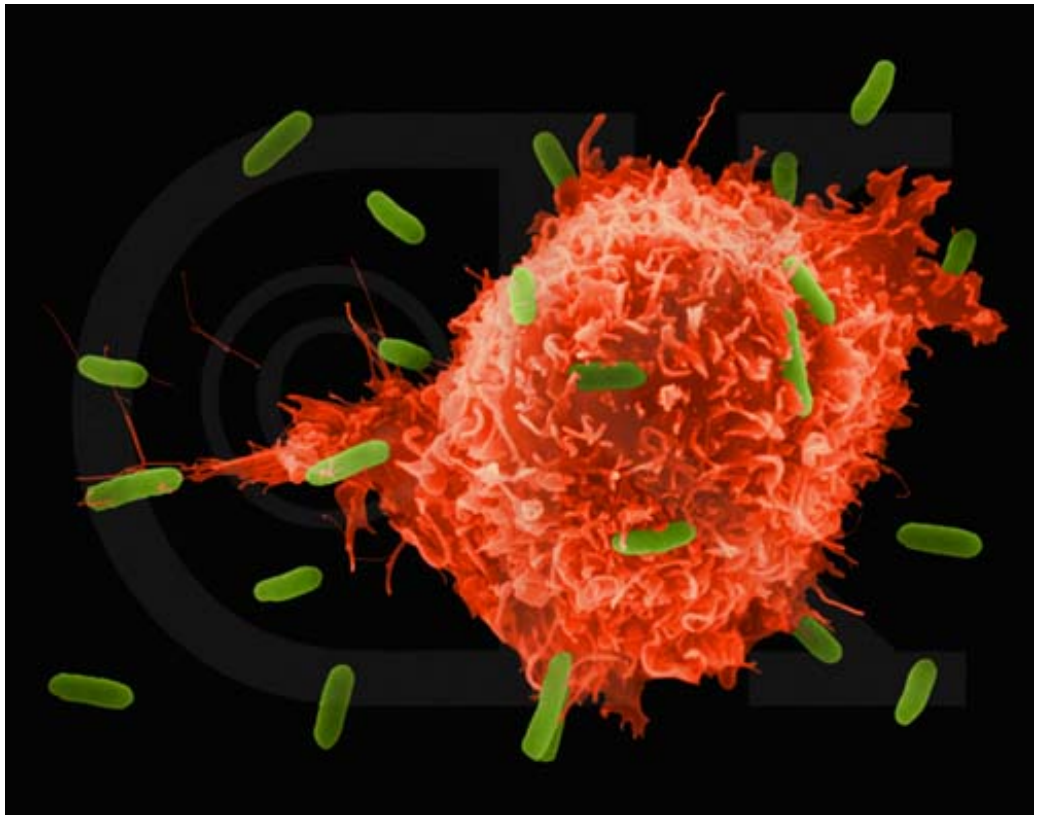
- Contribution to a "**beneficial**" **or** "**healthy microbiota**" or to **increases in lactobacilli or bifidobacteria, is not considered beneficial** *per se*.

- **Contribution to stimulation of immune responses or /immune system** is not considered beneficial *per se*.

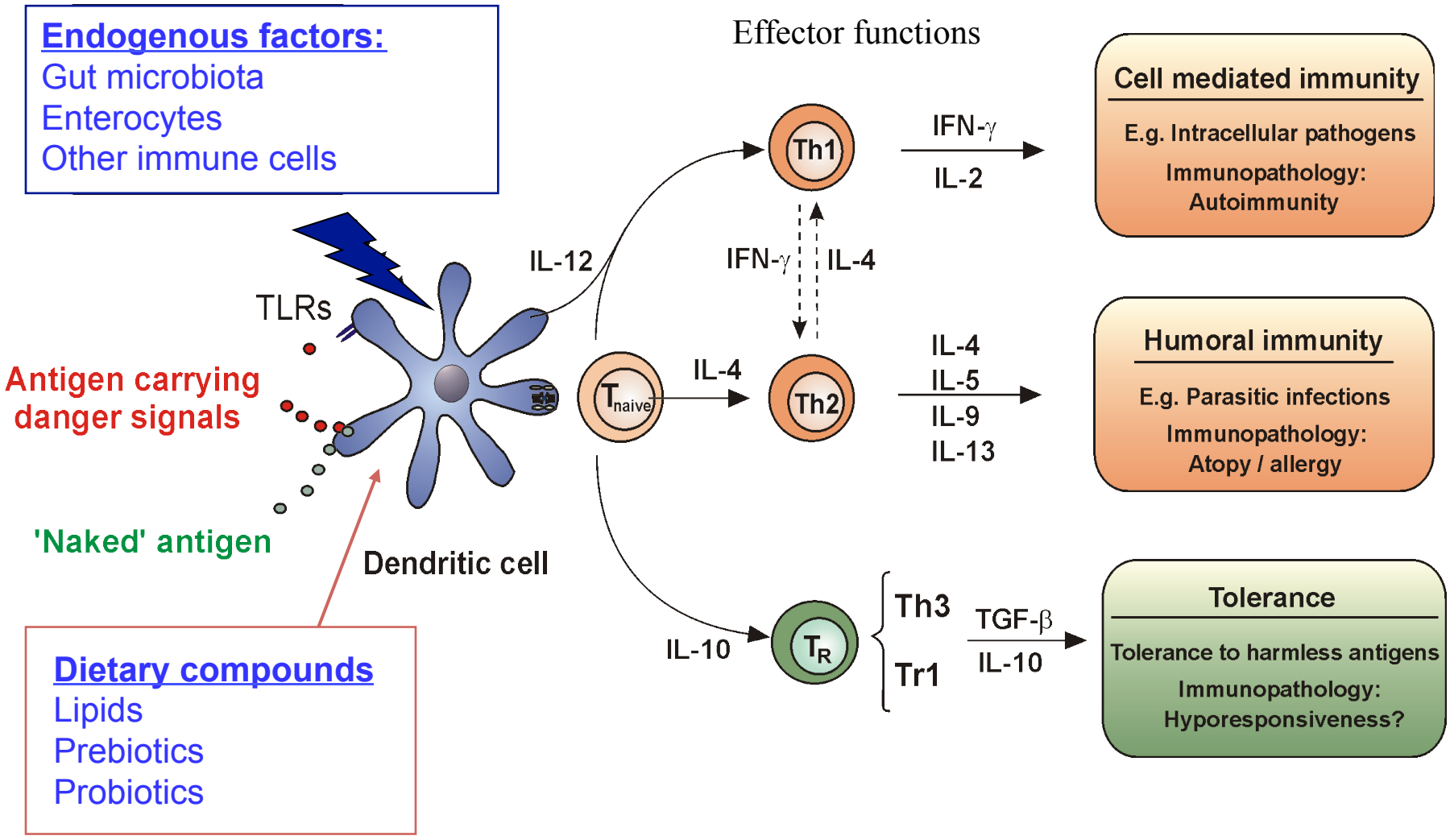
- **Reduction in inflammation** is not considered beneficial *per se*, might be in certain circumstances.

Evaluation criteria of health claim applications in Europe

Is stimulation/inhibition of one aspect of immunity beneficial?



Evaluation criteria of health claim applications in Europe



Evaluation criteria of health claim applications in Europe

Eur J Nutr (2004) [Suppl 2] 43 : II/118–II/173
DOI 10.1007/s00394-004-1205-4

John H. Cummings
Jean-Michel Antoine
Fernando Azpiroz
Raphaelle Bourdet-Sicard
Per Brandtzaeg
Philip C. Calder
Glenn R. Gibson
Francisco Guarner
Erika Isolauri
Daphne Pannemans
Colette Shortt
Sandra Tuijtelaars
Bernhard Watzl

PASSCLAIM[1] – Gut health and immunity

It is not absolutely certain that an increase (up to 10%) in one or more immune function parameters among healthy individuals will improve host resistance.

There is no one test that will define either the status or functional capacity of the immune system.

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Evaluation criteria of health claim applications in Europe

Establishment of a cause-effect relationship

- **What is the target population of health claims?**
  - General (healthy) population and subgroups thereof
- **Which populations can be study?**
  - Healthy human subjects
  - Human subjects at disease risk…, healthy anyway

Evaluation criteria of health claim applications in Europe

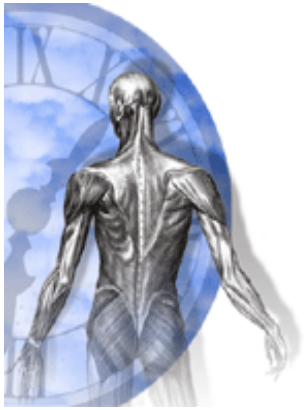
Establishment of a cause-effect relationship

- **When extrapolation from disease populations to general population is feasible?**
  - Reducing gastrointestinal comfort-IBS patients.
  - Maintaining normal joints-Osteoarthritis patients.
  - Case by case evaluation.

Briefing document for stakeholders on health claims evaluation of Art 13.1,13.5 & 14 claims (2010).

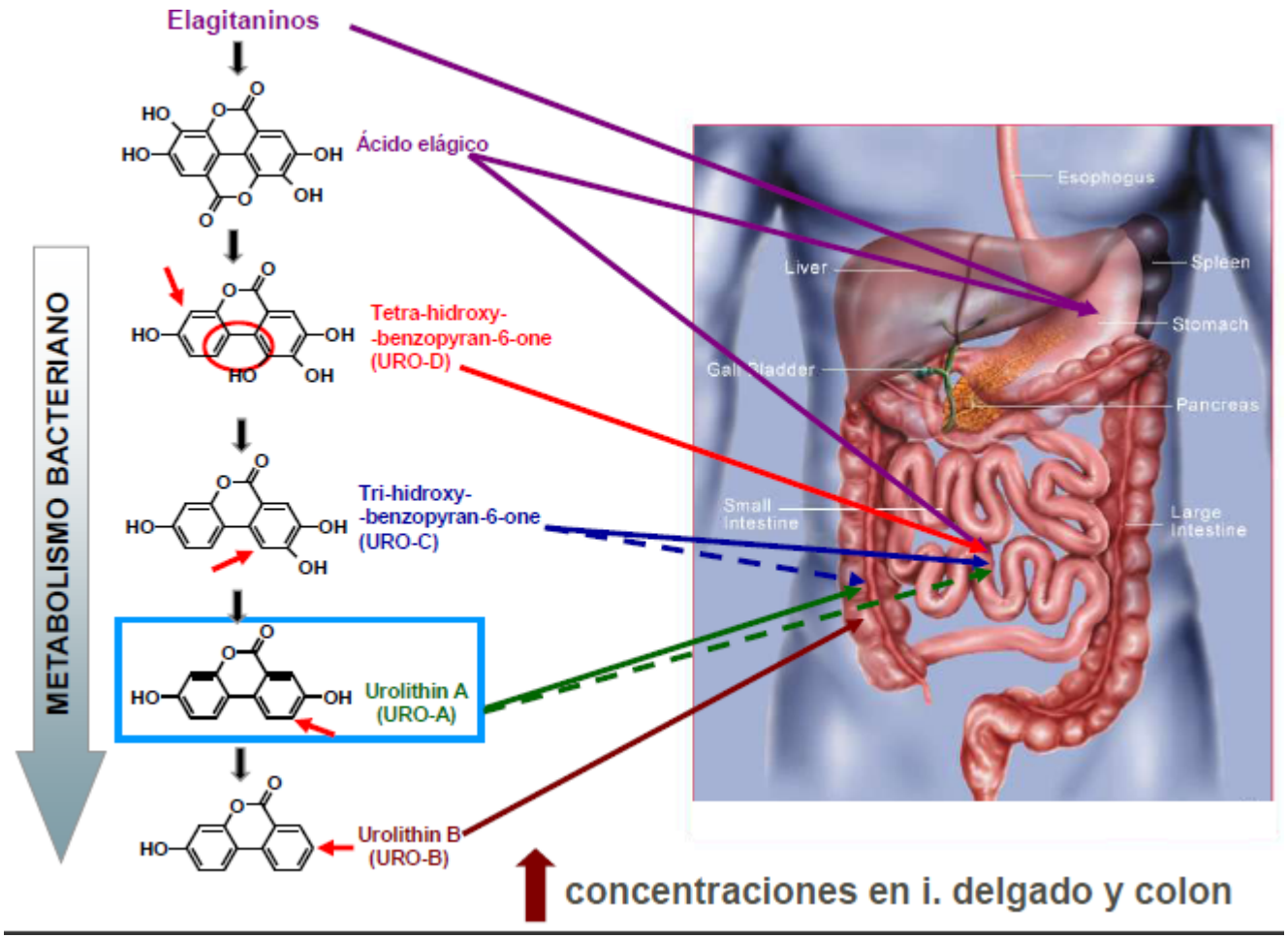
Evaluation criteria of health claim applications in Europe

Hierarchy of evidence



- **Human studies are central for substantiation of the claim**
  - Human intervention studies
  - Observational studies
  - Others
- **No pre-established formula** (number/type of studies needed)
- **Animal or *in vitro* studies may provide supportive evidence, but are not enough.**
- **Not different from other standards (**CODEX, U.S. FDA, Health Canada, etc.**).**

Equivalence between *in vitro* and human data?



Tomás-Barberán, F.A, 2001. Sumer curse UCAM, Murcia.

Number of human intervention studies

How many human intervention studies are necessary?

EFSA Journal 2011;9(4):2033

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to polyphenols in olive and protection of LDL particles from oxidative damage (ID 1333, 1638, 1639, 1696, 2865), maintenance of normal blood HDL-cholesterol concentrations (ID 1639), maintenance of normal blood pressure (ID 3781), "anti-inflammatory properties" (ID 1882), "contributes to the upper respiratory tract health" (ID 3468), "can help to maintain a normal function of gastrointestinal tract" (3779), and "contributes to body defences against external agents" (ID 3467) pursuant to Article 13(1) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

Number of human intervention studies

How many human intervention studies are necessary?

EFSA Journal 2011;9(4):2033

In weighing the evidence, the Panel took into account that one well conducted and powered study, and two smaller-scale studies, showed a dose-dependent and significant effect of olive oil polyphenol consumption (for three weeks) on appropriate markers of LDL peroxidation (oxLDL), that these results were supported by one short-term and one acute study, and by supportive markers of LDL peroxidation (conjugated dienes, *ex vivo* resistance of LDL to oxidation) going in the same direction, and that evidence for a biologically plausible mechanism by which olive oil polyphenols could exert the claimed effect has been provided.

Number of human intervention studies

How many human intervention studies are necessary?

EFSA Journal 2011;9(6):2167

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to *Lactobacillus rhamnosus* GG and maintenance of defence against pathogenic gastrointestinal microorganisms pursuant to Article 13(5) of Regulation (EC) No 1924/2006[1]

The applicant submitted a total of 45 human studies and 41 non-human studies for the scientific substantiation of the health claim.

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- Main challenges in research oriented to claims

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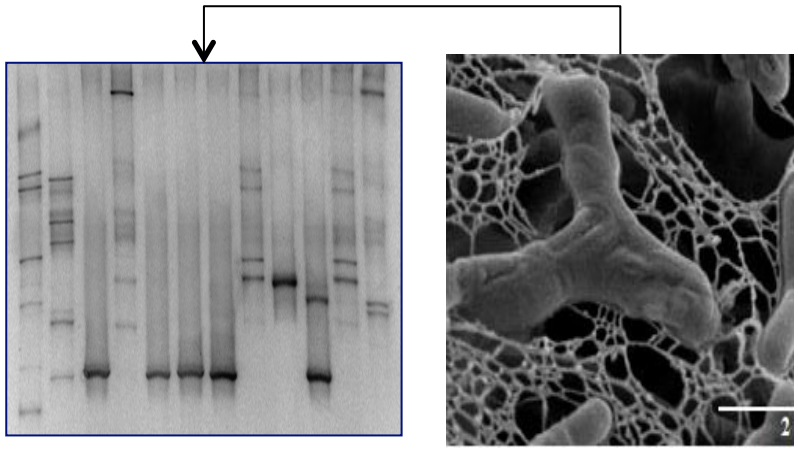
Lessons from health claim applications

Insufficient characterisation

- Species but not strain identification (genetic typing)

"Given that effects are strain-specific, data from one strain can not be extrapolate to another strain and the applicant should provide data on strain characterization"



Evaluation criteria for probiotics in foods (FAO/WHO, 2001-2002)

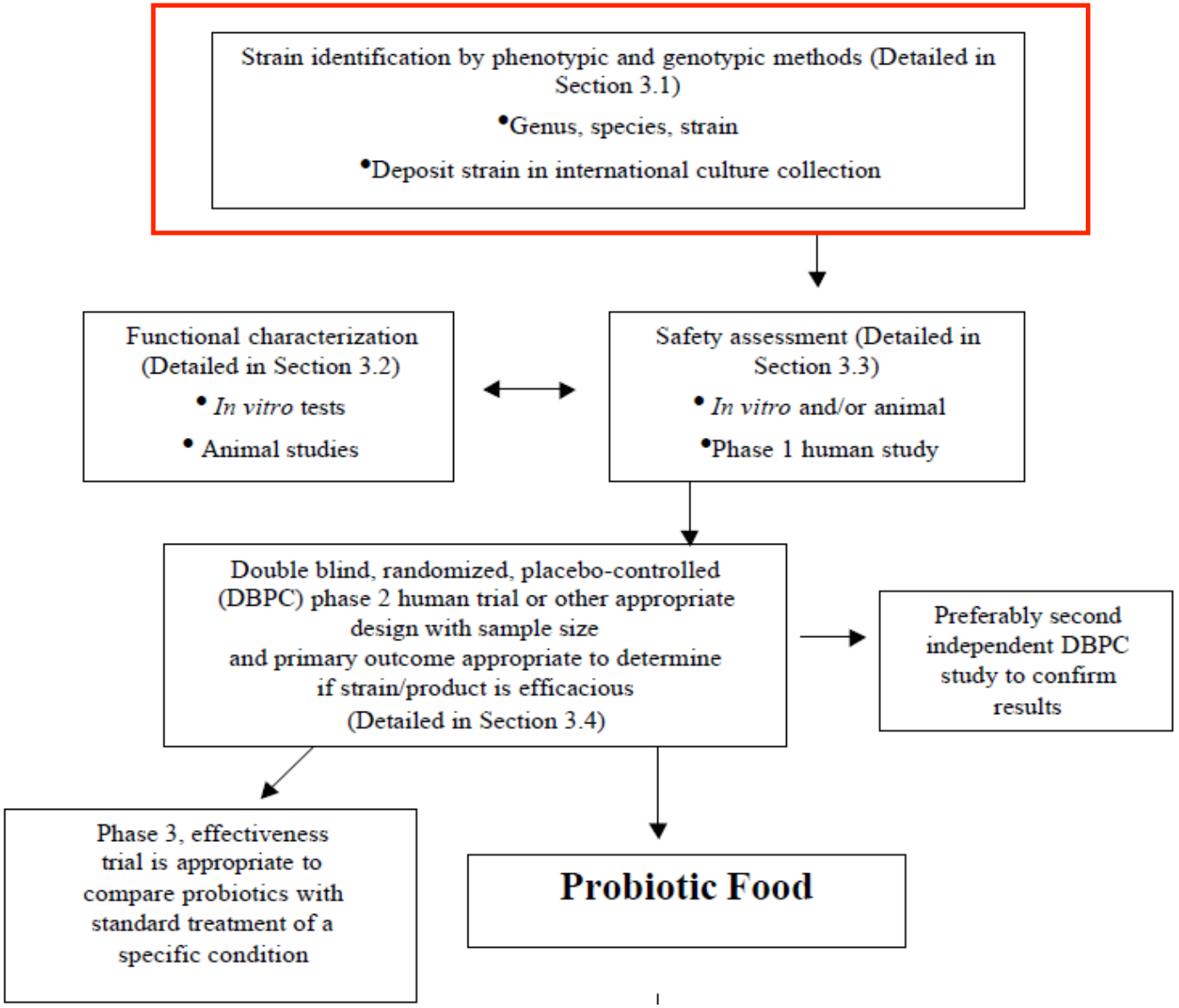
Food and Agriculture Organization of the United Nations

World Health Organization

Guidelines for the Evaluation of Probiotics in Food

Report of a Joint FAO/WHO Working Group on Drafting Guidelines for the Evaluation of Probiotics in Food London Ontario, Canada April 30 and May 1, 2002

Evaluation criteria for probiotics in foods (FAO/WHO, 2001-2002)



Lessons from health claim applications

Identification at species level is sufficient only in case:

- Effect depends on species: lactose digestion

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EFSA Journal 2010;8(10):1763

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to live yoghurt cultures and improved lactose digestion (ID 1143, 2976) pursuant to Article 13(1) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

The food constituent that is the subject of the health claim is "yoghurt cultures (live)", which contain the starter micro-organisms "*Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus*" as specified by Codex Alimentarius Standard No. 243/2003. The Panel considers that live yoghurt cultures, which are the subject of the health claim, are sufficiently characterised in relation to the claimed effect.

Lessons from health claim applications

Non defined health claims

Scientific Opinion on the substantiation of health claims related to various foods/food constituents and "immune function/immune system" (ID 573, 586, 1374, 1566, 1628, 1778, 1793, 1817, 1829, 1939, 2155, 2485, 2486, 2859, 3521, 3774, 3896), "contribution to body defences against external agents" (ID 3635), stimulation of immunological responses (ID 1479, 2064, 2075, 3139), reduction of inflammation (ID 546, 547, 641, 2505, 2862), increase in renal water elimination (ID 2505), treatment of diseases (ID 500), and increasing numbers of gastro-intestinal microorganisms (ID 762, 764, 884) pursuant to Article 13(1) of Regulation (EC) No 1924/2006[1]

EFSA Journal 2011;9(4):2061

Lessons from health claim applications

Non defined health claims

Scientific Opinion on the substantiation of health claims related to *Lactobacillus rhamnosus* ATCC 53103 (LGG) and "gastro-intestinal health" (ID 906) and maintenance of tooth mineralisation (ID 3018) pursuant to Article 13(1) of Regulation (EC) No 1924/2006[1]

"Gastro-intestinal health"

The claimed effect is "gastro-intestinal health". The claimed effect is not sufficiently defined, and no further details were provided in the proposed wordings. The Panel notes that the **references provided addressed several effects, and that it was not possible to establish the effect which is the target for the claim.** .

The Panel considers that the **claimed effect is general and non specific**, and does not refer to any specific health **claim as required by Regulation** (EC) No 1924/2006

Lessons from health claim applications

Non defined health claims-redefined by the NDA Panel

Scientific Opinion on the substantiation of health claims related to *Lactobacillus rhamnosus* ATCC 53103 (LGG) and "gastro-intestinal health" (ID 906) and maintenance of tooth mineralisation (ID 3018) pursuant to Article 13(1) of Regulation (EC) No 1924/2006[1]

"**Oral health/flora**" interpreted as **maintenance of tooth mineralisation**

The claimed effect is "**oral health/flora**". From the information provided, the Panel assumes that the claimed effect refers to the **maintenance of tooth mineralisation by reducing mutans streptococci in the oral** cavity.

Acid is produced in plaque through the fermentation of carbohydrates by acid-producing bacteria, such as *Streptococcus mutans*. Lowering plaque pH contributes to demineralisation of tooth tissues.

The Panel considers that maintenance of tooth mineralisation **is a beneficial physiological effect.**

Lessons from health claim applications

Scientific substantiation: lack of human studies

Scientific Opinion on the substantiation of health claims related to *Lactobacillus plantarum* 299v and reduction of flatulence and bloating (ID 902), and protection of DNA, proteins and lipids from oxidative damage (ID 1083) pursuant to Article 13(1) of Regulation (EC) No 1924/2006[1]

Protection of DNA, proteins and lipids from oxidative damage

The claimed effect is "antioxidant properties". The Panel considers that protection of DNA, proteins and lipids from oxidative damage may be a beneficial physiological effect.

No human studies that addressed the effect of *Lactobacillus plantarum* 299v alone on outcomes related to the claimed effect were provided.

Lessons from health claim applications

Scientific substantiation: no appropriate outcomes

Scientific Opinion on the substantiation of health claims related to *Bifidobacterium animalis* ssp. *lactis* Bb-12 and immune defence against pathogens (ID 863), decreasing potentially pathogenic gastro-intestinal microorganisms (ID 866), "natural immune function" (ID 924), reduction of symptoms of inflammatory bowel conditions (ID 1469) and maintenance of normal blood LDL-cholesterol concentrations (ID 3089) pursuant to Article 13(1) of Regulation (EC) No 1924/2006[1]

Six human intervention studies evaluated the effect of *B. animalis* ssp. *lactis* Bb-12 on different microbial groups (bifidobacteria, lactic acid bacteria, *Bacteroidaceae*, *Eubacteria*, *Enterobacteriaceae*, etc..)

The Panel notes that these **microorganisms are part of the commensal intestinal microbiota**, and that the studies did **not** provide evidence for the **characterisation of any of these groups as pathogens.**

Scientific substantiation: non appropriate study group

Scientific Opinion on the substantiation of health claims related to *Bifidobacterium animalis* ssp. *lactis* Bb-12 and immune defence against pathogens (ID 863), decreasing potentially pathogenic gastro-intestinal microorganisms (ID 866), "natural immune function" (ID 924), reduction of symptoms of inflammatory bowel conditions (ID 1469) and maintenance of normal blood LDL-cholesterol concentrations (ID 3089) pursuant to Article 13(1) of Regulation (EC) No 1924/2006[1]

A human intervention study addressed the effect of *Bifidobacterium animalis* ssp. *lactis* Bb-12 on incidence/episodes of diarrhoea in infants younger than 8 months (Chouraqui et al., 2004).

The Panel considers that the **intestinal microbiota in early childhood is different**, and that the **evidence provided did not establish that these data from infants can be extrapolated to the general population**

Lessons from health claim applications

Scientific substantiation: non statistically significant

Scientific Opinion on the substantiation of health claims related to *Lactobacillus rhamnosus* ATCC 53103 (LGG) and "gastro-intestinal health" (ID 906) and maintenance of tooth mineralisation (ID 3018) pursuant to Article 13(1) of Regulation (EC) No 1924/2006[1]

Effects non significant or statistic data non reported

A randomised, double-blind, placebo-controlled study was provided (Nase et al., 2001) that examine the effects of a "probiotic" milk on children‟s health (GI and respiratory infections and oral health).

Concentrations of *S. mutans* in the intervention and control groups are reported, but no statistical analysis is provided to assess differences between groups. No statistically significant differences were observed between intervention and control groups with respect to dental caries.

Lessons from health claim applications

Scientific substantiation: study design and statistics

Scientific Opinion on the substantiation of health claims related to *Lactobacillus plantarum* 299v and reduction of flatulence and bloating (ID 902), and protection of DNA, proteins and lipids from oxidative damage (ID 1083) pursuant to Article 13(1) of Regulation (EC) No

Flaws in study design and statistics- No conclusions could be drown from 3 human studies due to their weakness:

-No information on diets of subjects enrolled in the study,
-No established that test and control groups were comparable
-No information about the validation of the scale used
-Recall bias
-No stratification of the type of IBS with respect to symptoms
-Correction for repeated measures

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Main challenges in research related to health claims

- **How to prove beneficial effects in healthy population?**
  - Increased disease risk populations.
  - Immunodepression (elderly, athletes, etc.)
  - Border line between health and disease (obese-overweight, etc.)
  - Extrapolation from disease populations when the mode of action is the same, but requires case by case evaluation.

- **How to improve nº responders and magnitude of response?**
  - Selection of study groups (confounders, genetic selection, etc.)

- **Validation of risk factors**

- **Overcome flaws in the study design**

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¡Gracias!