SCIENTIFIC OPINION

DRAFT

Guidance on the scientific requirements for health claims related to gut and immune function

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

The European Food Safety Authority (EFSA) asked the Panel on Dietetic Products Nutrition and Allergies to draft guidance on scientific requirements for health claims related to gut and immune function. This guidance has been drawn from EFSA’s scientific opinions on health claims related to the gastrointestinal tract and immune system. Thus, it represents the views of the NDA Panel based on the experience gained to date with the evaluation of health claims in these areas. It is not intended that the document will include an exhaustive list of beneficial effects and studies/outcome measures that are acceptable. Rather it presents examples drawn from evaluations already carried out to illustrate the approach of the Panel as well as some examples which are currently under consideration within ongoing evaluations.

KEY WORDS

Health claims, scientific requirements, gut and immune

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**BACKGROUND AS PROVIDED BY EFSA**

Regulation (EC) No 1924/2006 harmonises the provisions that relate to nutrition and health claims and establishes rules governing the Community authorisation of health claims made on foods. According to the Regulation, health claims should be only authorised for use in the Community after a scientific assessment of the highest possible standard to be carried out by EFSA.

EFSA and its NDA Panel has been engaging in consultation with stakeholders and has published guidance on scientific substantiation of health claims since 2007. Most recently, a briefing document on scientific evaluation of health claims was published for consultation in April 2010, followed by a technical meeting with experts from the food industry, Member States and the European Commission in Parma, in June 2010.

Based on experiences gained with the evaluation of health claims and to further assist applicants in preparing and submitting their applications for the authorisation of health claims, the NDA Panel is asked to develop a guidance document on the scientific requirements for the substantiation of specific types of health claims.

**TERMS OF REFERENCE AS PROVIDED BY EFSA**

The NDA Panel is requested by EFSA to develop a guidance document on the scientific requirements for health claims related to gut and immune function. Specific issues to be addressed in this guidance include:

- which claimed effects are beneficial physiological effects?
- which studies/outcome measures are appropriate for the substantiation of function claims and disease risk reduction claims?

The NDA Panel is initially requested to draft a guidance to be released for public consultation and to be discussed at a technical meeting with scientific experts in the fields of health claims related to gut and immune functions.

Before its adoption by the NDA Panel the draft guidance needs to be revised taking into account the comments received during the public consultation and at the technical meeting.

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ASSESSMENT

1. Introduction

To assist applicants in preparing and submitting their applications for the authorisation of health claims, EFSA has had ongoing consultation with stakeholders and has published guidance on scientific substantiation of health claims since 2007\(^6\). Most recently, a briefing document on scientific evaluation of health claims was published for consultation in April 2010, followed by a technical meeting with experts from the food industry, Member States and the European Commission in Parma, in June 2010\(^7\). This outlines EFSA’s approach to evaluation of health claims in general. In response to requests from industry EFSA has indicated that it will engage in further consultation with stakeholders and develop additional guidance on specific types of claims.

The objective of the present public consultation is to discuss with scientific experts in the field the scientific requirements for the substantiation of health claims related to the gastrointestinal tract and immune system. This consultation document will be revised to take into account the comments received in order to provide additional guidance to applicants for the substantiation of health claims in these areas.

The consultation document focuses on two key issues related to substantiation of health claims on the gastrointestinal tract and immune system:

- which claimed effects are considered beneficial physiological effects?
- which studies/outcome measures are considered appropriate for the substantiation of health claims?

Issues related to substantiation that are common to health claims in general (e.g. characterization of the food/constituent) are addressed in the briefing document.

This document has been drawn from EFSA’s scientific opinions on health claims related to the gastrointestinal tract and immune system. Thus, it represents the views of the NDA Panel based on the experience gained to date with the evaluation of health claims in these areas. The document should be read in conjunction with the briefing document for stakeholders on the evaluation of Article13.1, 13.5 and 14 health claims, 2010 (see footnote 7).

It is not intended that the document will include an exhaustive list of beneficial effects and studies/outcome measures that are acceptable. Rather it presents examples drawn from evaluations already carried out to illustrate the approach of the Panel as well as some examples which are currently under consideration within ongoing evaluations.

2. General considerations

2.1. Beneficial physiological effect

According to the Regulation, the use of health claims shall only be permitted if the food/constituent, for which the claim is made, has been shown to have a beneficial physiological effect. In assessing each claim, the NDA Panel makes a scientific judgement on whether the claimed effect is considered to be a beneficial physiological effect in the context of the specific claim as described in the information provided and taking into account the population group for whom the claim is intended.

For function claims, a beneficial effect may relate to maintenance or improvement of a function.

For reduction of disease risk claims, ‘beneficial’ refers to whether the claimed effect relates to the reduction (or beneficial alteration) of a risk factor for the development of a human disease (not reduction of the risk of disease). A risk factor is a factor associated with the risk of a disease that may serve as a predictor of development of that disease. Whether or not the alteration of a risk factor is considered to be beneficial in the context of a reduction of disease risk claim, depends on the extent to which it is established that:

- The risk factor is an independent predictor of disease risk (such a predictor may be established from intervention and/or observational studies);
- The relationship of the risk factor to the development of the disease is biologically plausible.

The extent to which the reduction of a risk factor is beneficial in the context of a reduction of disease risk claim needs to be considered on a case-by-case basis.

The NDA Panel considers that the population group for which health claims are intended is the general (healthy) population or specific subgroups thereof, e.g. elderly people, athletes, pregnant women. In its evaluation, the NDA Panel considers that where a health claim relates to a function/effect that may be associated with a disease, subjects with the disease are not the target population for the claim, e.g. joint health and osteoarthritis patients. Applications for claims that specify target groups other than the general (healthy) population are the subject of ongoing discussions with the Commission and Member States with regard to their admissibility.

The NDA Panel also considers whether the claimed effect is sufficiently defined to establish that the studies identified for substantiation of the claim were performed with (an) appropriate outcome measure(s) of that claimed effect. Reference to general, non-specific benefits of the nutrient or food for overall good health or health-related well-being may only be made if accompanied by a specific health claim.

### 2.2. Studies/outcome measures appropriate for substantiation of claims

As human studies are central for substantiation of health claims, the document focuses in particular on these. In considering whether the studies provided are pertinent (i.e. studies from which scientific conclusions can be drawn for the substantiation of the claim), the NDA Panel addresses a number of questions, including:

- whether the studies have been carried out with the food/constituent for which the claim is made. This requirement means that there should be sufficient definition of the food/constituent for which the claim is made and of the food/constituent that has been investigated in the studies that have been provided for substantiation of the claim. The evaluation also considers how the conditions under which the human studies were performed relate to the conditions of use (e.g. quantity and pattern of consumption of the food/constituent) proposed for the claim.
- whether the design and quality of the studies allow scientific conclusions to be drawn for the substantiation of the claim. The evaluation takes into account the hierarchy of evidence as described in the EFSA guidance (ref), e.g. intervention studies generally provide stronger evidence than observational studies. Intervention studies should be appropriately conducted so as to minimise bias. In observational studies adequate control of confounders is important. Each health claim is assessed separately and there is no pre-established formula as to how many or what type of studies are needed to substantiate a claim. In this regard, the reproducibility of the effect of the food/constituent as indicated by consistency between studies is an important consideration.
- whether the studies have been carried out in a study group representative of the population group for which the claim is intended such that the results obtained in the studied population
can be extrapolated to the target population. For studies in groups (e.g. subjects with a disease) other than the target group (e.g. general population) for a claim, the NDA Panel considers on a case-by-case basis, the extent to which it is established that extrapolation from the study group to the target group is biologically justifiable.

- whether the studies used (an) appropriate outcome measure(s) of the claimed effect. For this, the NDA Panel considers what is generally accepted in the relevant research fields and consults experts from various disciplines, as appropriate.

3. Gastro-intestinal tract

3.1. Claims on bowel function

Normal bowel habits vary considerably from person to person with regard to frequency of bowel movements and bulk and consistency of stool. Constipation is associated with longer transit time, less frequent bowel movements, reduced faecal bulk and harder stools and may contribute to diverticular disease. Changes in bowel function within the normal range might be considered beneficial physiological effects.

Appropriate outcome measures of the claimed effect in human studies include transit time, frequency of bowel movements, stool bulk. These outcomes may be measured by generally accepted methods.

3.2. Claims on gastrointestinal discomfort

Episodes of abdominal pain or discomfort (e.g. distension/bloating, abdominal pain/cramp, borborygmi (rumbling) etc.) in the absence of organic disease or biochemical abnormalities are commonly associated with food or drug intake or alterations of bowel habit and vary between individuals in frequency and severity.

Reducing gastrointestinal discomfort is considered a beneficial physiological effect.

Appropriate outcome measures of the claimed effect in human studies include validated subjective global symptom severity questionnaire(s).

Irritable Bowel Syndrome (IBS) is a functional bowel disorder characterized by chronic or recurrent abdominal pain or discomfort mostly associated with changes in defecation or bowel habit and in the absence of a detectable organic cause. Episodes of abdominal pain or discomfort occur both in healthy people and in individuals suffering from IBS, the difference being the higher frequency and greater severity of the symptoms in IBS. IBS patients are generally considered an appropriate study group to support claims on gastrointestinal discomfort intended for the general population.

3.3. Claims on gastrointestinal microbiota

The composition of the microbiota in the intestine may be altered by food constituents. Based on current scientific knowledge, it is not possible to define the exact numbers of the different bacterial groups that would constitute a normal microbiota. The evidence available to the panel does not establish that increasing the number of specific microorganisms or any groups of microorganisms, including lactobacilli and/or bifidobacteria, is in itself a beneficial physiological effect.

The abnormal presence of pathogenic or toxicogenic microorganisms in the intestine may lead in certain circumstances to gastrointestinal infection. The Panel considers that reducing the numbers of specific pathogenic microorganisms in the these ecosystems is a beneficial physiological effect.
The presence of pathogens and/or toxinogenic microorganisms in the gastrointestinal tract is also considered by the Panel as a risk factor for infections and reducing the numbers of specific pathogenic microorganisms or their toxins in these ecosystems is considered a beneficial physiological effect in the context of reducing a risk factor for infection.

Appropriate outcome measures of the claimed effect in human studies include reduction of numbers of pathogenic microorganisms or their toxins in stools or other suitable samples. The composition of microbiota in the gastrointestinal tract show great variability. Therefore, a microbiologically relevant reduction of pathogens, which is sustained over time in the same study group, should be demonstrated. Generally, a decrease by less than 1 log value is not considered meaningful.

There is a distinction in evaluation of effects on pathogenic or toxicogenic microorganisms for function claims and for disease reduction claims.

For disease risk reduction claims studies that show only a reduction in incidence or duration of infection(s) would not constitute evidence for a reduction of the risk factor (e.g. numbers of pathogens). However, clinical outcomes (e.g. number of episodes of infection, severity of symptoms, or duration of infection such as indicated by diarrhoea diagnosed as infection-related using specific criteria), demonstrated in human intervention studies could be supportive of the claimed effect related to pathogens.

The following is a non-exhaustive list of groups of microorganisms that are considered “pathogenic or toxicogenic” and do not need further characterisation of their pathogenicity:

A) Food-borne microorganisms, e.g.: Salmonella, Campylobacter, Listeria, some Escherichia coli strains (including e.g. ETEC, EHEC, EPEC, EIEC strains), Yersinia, Shigella; Toxin producing bacteria such as Staphylococcus aureus, Clostridium botulinum, Bacillus cereus (living organism is not needed for disease, only toxin), Vibrio vulnificus/parahaemolyticus, rotavirus, noroviruses, verotoxigenic E. coli, Enterobacter sakazakii, toxigenic C. perfringens (type A and B), food-borne parasites (Echinococcus, Toxoplasma, Giardia);

B) Gastrointestinal pathogens that are transmitted between humans or originate from environment: e.g. Helicobacter pylori, Clostridium difficile, Clostridium tetani (note: disease via wound infections although can be part of the GI microbiota).

The following is a non-exhaustive list of groups of microorganisms that are considered potentially “pathogenic or toxicogenic” at genus or species level, but that require further characterisation to establish their pathogenicity (i.e. the pathogenicity depends on individual properties/specific characteristics):

Candida, Clostridium perfringens (when producing enterotoxin), other clostridia, Escherichia coli (certain serotypes). Sufficient characterisation is required in the studies to confirm their pathogenicity.

For claims related to maintaining normal defence against pathogens in the gastrointestinal tract, appropriate outcome measures could include reduction of numbers of pathogenic microorganisms or their toxins in suitable samples as well as clinical outcomes (e.g. number and duration of episodes of infection, severity of symptoms, duration of infection, e.g. as measured by infection-related diarrhoea), demonstrated in human intervention studies. (A similar approach would be appropriate for claims related to maintaining normal defence against pathogens at other sites, e.g. urinary tract, upper respiratory tract). While effects on intestinal permeability, production of short chain fatty acids, pH, can be assessed in human studies, such outcomes are in themselves insufficient for the substantiation of the claim. However, they may be considered supportive evidence of the claim in as much as they are proposed as mechanism of action leading to the effect.
3.4. Claims on digestion/absorption of nutrients

Improved digestion or absorption of nutrients might be considered as beneficial physiological effects. Examples of effects considered beneficial to date include improved lactose digestion and improved iron absorption.

In Europe, around 4-60% of the population groups has lactose maldigestion due to a reduced enzyme capacity to digest lactose. Individuals with clinical symptoms of after lactose intake often display nausea, cramping, bloating, diarrhoea and flatulence. Improvement in lactose digestion may alleviate lactose intolerance symptoms and is considered a beneficial physiological effect. The format of such claims may relate to the effect of a food/constituent (e.g. lactose hydrolysing bacteria or enzymes) on lactose digestion when consumed with lactose containing foods.

To assess lactose digestion, studies in susceptible populations, defined either by clinical symptoms or by lactase genotyping, with appropriate assessment of symptoms, and/or measurement of breath hydrogen and methane are required.

Iron deficiency is one of the most common micronutrient deficiencies in the EU and can result in anemia. Non-haem iron is generally not well absorbed in the human intestine and can be a limiting factor for the maintenance of adequate iron status. Improving iron absorption is considered a beneficial physiological effect. The format of such claims may relate to the effect of a food/constituent (e.g. ascorbic acid) on iron absorption when consumed with iron containing foods.

Iron absorption can be measured in humans by generally accepted methods.

It should be noted that the claimed effect (improved nutrient absorption) is only considered beneficial where absorption is a limiting factor for the maintenance of adequate status of the nutrient.

4. Immune System

4.1. Claims on the function of the immune system

An effectively functioning immune system is crucial for maintaining physiological integrity and thus health. The immune system provides defence against infections caused by pathogenic microorganisms. Allergic manifestations, such as asthma, urticaria, and eczema, are caused by undesired immune responses to environmental allergens.

The Panel considers that maintaining a normal immune function is a beneficial physiological effect. Given the multiple roles of the immune system, the specific aspect of immune function that is the subject of the claim should be indicated, e.g. related to defence against pathogens or response to allergens. In this regard, it is considered that claims related to ‘natural defences’ need to be defined more clearly regarding the specific aspect of immune function that is the subject of the claim.

Outcome measures of the claimed effect in human studies include incidence of infection (e.g. in upper respiratory tract, gastrointestinal tract, urinary tract, etc.) and reduction of numbers of pathogens for claims related to defence against pathogens, and incidence of allergic manifestations for claims related to response to allergens. However, since the incidence of infection may not necessarily represent an effect on the immune system, for claims involving the immune system, appropriate evidence of a concomitant change in immunological parameters needs to be provided (see section 3.3).

Similarly, allergic symptoms are not always easy to distinguish from non-allergic phenomena, and self-reported allergies are usually unreliable and insufficient for diagnosis of allergy. Studies on allergic diseases need to include physician diagnosed allergies, and the immunologic nature of these allergies.
needs to be corroborated with appropriate measures. Clinical as well as laboratory measures are preferentially shown in the same intervention studies.

Vaccination confers immunity to certain infectious diseases. Even if a strict correlation between vaccination titres and protection against infection is not always evident, cut off values of vaccination titres indicating protection have been established for many vaccines. It is generally accepted that higher vaccination responses (as measured by increased numbers of individuals attaining protective levels as well as by increments in titres in groups of individuals) are beneficial. For that reason vaccines are usually produced with adjuvants, so that the majority of recipients of vaccines attain sufficient titres to be protected. Stimulation of protective antibody titres could be used to substantiate a health claim on the function of the immune system related to defence against pathogens.

Many other markers of the function of the immune system have been proposed as outcomes for substantiation of claims on immune function. These include numbers of various lymphoid subpopulations in the circulation, proliferative responses of lymphocytes, phagocytic activity of phagocytes, lytic activity of natural killer cells and cytolytic T cells, production of cellular mediators, immunoglobulin levels, delayed-type hypersensitivity responses, etc. They may be considered as supportive evidence, in as much as they are proposed as mechanism of the effect.

4.2. Claims on reduction of inflammation

Claims referring to the reduction of inflammation have been proposed. Inflammation is a non-specific physiological response to tissue damage that is mediated by the immune system. Adequate inflammatory responses are of primary importance for the defence against injury of any origin. Changes in markers of inflammation such as various interleukins do not indicate a beneficial physiological effect per se.

Chronic inflammation is associated with a number of diseases, and under certain circumstances reducing levels of markers of inflammation might indicate a beneficial physiological effect.

Whether or not reduction of inflammatory markers is considered beneficial would depend on the context in which the claim is made (i.e., the health benefit of reducing inflammatory responses and the appropriateness of the markers used for the assessment of the effect would have to be considered on a case-by-case basis).

4.3. Claims on reducing a risk factor for infections or allergy

It is noted that for claims related to reduction of a risk factor for infections or allergy the risk factor may or may not be related to the function of the immune system.

Appropriate outcome measures of the risk factor should be assessed in human studies. While human intervention studies that show only a reduction in the incidence or duration of the infectious or allergic diseases could not substitute for evidence of a reduction in a risk factor for the disease, such studies could be supportive for the claim.

For claims related to infections the presence of pathogens is considered by the Panel as a risk factor and reducing the numbers of specific pathogenic microorganisms is considered a beneficial physiological effect (see section 4.3). Appropriate outcome measures in human studies include numbers of pathogenic microorganisms in suitable samples.

The extent to which the reduction of the risk factor is beneficial in the context of a reduction of disease risk claim needs to be considered on a case-by-case basis. Human intervention studies with clinical outcomes (e.g. number of episodes of infection, duration of infection, incidence of allergic
manifestations) could be used to support the validity of the risk factor for a specific dietary intervention.

**CONCLUSIONS**

To follow