

SCIENTIFIC OPINION

Guidance on the scientific requirements for health claims related to gut and immune function¹

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)^{2,3}

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

The European Food Safety Authority (EFSA) asked the Panel on Dietetic Products Nutrition and Allergies (NDA) to draft guidance on scientific requirements for health claims related to gut and immune function. This guidance has been drawn from scientific opinions of the NDA Panel on such health claims. Thus, this guidance document 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 which 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. A draft of this guidance document, endorsed by the NDA Panel on 10 September 2010, was subjected to public consultation (28 September 2010 to 22 October 2010), and was also discussed at a technical meeting with experts in the field on 2 December 2010 in Amsterdam.

KEY WORDS

Health claims, scientific requirements, gut and immune.

¹ On request from EFSA, Question No EFSA-Q-2010-01139, adopted on 28 January 2011.

² Panel members: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Hannu Korhonen, Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley, Monika Neuhäuser-Berthold, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Stephan Strobel, Inge Tetens, Daniel Tomé, Hendrik van Loveren and Hans Verhagen. Correspondence: nda@efsa.europa.eu

³ Acknowledgement: The Panel wishes to thank for the preparatory work on this scientific opinion: The members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Marina Heinonen, Hannu Korhonen, Martinus Løvik, Ambroise Martin, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Inge Tetens, Hendrik van Loveren and Hans Verhagen. The members of the Claims Sub-Working Group on Gut/Immune: Jean-Louis Bresson, Maria Carmen Collado, Miguel Gueimonde, Daisy Jonkers, Martinus Løvik, Bevan Moseley, Maria Saarela, Seppo Salminen, Yolanda Sanz, Stephan Strobel, Daniel Tomé and Hendrik van Loveren.

TABLE OF CONTENTS

Summary	1
Table of contents	2
Background as provided by EFSA	3
Terms of reference as provided by EFSA	3
Assessment	4
1. Introduction	4
2. General considerations	5
2.1. Beneficial physiological effect	5
2.2. Studies/outcome measures appropriate for substantiation of claims	5
3. Gastro-intestinal tract	6
3.1. Claims on bowel function	6
3.2. Claims on gastro-intestinal discomfort	7
3.3. Function claims related to defence against pathogens	7
3.4. Claims on the reduction of a risk factor for infection	8
3.5. Function claims on gastro-intestinal microbiota	8
3.6. Function claims on digestion/absorption of nutrients	9
4. Immune system	9
4.1. Claims on the function of the immune system	9
4.2. Function claims related to resistance to allergens	10
4.3. Claims on the reduction of a risk factor for allergy	10
4.4. Claims on reduction of inflammation	11
Conclusions	11
Glossary and Abbreviations	12

BACKGROUND AS PROVIDED BY EFSA

Regulation (EC) No 1924/2006⁴ 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 only be authorised for use in the Community after a scientific assessment of the highest possible standard has been carried out by EFSA.

EFSA and its NDA Panel have been engaging in consultation with stakeholders, and have published guidance on scientific substantiation of health claims, since 2007⁵. 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 2010⁶.

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.

⁴ Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

⁵ <http://www.efsa.europa.eu/en/nda/ndaclaims.htm>

⁶ <http://www.efsa.europa.eu/en/ndameetings/docs/nda100601-ax01.pdf>

ASSESSMENT

1. Introduction

To assist applicants in preparing and submitting their applications for the authorisation of health claims, EFSA and in particular its Scientific Panel on Dietetic Products, Nutrition and Allergies (NDA) has ongoing consultations with stakeholders, and has published guidance on the scientific substantiation of health claims, since 2007⁷. In April 2010, a draft briefing document on the scientific evaluation of health claims was published for consultation, followed by a technical meeting with experts from the food industry, Member States and the European Commission in Parma in June 2010. The draft briefing document has been transformed into a Panel output, taking into account the questions/comments received. This document constitutes the general guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims, and outlines the approach of the NDA Panel to the evaluation of health claims in general. In response to requests from industry, EFSA is engaged in further consultation with stakeholders, and is developing additional guidance on specific types of claims.

The present guidance, prepared by the NDA Panel, on the scientific requirements for the substantiation of health claims related to the gastro-intestinal tract and immune system was, prior to its finalisation, endorsed by the NDA Panel on 10 September 2010 for public consultation (which was open from 28 September to 22 October 2010), and discussed with scientific experts in the field at a technical meeting on 2 December 2010 in Amsterdam. The technical meeting was also broadcasted⁸. All the public comments received that related to the remit of EFSA were assessed, and the guidance has been revised taking into consideration relevant comments. The comments received and a report on the outcome of the public consultation have been published on the EFSA website.

The guidance document focuses on two key issues regarding the substantiation of health claims related to the gastro-intestinal tract and immune system:

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

Issues which are related to substantiation that are common to health claims in general (e.g. characterisation of the food/constituent) are addressed in the general guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims⁹.

This document has been drawn from scientific opinions of the NDA Panel on health claims related to the gastro-intestinal 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 general guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims.

It is not intended that the document should include an exhaustive list of beneficial effects and studies/outcome measures which 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.

⁷ <http://www.efsa.europa.eu/en/ndaclaims/ndaguidelines.htm>

⁸ <http://www.efsa.europa.eu/en/events/event/nda101202.htm>

⁹ EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2011. General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims. EFSA Journal, 9(4):2135, 24 pp.

2. General considerations

2.1. Beneficial physiological effect

According to Regulation (EC) No 1924/2006, 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 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.

Except for well established risk factors, the extent to which the reduction of a 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, for example, elderly people, physically active subjects, or pregnant women. In its evaluation, the NDA Panel considers that where a health claim relates to a function/effect which may be associated with a disease, subjects with the disease are not the target population for the claim. Applications for claims which 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, this document focuses in particular on such studies. 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 which has been investigated in the studies which 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 conclusions to be drawn for the scientific substantiation of the claim. The evaluation takes into account the hierarchy of evidence as described in the scientific and technical guidance of the NDA Panel¹⁰, for example 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 for factors other than the food/constituent known to have an impact on the claimed effect 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. Can the results obtained in the studied population be extrapolated to the target population? For studies in groups (e.g. subjects with a disease) other than the target group for a claim (e.g. the general population), 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 stools. Constipation is associated with longer transit time, less frequent bowel movements, reduced faecal bulk and harder stools, and may contribute to diseases such as diverticular disease.

For claims related to bowel function for the general population, changes in bowel function such as reduced transit time, more frequent bowel movements, increased faecal bulk, or softer stools, may be considered beneficial physiological effects, provided they do not result in diarrhoea.

Appropriate outcome measures of the claimed effect in human studies include transit time, frequency of bowel movements, stool bulk and stool consistency. These outcomes should be measured by generally accepted methods including validated questionnaire-based assessments.

The specific aspect of bowel function which is the subject of the claim should be indicated. More than one outcome measure can be considered to substantiate a specific claim if outcome measures are interrelated.

Patients with functional constipation are generally considered an appropriate study group to support claims on bowel function intended for the general population. Irritable Bowel Syndrome (IBS) patients or subgroups of IBS patients with constipation are generally considered an appropriate study

¹⁰ EFSA (European Food Safety Authority), 2007. Opinion of the Panel on dietetic products, nutrition and allergies (NDA) on a request from the Commission related to scientific and technical guidance for the preparation and presentation of the application for authorisation of a health claim. The EFSA Journal, 530, 1-44.

group to substantiate claims on bowel function intended for the general population (adults and children).

Diarrhoea is not considered in the context of claims related to bowel function for the general population, but may be used as an outcome measure for other claims, for example, claims related to defence against pathogens in the gastro-intestinal tract.

3.2. Claims on gastro-intestinal discomfort

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

Reducing gastro-intestinal discomfort is considered an indicator of improved gastro-intestinal function, and is considered to be a beneficial physiological effect.

Appropriate outcome measures of the claimed effect in human studies include validated questionnaire(s) on severity and frequency of symptoms (e.g. abdominal pain, cramp, bloating, straining, borborygmi [rumbling] and sensation of incomplete evacuation). Questionnaires developed following general validation principles, and appropriate for the purpose of the study, are required. Validated general “quality of life questionnaires” alone are insufficient as outcome measures, but may provide indirect evidence for claims on gastro-intestinal discomfort.

IBS is a functional bowel disorder characterised by chronic or recurrent abdominal pain or discomfort, mostly associated with changes in defecation or bowel habit 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 patients. IBS patients or subgroups of IBS patients are generally considered an appropriate study group to substantiate claims on gastro-intestinal discomfort intended for the general population (adults and children).

3.3. Function claims related to defence against pathogens

Defence against pathogens comprises different mechanisms which act in concert to protect against infection. The presence of pathogenic microorganisms may cause infections at various sites of the body, and defence against pathogens at a specific site of the body is considered a beneficial physiological effect. The type of infection and the target population should be specified for function claims on defence against pathogens (e.g. defence against pathogens in the gastro-intestinal tract, in the upper respiratory tract or in the urinary tract).

For function claims related to defence against pathogens in the gastro-intestinal tract, appropriate outcome measures are gastro-intestinal infections (e.g. number of episodes and severity or duration of infection). The infectious nature of the disease should be established, e.g. by clinical diagnosis and/or the use of validated questionnaires for recording self-reported data and/or microbiological data depending on the type of the infection.

For function claims related to defence against pathogens at other sites of the body, for example upper respiratory tract or urinary tract, a similar approach would be appropriate.

Another appropriate outcome measure for function claims related to defence against pathogens in the gastro-intestinal tract would be the reduction of the presence of specific pathogens, their toxins or other virulence factors, as measured in suitable samples (e.g. stools). A relevant reduction of

pathogens, measured at appropriate time-points and in appropriately controlled studies, should be demonstrated. The relevance of such reductions should be justified, for example by the magnitude of reduction or by evidence of a reduction in clinical outcomes related to infection accompanying the reduction in pathogens/toxins. This outcome measure would also be suitable for substantiation of a function claim related to defence against pathogens at other sites of the body.

Outcome measures such as decrease in stool pH, changes in short-chain fatty acid production and reduction of intestinal permeability, are not considered beneficial physiological effects *per se*, but may provide evidence on the mechanisms and the biological plausibility of a claim related to defence against pathogens.

The following is a non-exhaustive list of groups of microorganisms which are considered to be pathogenic, and which do not need further characterisation of their pathogenicity:

Food-borne pathogenic or toxigenic microorganisms, for example, *Salmonella* spp., *Campylobacter* spp., *Listeria monocytogenes*, some *Escherichia coli* serotypes (e.g. ETEC, EHEC, EPEC, EIEC, VTEC), *Yersinia* spp., *Shigella* spp., *Staphylococcus aureus*, *Clostridium botulinum*, *Bacillus cereus*, *Vibrio vulnificus/parahaemolyticus*; *Cromobacter sakazakii*, toxigenic *Clostridium perfringens* (type A and B); rotavirus, noroviruses; food-borne parasites (*Echinococcus*, *Toxoplasma*, *Giardia*, etc.).

Gastro-intestinal pathogens that are transmitted between humans or originate from the environment: for example, *Helicobacter pylori*, *Clostridium difficile*, *Clostridium tetani*.

For other groups of microorganisms that are considered potentially “pathogenic” at genus or species level, sufficient characterisation is required in the studies to confirm their pathogenicity, as this depends on specific features (e.g. expression of virulence factors or production of toxins).

3.4. Claims on the reduction of a risk factor for infection

For reduction of disease risk claims related to infections, evidence is required for reduction (or beneficial alteration) of a risk factor for the development of the infection.

For reduction of disease risk claims related to gastro-intestinal infections, the presence of pathogens or toxins in the gastro-intestinal tract is associated with development of infections, and a relevant reduction of specific pathogenic microorganisms or their toxins in the gastro-intestinal tract, as measured in suitable samples (e.g. stools), is considered a beneficial physiological effect in the context of reducing a risk factor for gastro-intestinal infections. The relevance of such reductions should be justified in relation to the type of infection, for example, by the magnitude of reduction or by evidence of a reduction of clinical outcomes related to infection accompanying the reduction in pathogens/toxins. This approach would also be suitable for substantiation of a disease risk reduction claim related to infections at other sites of the body.

3.5. Function claims on gastro-intestinal microbiota

The composition of the microbiota in the gastro-intestinal tract may be altered by food constituents. Based on current scientific knowledge, it is not possible to define the exact numbers of the different microbial groups which constitute a normal microbiota. The evidence available to the Panel does not establish that increasing the number of any groups of microorganisms, including lactobacilli and/or bifidobacteria, is in itself a beneficial physiological effect. For function claims related to changes in gastro-intestinal microbiota these changes should be accompanied by a beneficial physiological or clinical outcome. This applies to both adult and infant/children populations.

The presence of pathogenic microorganisms in the gastro-intestinal tract may cause infections. Function claims related to defence against pathogens, and reduction of disease risk claims related to gastro-intestinal infections, have been addressed in sections 3.3 and 3.4.

3.6. Function claims on digestion/absorption of nutrients

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

In Europe, around 4-60 % of the population have lactose maldigestion due to a reduced enzymatic capacity to digest lactose. Individuals with clinical symptoms after lactose intake often display nausea, cramping, bloating, diarrhoea and flatulence. Improvement in lactose digestion may alleviate lactose maldigestion 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 genotyping lactase non persistence polymorphism, with appropriate assessment of symptoms, and/or measurement of breath hydrogen and methane, are required.

For other nutrients, whether improved digestion is considered a beneficial physiological effect may depend on the consequences of reduced digestion (e.g. the effect of undigested nutrient in the gastro-intestinal tract, or whether absorption and retention is limited by digestion).

Iron deficiency is one of the most common micronutrient deficiencies in the EU, and can result in anaemia. 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 an adequate status of the nutrient, and where the absorbed nutrient can be utilised.

Claims related to reduced absorption of nutrients such as glucose and cholesterol are considered in the context of reduced blood concentrations of these nutrients.

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 undesirable 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 which is the subject of the claim should be indicated.

For a claim related to immune defence against pathogens, appropriate outcome measures are those which may be used to substantiate claims related to defence against pathogens (see section 3.3), together with concomitant changes in relevant immunological parameters, preferably shown in the same intervention studies.

Similarly, for a claim on immune resistance to allergens appropriate outcome measures are those which may be used to substantiate claims related to resistance to allergens (see section 4.2), together with appropriate immunological parameters, preferably shown in the same intervention studies.

Many markers of the function of the immune system have been proposed as outcomes for substantiation of claims on immune function. These proposed markers include the 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, serum and secretory immunoglobulin levels, delayed-type hypersensitivity responses, etc. The evidence available to the Panel does not establish that stimulation of any of these markers is in itself a beneficial physiological effect, but changes need to be accompanied by a beneficial physiological or clinical outcome, preferably shown in the same intervention studies.

For claims on maintaining normal immune function in population groups considered to be at risk of immunosuppression (e.g. older adults, individuals experiencing stress or engaging in heavy physical exercise, or after exposure to ultraviolet radiation), studies on subjects with immunosuppression (confirmed by symptoms and/or immune markers) showing improvement of those symptoms and/or immune markers may be considered appropriate.

Vaccination confers immunity to certain infectious diseases. Even if a strict correlation between titres in response to vaccination and protection against infection is not always evident, cut-off values of antibody-titres in response to vaccination 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. Stimulation of protective antibody titres, as measured by increased numbers of individuals attaining protective levels, could be used to substantiate a health claim on the function of the immune system related to defence against pathogens.

For studies carried out in children to substantiate a claim on the function of the immune system, the Panel notes that, in general, data from infants and young children cannot be extrapolated to the adult population, as the immune system in early childhood is still developing; hence the immune system in early childhood is different from adults.

4.2. Function claims related to resistance to allergens

Resistance to allergens may comprise different mechanisms which act in concert to reduce allergic reactions. The Panel considers that resistance to allergens is a beneficial physiological effect. Appropriate measures include clinical outcomes related to allergy (e.g. the incidence, severity or frequency of allergic manifestations). Allergic symptoms are not always easy to distinguish from non-allergic phenomena, and data from self-reported allergies are usually unreliable and insufficient for a diagnosis of allergy. Studies on allergic diseases need to include appropriate diagnostic procedures. It should be noted that effects of a food on one clinical type of allergy do not necessarily predict an effect on another type of allergy.

4.3. Claims on the reduction of a risk factor for allergy

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

If it can be shown that an alteration of a (immunological) marker(s) is accompanied by an improvement of clinical outcomes related to allergy (e.g. a reduced incidence, severity or frequency of allergic manifestations) then such alteration in the (immunological) marker might be considered beneficial in the context of a reduction of disease risk claim for allergy for that specific dietary intervention.

For example, some evidence is available to indicate that increased concentrations of allergen specific IgE during the early years of life is associated with a higher incidence of allergic disease. Allergen-specific IgE concentrations during the first years of life might serve as a risk factor, and reduction of allergen-specific IgE concentrations early in life may be used to substantiate disease risk reduction claims related to allergy, if accompanied by improvements in clinical outcomes related to allergy (e.g. a reduced incidence, severity or frequency of allergic manifestations).

4.4. Claims on reduction of inflammation

Inflammation is a non-specific physiological response to tissue damage which is mediated by the immune system. Adequate inflammatory responses are of primary importance for the defence against injury of any origin.

For function claims referring to reduction of inflammation, a change in markers of inflammation such as various interleukins does not indicate a beneficial physiological effect *per se*, but should be accompanied by a beneficial physiological or clinical outcome.

Chronic inflammation is associated with the development of a number of diseases, and altering levels of markers of inflammation might indicate a beneficial physiological effect in the context of a reduction of disease risk claim, if it can be demonstrated that altering the levels of inflammatory markers is accompanied by a reduced incidence of a disease for a specific dietary intervention.

CONCLUSIONS

The guidance document focused on two key issues regarding the substantiation of health claims related to the gastro-intestinal tract and immune system:

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

The document has been drawn from scientific opinions of the NDA Panel on health claims related to the gastro-intestinal tract and immune system function. 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.

GLOSSARY AND ABBREVIATIONS

EHEC	Enterohemorrhagic <i>Escherichia coli</i>
EIEC	Enteroinvasive <i>Escherichia coli</i>
EPEC	Enteropathogenic <i>Escherichia coli</i>
ETEC	Enterotoxigenic <i>Escherichia coli</i>
IBS	Irritable Bowel Syndrome
IgE	Immunoglobulin E
VTEC	Verotoxigenic <i>E. coli</i>