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# Guidance on the scientific requirements for health claims related to the immune system, the gastrointestinal tract and defence against pathogenic microorganisms

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

## Abstract

The European Food Safety Authority (EFSA) has asked the Panel on Dietetic Products, Nutrition and Allergies (NDA) to update the guidance on the scientific requirements for health claims related to gut and immune function published in 2011. Since then, the NDA Panel has completed the evaluation of Article 13.1 claims except for claims put on hold by the European Commission, and has evaluated additional health claim applications submitted pursuant to Articles 13.5 and 14, which are in the area covered by this guidance. In addition, the NDA Panel has developed the general scientific guidance for stakeholders for health claims applications which addresses general issues that are common to all health claims. This guidance is intended to assist applicants in preparing applications for the authorisation of health claims related to the immune system, the gastrointestinal tract and defence against pathogenic microorganisms. Examples of claims evaluated favourably by the Panel will be used to provide guidance to applicants on the scientific requirements for the substantiation of health claims in specific areas, whereas examples of claims evaluated unfavourably by the Panel will be used to illustrate the shortcomings that prevented the substantiation of these claims. The general document represents the views of the NDA Panel based on the experience gained to date with the evaluation of health claims, and it may be further updated, as appropriate, in the light of experiences gained from the evaluation of additional health claim applications.



**Keywords:** health claims, immune system, gastrointestinal tract, pathogens, microorganisms, applications, guidance

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## Summary

The European Food Safety Authority (EFSA) has asked the Panel on Dietetic Products, Nutrition and Allergies (NDA) to revise the guidance on the scientific requirements for health claims related to gut and immune function published in 2011.

Since then, the NDA Panel has completed the evaluation of Article 13.1 claims (except for claims put on hold by the European Commission) and has evaluated additional health claim applications submitted pursuant to Articles 13.5 and 14 which are in the area covered by this guidance. In addition, the NDA Panel has developed the general scientific guidance for stakeholders for health claims applications which addresses general issues that are common to all health claims.

The guidance document has been structured to avoid overlapping with the general scientific guidance for stakeholders on health claim applications. This guidance is intended to assist applicants in preparing applications for the authorisation of health claims related to the immune system, the gastrointestinal tract and defence against pathogenic microorganisms. Examples of claims evaluated favourably by the Panel are used to provide guidance to applicants on the scientific requirements for the substantiation of health claims in specific areas, whereas examples of claims evaluated unfavourably by the Panel are used to illustrate the shortcomings that prevented the substantiation of these claims.

The guidance does not intend to provide an exhaustive list of beneficial physiological effects and studies/outcome variables which could be acceptable, or address potential health relationships and related outcome measures which have not yet been considered by the Panel in the context of a particular application.

This guidance supersedes the guidance on the scientific requirements for health claims related to gut and immune function published in 2011.

The guidance has been subject to public consultations, first on a discussion paper (from 18 June to 10 September 2014) and subsequently on an updated version of the guidance (from 9 February to 23 March 2015). This guidance document represents the views of the NDA Panel based on the experience gained to date with the evaluation of health claims, and it may be updated in the future following the evaluation of additional health claim applications.

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## Background as provided by EFSA

Regulation (EC) No 1924/2006[1] harmonises the provisions related 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 the European Food Safety Authority (EFSA).

Owing to the scientific and technical complexity of health claims, the EFSA Panel on Dietetic products, Nutrition and Allergies (NDA Panel) has placed considerable focus on developing scientific criteria for substantiation of health claims and has published guidance on scientific substantiation of health claims since 2007.[2]

To date, over 570 scientific opinions related to health claims have been published and the Panel notes that additional health relationships and outcome measures for specific claimed effects have been considered in the context of specific applications.

Based on experiences gained with the evaluation of health claims, and to further assist applicants in preparing and submitting their applications for the scientific evaluation of health claims, the NDA Panel considers it necessary to update existing guidance documents, and/or to develop new guidance documents, on the scientific requirements for the substantiation of health claims.

The NDA Panel also emphasises the importance of engaging in consultation with experts/stakeholders in the process of updating existing guidance documents and/or developing new guidance documents.

It is proposed to undertake this task in a stepwise manner, taking into account the experience gained and new scientific evidence available to the NDA Panel, including outcomes of public consultations with experts/stakeholders.

Owing to a high demand from stakeholders and questions received from applicants requesting clarification related to gut and immune function claims, it is proposed to start updating the existing Guidance document on the scientific requirements for health claims related to gut and immune functions (EFSA NDA Panel, 2011e).

## Terms of Reference as provided by EFSA

The NDA Panel is requested by EFSA to update the existing Guidance document on scientific requirements for health claims related to gut and immune function.

In this context, as an initial step, the Panel is requested to issue a statement to be released for public consultation to gather views from experts/stakeholders in the field before proceeding with the updating of the guidance document. The statement shall point out the issues to be covered in the guidance document, propose recommendations for the updating of the guidance document, and propose a timetable for the release of draft and final guidance.

As a second step, taking into account the experience gained and new scientific evidence available to the NDA Panel, including the outcome of the public consultation on the statement, the Panel is requested to update and draft the Guidance document to be released for public consultation before finalisation.

Before the adoption of the guidance document by the NDA Panel, the draft guidance needs to be revised taking into account the comments received during the public consultation.

A technical report on the outcome of the public consultation on the guidance document shall be published, in which comments received on the statement shall be included.

[1] 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.
[2] http://www.efsa.europa.eu/en/nda/ndaclaims.htm

# Assessment

## 1. Introduction

The Guidance on the scientific requirements for health claims related to gut and immune function (EFSA NDA Panel, 2011e) published in April 2011, laid down recommendations on specific issues that need to be addressed in the applications submitted for the substantiation of health claims in this area and was based on the experience gained by the European Food Safety Authority (EFSA) Panel on Dietetic products, Nutrition and Allergies (NDA Panel) with the evaluation of health claims. Since then, the NDA Panel has evaluated additional health claims related to the immune system, the gastrointestinal (GI) tract and defence against pathogenic microorganisms.

Among the 2,758 IDs evaluated by the NDA Panel under Article 13(1) (function claims), 421 IDs were in the area covered by this guidance. A total of 157 IDs were on GI functions, 41 IDs on the absorption/digestion of nutrients, 120 IDs on immune functions, 87 IDs on defence against pathogens, 15 IDs on inflammation and one ID referred to a beneficial change in response to allergens. Of these, the following claims were evaluated favourably by the Panel:

- claims based on the essentiality of nutrients (for copper, folate, iron, selenium, zinc, and vitamins C, D, A, B12 and B6);
- claims related to bowel function/normal defecation (for dried prunes, lactulose, wheat bran fibre, rye fibre, oat and barley grain fibre);
- one claim on GI discomfort caused by lactose intake in lactose intolerant individuals (for foods with reduced lactose content);
- one claim on the reduction of intestinal gas accumulation (for activated charcoal);
- claims related to the absorption of micronutrients (for vitamins C, D, meat or fish, fats), to the digestion of food (for calcium, chloride) and to lactose digestion (for lactase and live yoghurt cultures).

Among the 463 applications submitted to EFSA as of 29/07/2015 under Article 13(5) and Article 14, 155 claims were relevant to this guidance (90 were withdrawn during the evaluation, 58 were evaluated/finalised by the NDA Panel and seven were under evaluation). Of these, the following claims were evaluated favourably by the Panel: claims on immune function which were based on the essentiality of nutrients (for vitamin D and zinc), claims on bowel function/maintenance of normal defecation (for sugar beet fibre, chicory inulin and hydroxyanthracene derivatives) and one claims on the absorption of micronutrients (for vitamin C).

## 2. Objectives and scope

This guidance is intended to assist applicants in preparing applications for the authorisation of health claims related to the immune system, the GI tract and defence against pathogenic microorganisms. It takes into account the outcomes of public consultations (i.e. on 'a discussion paper' (EFSA NDA Panel, 2015a) and on the draft 'guidance on the scientific requirements for health claims related to the gastro-intestinal tract, the immune system, and defence against pathogenic microorganisms'). The guidance document has been restructured to avoid overlapping with the general scientific guidance for stakeholders on health claim applications, which addresses general issues that are common to all health claims and has been updated.

Examples of claims evaluated by the Panel with a favourable opinion will be used to provide guidance to applicants on the scientific requirements for the substantiation of health claims in specific areas, whereas examples of claims evaluated by the Panel with an unfavourable opinion will be used to illustrate the shortcomings that prevented the substantiation of these claims. The Panel cannot, however, provide guidance to applicants on the scientific requirements for the substantiation of health claims (e.g. type and amount of studies needed for substantiation) in specific areas where no examples of favourable evaluations are available (i.e. claims on GI discomfort, on defence against pathogens, on beneficial changes in response to allergens, on the reduction or beneficial alteration of a risk factor for infections in the context of disease risk reduction claims, on claims related to functions of the immune system which are not based on the essentiality of nutrients).

Issues related to the scientific substantiation that are common to all health claims are addressed in the general scientific guidance for stakeholders on health claim applications (EFSA NDA Panel, 2016) and will not be reiterated in this document. This guidance does not intend to provide an exhaustive list of beneficial physiological effects and of studies/outcome variables which could be acceptable for claims substantiation, or address potential health relationships and related outcome measures which have not been considered by the Panel yet in the context of a particular application. The guidance will be kept under review and will be amended and updated in the light of experiences gained from the evaluation of additional health claim applications in this area.

This guidance supersedes the guidance on the scientific requirements for health claims related to gut and immune function published in 2011 and should be read in conjunction with the General scientific guidance for stakeholders on health claim applications (EFSA NDA Panel, 2016), the Scientific and technical guidance for the preparation and presentation of an application for authorisation of a health claim (EFSA NDA Panel, 2011c), Regulation on Nutrition and Health Claims made on foods,[3] the Guidance on the implementation of Regulation (EC) No 1924/2006 (Standing Committee on the Food Chain and Animal Health, 2007), Commission Regulation (EC) No 353/2008,[4] the Commission Implementing Decision of 24 January 2013,[5] and future guidelines and regulations, as applicable.

# 3. Function claims

## 3.1. Claims on the functions of the immune system

### 3.1.1. Claims based on the essentiality of nutrients

Claims on the maintenance of (unspecified) functions of the immune system which were based on the essentiality of nutrients (e.g. vitamins C (EFSA NDA Panel, 2009b), D (EFSA NDA Panel, 2010d), A (EFSA NDA Panel, 2009a), B12 (EFSA NDA Panel, 2009d), B6 (EFSA NDA Panel, 2009e), zinc (EFSA NDA Panel, 2009f), copper (EFSA NDA Panel, 2009g), folate (EFSA NDA Panel, 2009h), iron (EFSA NDA Panel, 2009i), selenium (EFSA NDA Panel, 2009c)) were evaluated by the NDA Panel with a favourable opinion.

The scientific substantiation of claims on the maintenance of (unspecified) functions of the immune system was based on the essentiality of these nutrients, i.e. on the well-established biochemical role of such nutrients, and/or on deficiency symptoms involving the immune system. The use of unspecified functions of the immune system to substantiate such claims is because symptoms of deficiency of a nutrient can result from effects on multiple physiological functions, and it is sometimes not possible or appropriate to single out a precise function that is affected by deficiency of that nutrient in a particular organ or system. For these claims, the NDA Panel did not review the primary scientific studies submitted and it did not weigh the evidence.

### 3.1.2. Claims other than those based on the essentiality of nutrients

Claims proposed for nutrients which do not fulfil the concept of essentiality (e.g. vitamin C and function of the immune system in subjects performing intense physical activity was assessed in terms of duration and severity of common cold symptoms during and after extreme physical exercise (EFSA NDA Panel, 2009b)) are evaluated by the NDA Panel following the same general principles applied to other claims.

Claims on the improvement or maintenance of unspecified functions of the immune system which are not based on the essentiality of nutrients are not sufficiently defined for a scientific evaluation. The

[3] 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. Available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2006R1924:20100302:EN:PDF

[4] Commission Regulation (EC) No 353/2008 of 18 April 2008 establishing implementing rules for applications for authorisation of health claims as provided for in Article 15 of Regulation (EC) No 1924/2006 of the European Parliament and of the Council (Text with EEA relevance) (OJ L 109, 19.4.2008, p. 11): http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2008R0353:20091221:EN:PDF

[5] Commission Implementing Decision of 24 January 2013 adopting guidelines for the implementation of specific conditions for health claims laid down in Article 10 of Regulation (EC) No 1924/2006 of the European Parliament and of the Council. OJ L 22, 25.1.2013, p. 25–28. Available at http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32013D0063

specific function of the immune system and the appropriate outcome variables(s) which may be used for the scientific evaluation of the claimed effect *in vivo* in humans must be identified.

In this context, outcome variable(s) which can be measured *in vivo* in humans by generally accepted methods but do not refer to a benefit on specific functions of the body cannot constitute the only basis for the scientific substantiation of a health claim. These include:

i) changes in immune markers, e.g. 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;

ii) changes in markers of inflammation (including markers of chronic, subclinical inflammation), such as interleukins or C-reactive protein;

iii) changes in short-chain fatty acid production (including butyrate) in the gut;

iv) changes in the structure of the intestinal epithelium;

v) changes in the composition of the gut microbiota.

Changes in these outcome variable(s) should be accompanied by evidence of a beneficial physiological effect or clinical outcome in the application. Alternatively, changes in some of these outcome variables could be proposed as part of the mechanism(s) by which a food may exert the claimed effect, i.e. induce a beneficial change on a specific function of the body.

## 3.2. Claims on gastrointestinal discomfort

Occasional episodes of abdominal pain or discomfort (e.g. bloating, abdominal pain/cramps, straining 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 habits and vary between individuals in frequency and severity.

Claims on the reduction of GI discomfort have been proposed. Symptoms such as abdominal pain, cramps, bloating, straining, borborygmi (rumbling) and sensation of incomplete evacuation are associated with GI discomfort. Reducing GI discomfort is considered an indicator of improved GI function, which is a beneficial physiological effect for the general population.

### 3.2.1. Claims on gastrointestinal discomfort for the general population

GI discomfort may be measured by using validated subjective global symptom questionnaires, as described in consensus opinions (Veldhuyzen van Zanten et al., 1999; Irvine et al., 2006), and in an EFSA opinion (EFSA NDA Panel, 2014a). Changes in one or more of the individual symptoms (e.g. representing different domains of the questionnaire), as well as changes in defecation habits (e.g. outcome variable(s) related to the maintenance of normal defecation), may be used as supportive evidence for the mechanisms by which the food/constituent could exert the claimed effect, but cannot be used alone for the substantiation of a claim on the reduction of GI discomfort. Validated 'quality of life questionnaires' may also provide supportive evidence for claims on GI discomfort (EFSA NDA Panel, 2016).[6]

All claims on the reduction of GI discomfort for the general population were evaluated by the Panel with an unfavourable opinion (for example EFSA (2008) and EFSA NDA Panel (2012d, 2013d, 2014a, 2014d)). Lack of validation of the measurement scales/questionnaires used to assess the claimed effect (EFSA NDA Panel, 2014d), lack of assessment of the subjective global symptoms (a combined measure of efficacy which would indicate adequate relief of symptoms of GI discomfort) but rather of the individual symptoms (EFSA NDA Panel, 2014a), and the short duration of the human intervention studies provided (EFSA NDA Panel, 2011i) were some of the reasons preventing a favourable opinion. Owing to the fluctuating nature of GI symptoms, evidence for a sustained effect with continuous

[6] General considerations on the validation of questionnaires for self-reported outcomes and their use as outcome variables for the scientific substantiation of health claims are given in section 7.4 and Annex C of the general scientific guidance for stakeholders for health claim applications. Available at http://www.efsa.europa.eu/en/efsajournal/pub/4367

consumption of the food/constituent over extended periods of time (e.g. 4–8 weeks) should be provided (Irvine et al., 2006).

With respect to the study group, irritable bowel syndrome (IBS) is a functional GI disorder characterised by chronic or recurrent abdominal pain or discomfort, mostly associated with defecation abnormalities (consistency of stools and frequency of defecations) in the absence of a detectable organic or pathological cause. Episodes of abdominal pain or discomfort occur both in healthy people and in individuals suffering from IBS, and the difference between the two is the higher frequency and/or greater severity of the symptoms in IBS patients. IBS patients or subgroups of IBS patients (Rome III criteria) are generally considered a suitable study group to substantiate claims on GI discomfort intended for the general population.

### 3.2.2. Claims on gastrointestinal discomfort for infants

Reduction of GI discomfort is a beneficial physiological effect for infants and young children. Unexplained bouts of crying in infants have been traditionally attributed to GI disturbances and pain (Shamir et al., 2013). The term infant colic is commonly used to reflect this situation in infants. Infant colic has been included in the list of childhood functional GI disorders of the Rome III Coordinating Committee, with diagnostic criteria based on infant crying time and frequency, after excluding other reasons for crying (Hyman et al., 2006). Crying time can be used to assess GI discomfort in infants diagnosed with infant colic.

In principle, owing to the variability and fluctuating nature of infant colic, its diagnosis relies on the duration of symptoms for at least 1 week according to the Rome III criteria, and for the same reason, evidence for an effect of the food/constituent on infant's colic could be provided by studies of similar duration. Similarly, owing to the interindividual variability and fluctuating nature of infant colic, asymptomatic infants should be included in these studies, both in the treatment and control groups.

Two claims on the reduction of GI discomfort targeting infants and young children (EFSA NDA Panel, 2014b, 2015c) were evaluated by the Panel with an unfavourable opinion.

### 3.2.3. Claims on the reduction of excessive intestinal gas accumulation

A claim on activated charcoal and reduction of excessive intestinal gas accumulation, which can be measured *in vivo* in humans by generally accepted methods, was evaluated by the NDA panel with a favourable opinion (EFSA NDA Panel, 2011j). Although the reduction of intestinal gas accumulation per se does not refer to a benefit on a function of the body directly, the Panel considered that the reduction of excessive intestinal gas accumulation generally[7] leads to a reduction in GI discomfort, which is a beneficial physiological effect for the general population.

Appropriate outcome variables include, for example, breath hydrogen levels measured by hydrogen breath test, and intestinal gas volume assessed by imaging techniques (e.g. functional magnetic resonance imaging).

The claim on activated charcoal and reduction of excessive intestinal gas accumulation was based particularly on human intervention studies which consistently showed an effect of the food/constituent on decreasing the amount of intestinal gas accumulation and on a known mechanism of action. Single meal studies were sufficient in this case for the scientific substantiation of the claim because activated charcoal is expected to induce the claimed effect within hours of consumption and adaptation to the effect of charcoal upon repeated consumption through compensatory mechanisms is unlikely.

## 3.3. Claims on maintenance of normal defecation

Normal bowel habits vary considerably from person to person with regard to the frequency of bowel movements (i.e. number of defecations per interval of time), the consistency of stools and faecal bulk.

[7] In most, but not all subjects.

Functional constipation is a disorder characterised by the absence of a detectable organic or pathological cause for which diagnostic criteria have been established.[8] Subjects in the general population may, however, experience one or more symptoms of functional constipation without meeting the diagnostic criteria for the disorder (e.g. low frequency of defecations, lumpy or harder stools, sensation of incomplete evacuation).

Claims on the maintenance of normal defecation (a bowel function) have been proposed only in the context of facilitating defecation (e.g. by one or more of the following means: increasing the frequency of bowel movements, increasing faecal bulk, decreasing the consistency of stools, decreasing transit time) in subjects with one or more signs/symptoms of functional constipation. In this context, maintenance of normal defecation is considered a beneficial physiological effect for the general population provided that it does not result in diarrhoea.

Several claims on the maintenance of normal defecation were evaluated by the Panel with a favourable opinion (e.g. for dried prunes (EFSA NDA Panel, 2012c), lactulose (EFSA NDA Panel, 2010b), wheat bran fibre (EFSA NDA Panel, 2010f), rye fibre (EFSA NDA Panel, 2011k), oat and barley grain fibre (EFSA NDA Panel, 2011l), chicory inulin (EFSA NDA Panel, 2015b), hydroxyanthracene derivatives (EFSA NDA Panel, 2013c), lactitol (EFSA NDA Panel, 2015d)). The scientific substantiation of these claims was based on human intervention studies showing an effect of the food/constituent on different outcomes which, in the context of the known mechanism(s) by which the food/constituent could exert the claimed effect, contributed to the maintenance of normal defecation. For example, changes in transit time may or may not contribute to the maintenance of normal defecation. However, a claim on lactulose and a reduction in transit time was evaluated by the Panel with a favourable opinion because, in the context of the human intervention studies provided and of the mechanisms of action, it is well established that lactulose contributes to normal defecation by increasing the stool water content and softening the stools via increasing the osmotic pressure and slightly acidifying the colonic content. Similarly, faecal bulk is not among the signs/symptoms in the definition of functional constipation. However, claims on dietary fibre (wheat bran fibre, oat and barley grain fibre) and an increase in faecal bulk have been evaluated by the Panel with favourable opinions because in the context of the human intervention studies provided and of the mechanism of action, it is well established that cereal grain fibre contributes to the maintenance of normal defecation and dietary reference values for dietary fibre in mixed diets have been established on the basis of maintaining normal bowel function in relation to normal defecation.

Based on the experience gained during the scientific evaluation of these claims, the Panel considers that maintenance of normal defecation may be assessed by a number of outcome variables which could provide information about the function and eventually about the underlying mechanism of action, some of which may be interrelated (e.g. stool frequency, stool consistency, sensation of complete/incomplete evacuation, faecal bulk, transit time). The Panel will consider the information provided on these variables to evaluate the claim.

Frequency of defecations, stool consistency (e.g. by using the Bristol Stool Form Scale), sensation of complete/incomplete evacuation and faecal bulk can be assessed directly by the investigators or by using validated questionnaires for self-reported outcomes.[9] Changes in transit time may be measured, e.g. by using radiopaque markers.

The study duration will depend on the food/constituent and its characteristics. In principle, the duration should be adequate in order to exclude adaptation to the continuous consumption of the food/constituent through compensatory mechanisms and chance findings for fluctuating outcome measures (e.g. 4–8 weeks).

[8] Diagnostic criteria which must be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis (Rome III):
1. Must include two or more of the following: a. Straining during at least 25% of defecations; b. Lumpy or hard stools in at least 25% of defecations; c. Sensation of incomplete evacuation for at least 25% of defecations; d. Sensation of anorectal obstruction/blockage for at least 25% of defecations; e. Manual manoeuvres to facilitate at least 25% of defecations (e.g. digital; evacuation, support of the pelvic floor); f. Fewer than three defecations per week;
2. Loose stools are rarely present without the use of laxatives;
3. Insufficient criteria for irritable bowel syndrome.

[9] General considerations on the validation of questionnaires for self-reported outcomes and their use as outcome variables for the scientific substantiation of health claims are given in Section 7.4 and Annex C of the general scientific guidance for stakeholders for health claim applications. Available at http://www.efsa.europa.eu/en/efsajournal/pub/4367

With respect to the study group, results from studies conducted in individuals with functional (chronic) constipation, including subjects with IBS, could be used for the scientific substantiation of these claims for the general population. However, the rationale for extrapolation of results obtained in subjects with chronic constipation under pharmacological treatment to the target population for the claim should be provided, and will be considered on a case-by-case basis (e.g. evidence for a lack of interaction between the food and the medications used on the claimed effect).

## 3.4. Claims on digestion and/or absorption of nutrients

### 3.4.1. Claims on digestion and/or absorption of macronutrients

Whether improved digestion of macronutrients is considered a beneficial physiological effect may depend on the consequences of reduced digestion of that nutrient (e.g. the effect of undigested nutrient in the GI tract).

Claims related to the reduced absorption of macronutrients, such as glucose or cholesterol, are considered in the context of reduced blood concentrations of these nutrients (EFSA NDA Panel, 2011m, 2012a).

**Claims on improved lactose digestion**

Lactose maldigestion results from a reduced enzymatic capacity to digest lactose. Individuals with lactose maldigestion may display symptoms after lactose consumption such as nausea, diarrhoea and GI discomfort (e.g. cramping, bloating and flatulence). Improved lactose digestion may alleviate lactose maldigestion symptoms, and is considered a beneficial physiological effect for individuals with symptoms of lactose maldigestion.

Two claims related to the effect of food/constituents (live yoghurt cultures (EFSA NDA Panel, 2010c) and lactase (EFSA NDA Panel, 2009k)) which are able to break down lactose and which therefore facilitate lactose digestion when consumed with lactose-containing foods have been evaluated by the Panel with favourable opinions. The scientific substantiation of these claims was based on human intervention studies showing an effect of the food/constituent on symptoms of lactose maldigestion (subjective outcomes), as well as an increase in lactose digestion (objectively measured by the breath hydrogen concentration method) when consumed with lactose-containing foods by subjects with symptoms of lactose maldigestion, and also on the biological plausibility of the effect.

The characterisation of the study population (i.e. subjects with symptoms of lactose maldigestion, irrespective of the cause), in the studies submitted for the substantiation of these claims is particularly important. Subjects with symptoms of lactose maldigestion could be identified through the appearance of symptoms upon lactose consumption and which respond to lactose withdrawal.

Individuals with lactose maldigestion (i.e. with difficulties in digesting lactose) have been considered by risk managers as an acceptable target population for health claims made on foods.

### 3.4.2. Claims on digestion/absorption/utilisation of micronutrients

Claims related to absorption of micronutrients (vitamin C (EFSA NDA Panel, 2009b), meat and fish (EFSA NDA Panel, 2011n) and improvement of non-haem iron absorption; vitamin D and absorption and utilisation of calcium and phosphorus (EFSA NDA Panel, 2009j); fats and normal absorption of fat-soluble vitamins (EFSA NDA Panel, 2011o)) have been evaluated by the Panel with favourable opinions. The claimed effect (improved absorption of the above-mentioned nutrients) was considered by the Panel as a beneficial physiological effect because absorption was a limiting factor for the maintenance of an adequate status of the nutrient, and because the absorbed nutrient could be utilised by the body.

For example, iron deficiency is one of the most common micronutrient deficiencies in the European Union (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. An increase in iron absorption leading to an increase in iron retention is therefore a beneficial physiological effect for the general population.

Similarly, inadequate dietary calcium intake, low calcium absorption and low calcium retention may contribute to impaired bone development in early life. Calcium absorption can be a limiting factor to achieve the target retention rate for calcium in preterm infants, in healthy term infants, and in infants with disturbances of lipid digestion which can result in insufficient calcium in the body to meet the demands of growing bone. An increase in calcium absorption leading to an increase in calcium retention is, therefore, a beneficial physiological effect for infants (EFSA NDA Panel, 2011p).

## 3.5. Claims on (immune) defence against pathogens

### 3.5.1. General considerations

Defence against pathogens comprises different mechanisms, which act in concert to protect against infection. The presence of pathogenic microorganisms may cause clinical infections at various sites of the body, and defence against pathogens at a specific site of the body is considered a beneficial physiological effect for the general population. For function claims on defence against pathogens, the claim should specify the site of infection (e.g. defence against pathogens in the GI tract, in the upper respiratory tract or in the urinary tract), the type of pathogenic microorganism (e.g. bacteria, virus, fungi, any microorganism) and the target population.

The scientific evidence for the substantiation of health claims related to defence against pathogens can be obtained from human intervention studies showing an effect on clinical outcomes related to infections (e.g. incidence, severity and/or duration of symptoms). The infectious nature of the disease should be established, e.g. by clinical differential diagnosis alone or in combination with microbiological data and/or the use of validated questionnaires,[10] depending on the study context and type of infection.

Vaccination confers immunity to certain infectious diseases. Even if a strict correlation between antibody 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. An increase in the number of responders to vaccination (i.e. attaining antibody titres beyond a cut-off value which is considered to protect against the infection) is an appropriate outcome variable for the scientific substantiation of claims related to immune defence against pathogens.

The (transient) presence of microorganisms and/or their toxins at a particular body site may not reflect a clinical infection. However, if evidence is provided that the presence of a particular microorganism (and/or their toxins) at a particular body site, or the presence of a certain amount of the microorganism, would eventually lead to a clinical infection in the target population (general population or subgroups thereof), for which the claim is made, microbiological data could be used instead of (i.e. replace) clinical outcomes related to infections (e.g. incidence, severity and/or duration of symptoms). The evidence provided will be evaluated by the NDA Panel on a case-by-case basis.

Other outcome variables, such as changes in relevant immunological markers, may provide supportive evidence on the mechanism (e.g. through the activation of the immune system) by which the food/constituent could exert the claimed effect, but alone are not appropriate outcome variables for the substantiation of claims related to immune defence against pathogens.

All claims related to (immune) defence against pathogens at different body sites have been evaluated by the Panel with unfavourable opinions. A main weakness of the majority of the human intervention studies provided for the substantiation of these claims was the lack of appropriate clinical outcomes related to infections (e.g. incidence, severity and/or duration of symptoms) and uncertainties regarding the infectious nature of the disease.

With respect to the study group, subjects without an infection at baseline, including subjects at high risk for infection without an infection at baseline (e.g. travellers to high risk countries, subjects under intense physical exercise, elderly individuals in nursing homes, children attending day-care centres, subjects challenged with live viruses/bacteria) could be suitable study groups for the scientific substantiation of claims on (immune) defence against pathogens for the general population, as long

[10] General considerations on the validation of questionnaires for self-reported outcomes and their use as outcome variables for the scientific substantiation of health claims are given in Section 7.4 and Annex C of the general scientific guidance for stakeholders for health claim applications. Available at http://www.efsa.europa.eu/en/efsajournal/pub/4367

as the methods and the inclusion/exclusion criteria used to characterise the study group in relation to the absence of ongoing infectious diseases at baseline are clearly defined.

In general, results obtained in adults cannot be used for the scientific substantiation of health claims involving the GI tract and/or the immune system, including claims related to (immune) defence against pathogens, for which the target population is infants and young children, and vice versa. If the target group is wider or different from the study group, evidence or a rationale for extrapolation of the results from the study group to the target population should be provided and will be considered by the Panel on a case-by-case basis.

### 3.5.2. Claims on (immune) defence against pathogens in the gastrointestinal tract

The scientific evidence for the substantiation of health claims related to defence against pathogens in the GI tract can be obtained from human intervention studies showing an effect on clinical outcomes related to GI infections, for example incidence, severity and/or duration of diarrhoeal episodes. The infectious aetiology of diarrhoeal episodes, however, should be ascertained. In this context, GI infection clinically diagnosed by the primary care or hospital physician following well defined criteria can be used as an appropriate outcome variable for the scientific substantiation of the claim, provided that adequate exclusion criteria for the most common non-infectious causes of diarrhoea have been applied (EFSA NDA Panel, 2011a). Microbiological data could also be used to ascertain the infectious aetiology of diarrhoeal episodes.

### 3.5.3. Claims on (immune) defence against pathogens in the respiratory tract

The scientific evidence for the substantiation of health claims related to defence against pathogens in the respiratory tract can be obtained from human intervention studies showing an effect on clinical outcomes related to respiratory infections (e.g. incidence, severity and/or duration of symptoms), either of the upper respiratory tract (such us rhinitis, pharyngitis, sinusitis, otitis media and common cold), of the lower respiratory tract (such as pneumonia, bronchitis and bronchiolitis), or both. For instance, upper or lower respiratory tract infections clinically diagnosed by the primary care or hospital physician following well defined criteria can be used as an appropriate outcome variable for the scientific substantiation of the claim, provided that adequate exclusion criteria for the most common non-infectious causes (e.g. allergic diseases) of the signs and symptoms used for diagnosis of the respiratory infection have been applied (i.e. differential diagnosis). Microbiological data could also be used to ascertain the infectious aetiology of clinically diagnosed episodes.

A main weakness of the human intervention studies submitted for the substantiation of claims on defence against pathogens in the upper respiratory tract (e.g. EFSA NDA Panel (2010e, 2012b, 2013a, 2015e)) was the use of non-validated questionnaires on self-reported symptoms in order to assess the incidence/severity/duration of common cold episodes.

### 3.5.4. Claims on defence against pathogens in the lower urinary tract

Presence of bacteria in the urinary tract may cause symptomatic urinary tract infections (UTIs). UTI is the most common infection in girls and women, with the incidence rising with age and sexual activity. Symptomatic UTIs are usually accompanied by bacteriuria at levels of $\geq 10^5$/mL of midstream urine, and it has been estimated that uropathogenic strains of *Escherichia coli* are the most common cause of UTIs (Ronald, 2003). Defence against bacterial pathogens in the lower urinary tract is considered a beneficial physiological effect for the general population and subgroups thereof (e.g. postmenopausal women), for example EFSA NDA Panel (2011b, 2014c).

The scientific evidence for the substantiation of function claims related to defence against pathogens in the lower urinary tract can be obtained from human intervention studies showing an effect on clinical outcomes related to UTIs (e.g. incidence, severity and/or duration of symptoms). Microbiological data could be used instead of (i.e. replace) clinical outcomes related to infections under the conditions referred to in Section 3.5.1.

Bacterial adherence to mucosal surfaces is generally considered an important prerequisite for colonisation and infection with bacteriuria (Harber and Asscher, 1985). However, *in vitro* inhibition of the bacterial adhesion to uroepithelial cells, which has been proposed for the scientific substantiation

of these claims, is not a direct measure of defence against pathogens in the lower urinary tract and does not predict the occurrence of a clinically relevant inhibition of the bacterial adhesion to uroepithelial cells *in vivo* in humans (EFSA NDA Panel, 2013b). *In vitro* inhibition of the bacterial adhesion to uroepithelial cells could, therefore, provide evidence on the mechanism by which a food/constituent could exert the claimed effect, but alone it is not an appropriate outcome variable for the substantiation of the claim.

With respect to the study population, subjects without infections of the urinary tract at baseline, but at high risk of infections (e.g. women with past uncomplicated, sporadic or recurrent cystitis), are considered suitable study groups to substantiate claims on defence against bacterial pathogens in the lower urinary tract for the general population. Where appropriate, the confounding role of medication should be considered.

### 3.5.5. Claims on defence against vaginal pathogens

Bacterial pathogens (e.g. *Gardnerella vaginalis*) are the most common cause of vaginal infections. Unlike any other anatomical site of the body, most vaginal vaults are dominated by one or more species of *Lactobacillus*. In over 70% of women, vaginal microbiota is dominated by lactobacilli (> 50%). The diagnosis of bacterial vaginosis is currently based on the Nugent score.[11] Other pathogenic microorganisms also cause vaginal infections e.g. yeasts, such as *Candida albicans,* and parasites, such as *Trichomonas vaginalis*.

Defence against vaginal pathogens is a beneficial physiological effect for the general female population. The claimed effect can be achieved by increasing the proportion of lactobacilli and/or decreasing the proportion of potentially pathogenic bacteria and/or yeasts in the vagina, as assessed, for example by beneficial changes in Nugent scores (EFSA NDA Panel, 2011d) and/or by inducing beneficial changes in clinical outcomes related to vaginal infections (e.g. incidence, severity and/or duration of symptoms) upon oral consumption of the food/constituent. The intravaginal route of administration does not provide pertinent data for health claims on food.

With respect to the study group, women without vaginosis at baseline, but at high risk of infections (e.g. women with past uncomplicated, sporadic or recurrent vaginosis), are considered suitable study groups to substantiate claims on defence against vaginal pathogens for the general population. Where appropriate, the confounding role of medication should be considered.

## 3.6. Claims on a beneficial change in response to allergens

The general healthy population comprises persons with an increased risk of developing allergic (atopic) reactions, such as allergic rhinitis, allergic asthma, atopic dermatitis and food allergy. Allergic manifestations, such as asthma, urticaria, eczema and GI manifestations, are caused by undesirable immune responses to environmental allergens, including food allergens. Beneficial changes in response to allergens may comprise different mechanisms, which act in concert to reduce allergic reactions. A beneficial change in response to allergens is a beneficial physiological effect for subjects at risk of allergic reactions.

In principle, the scientific evidence for the substantiation of function claims related to a beneficial change in response to allergens can be obtained from human studies showing a decreased incidence, severity and/or duration of allergic manifestations in subjects at risk of allergic reactions but free of symptoms at baseline. 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. In addition, differences in exposure to the triggering allergen(s) in the intervention and control groups should be carefully considered.

It should be noted that an effect of a food/constituent on the risk of one clinical type of allergy (e.g. respiratory) does not necessarily predict an effect of the same food/constituent on the risk of another

[11] Nugent scores are classified into normal (0–3, lactobacilli are present, but not Gardnerella/Bacteroides or curved Gram-negative bacilli), intermediate (4–6, colonisation by Bacteroides/Gardenella and curved Gram-variable rods (Mobiluncus)), and BV (7–10, BV with domination of Gardnerella/Bacteroides or curved Gram-negative bacilli and absence of lactobacilli)

type of allergy (e.g. food allergy). The type of allergy that is the subject of the claim should be specified.

Other outcome variables, such as basophil activation test, tryptase in plasma and allergen specific immunoglobulin E (IgE), may provide supportive evidence on the (e.g. immune) mechanisms and biological plausibility of a claim related to a beneficial change in response to allergens, but they cannot be used alone for the substantiation of these claims.

A claim related to normal resistance to cedar pollen allergens has been evaluated by the Panel with an unfavourable opinion (EFSA NDA Panel, 2011f).

# 4. Disease risk reduction claims

## 4.1. Claims on the reduction (or beneficial alteration) of a risk factor for infections

All the disease risk reduction claims related to the reduction (or beneficial alteration) of a risk factor for infections have been evaluated by the NDA Panel with unfavourable opinions (e.g. increasing secretory immunoglobulin A (IgA) in the context of reducing the risk of common cold with sore throat (EFSA NDA Panel, 2011g, 2011h); reducing the risk of *Clostridium difficile* diarrhoea by reducing the presence of *C. difficile* toxins (EFSA NDA Panel, 2010a); reducing the risk of urinary tract infections by inhibiting the adhesion of certain bacteria to the urinary tract (EFSA, 2009b; EFSA NDA Panel, 2009l, 2014e); a decrease in bacterial, viral and parasitic enteric pathogens in the context of reducing the risk of travellers' diarrhoea (EFSA, 2009a)).

The presence of certain microorganisms (or an increase in the number of certain microorganisms) or their toxins at particular sites of the body has been independently associated with an increased risk of infections, and there is evidence for the biological basis through which the risk factor can contribute to the development of infections. For example, the presence of toxigenic *C. difficile* in the GI tract may be associated with the incidence of acute diarrhoea, and reducing the risk of *C. difficile* diarrhoea by reducing the presence of *C. difficile* toxins is a beneficial physiological effect in the context of disease risk reduction claims. In this case, evidence that the dietary intervention with the specific food/constituent induces a reduction (or beneficial alteration) of the risk factor (e.g. toxigenic *C. difficile* or *C. difficile* toxins) would be sufficient for the scientific substantiation of the claim. Evidence for an effect on clinical outcomes related to infections (e.g. incidence, severity and/or duration of symptoms) is not required.

For less well-established risk factors (e.g. reduced concentrations of secretory IgA as a risk factor for influenza or common cold, *in vitro* bacterial adhesion as a risk factor for lower urinary tract infections), evidence that the dietary intervention with the specific food/constituent induces a reduction (or beneficial alteration) of the risk factor and also a reduction of the risk of disease needs to be provided.

# References

EFSA (European Food Safety Authority), 2008. Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies on the scientific substantiation of a health claim related to LGG® MAX and reduction of gastro-intestinal discomfort. The EFSA Journal 2008, 853, 1-15. Available at http://www.efsa.europa.eu/en/efsajournal/pub/853

EFSA (European Food Safety Authority), 2009a. Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies on the scientific substantiation of a health claim related to BimunoTM and reduction of the bad bacteria that can cause travellers' diarrhoea. The EFSA Journal 2009, 1105, 1-9. Available at http://www.efsa.europa.eu/en/efsajournal/pub/1105

EFSA (European Food Safety Authority), 2009b. Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies on the scientific substantiation of a health claim on Ocean Spray Cranberry Products® and reduced risk of urinary tract infection in women by inhibiting the adhesion of

certain bacteria in the urinary tract. The EFSA Journal 2009, 943, 1-15. Available at http://www.efsa.europa.eu/en/efsajournal/pub/943

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2009a. Scientific Opinion on the substantiation of health claims related to vitamin A and cell differentiation (ID 14), function of the immune system (ID 14), maintenance of skin and mucous membranes (ID 15, 17), maintenance of vision (ID 16), maintenance of bone (ID 13, 17), maintenance of teeth (ID 13, 17), maintenance of hair (ID 17), maintenance of nails (ID 17), metabolism of iron (ID 206), and protection of DNA, proteins and lipids from oxidative damage (ID 209) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 on request from the European Commission. EFSA Journal 2009; 7(9):1221, 25 pp. doi:10.2903/j.efsa.2009.1221 Available at http://www.efsa.europa.eu/en/efsajournal/pub/1221

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2009b. Scientific Opinion on the substantiation of health claims related to vitamin C and protection of DNA, proteins and lipids from oxidative damage (ID 129, 138, 143, 148), antioxidant function of lutein (ID 146), maintenance of vision (ID 141, 142), collagen formation (ID 130, 131, 136, 137, 149), function of the nervous system (ID 133), function of the immune system (ID 134), function of the immune system during and after extreme physical exercise (ID 144), non-haem iron absorption (ID 132, 147), energyyielding metabolism (ID 135), and relief in case of irritation in the upper respiratory tract (ID 1714, 1715) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 on request from the European Commission. EFSA Journal 2009;7(9):1226, 28 pp. doi:10.2903/j.efsa.2009.1226 Available at http://www.efsa.europa.eu/en/efsajournal/pub/1226

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2009c. Scientific Opinion on the substantiation of health claims related to selenium and protection of DNA, proteins and lipids from oxidative damage (ID 277, 283, 286, 1289, 1290, 1291, 1293, 1751) , function of the immune system (ID 278), thyroid function (ID 279, 282, 286, 1289, 1290, 1291, 1293), function of the heart and blood vessels (ID 280), prostate function (ID 284), cognitive function (ID 285) and spermatogenesis (ID 396) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 on request from the European Commission. EFSA Journal 2009; 7(9):1220, 24 pp. doi:10.2903/j.efsa.2009.1220 Available at http://www.efsa.europa.eu/en/efsajournal/pub/1220

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2009d. Scientific opinion on the substantiation of health claims related to vitamin B12 and red blood cell formation (ID 92, 101), cell division (ID 93), energy-yielding metabolism (ID 99, 190) and function of the immune system (ID 107) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 on request from the European Commission. EFSA Journal 2009; 7(9): 1223, 16 pp. doi:10.2903/j.efsa.2009.1223 Available at http://www.efsa.europa.eu/en/efsajournal/pub/1223

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2009e. Scientific Opinion on the substantiation of health claims related to vitamin B6 and protein and glycogen metabolism (ID 65, 70, 71), function of the nervous system (ID 66), red blood cell formation (ID 67, 72, 186), function of the immune system (ID 68), regulation of hormonal activity (ID 69) and mental performance (ID 185) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 on request from the European Commission. EFSA Journal 2009;7(9):1225, 20 pp. doi:10.2903/j.efsa.2009.1225 Available at http://www.efsa.europa.eu/en/efsajournal/pub/1225

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2009f. Scientific Opinion on the substantiation of health claims related to zinc and function of the immune system (ID 291, 1757), DNA synthesis and cell division (ID 292, 1759), protection of DNA, proteins and lipids from oxidative damage (ID 294, 1758), maintenance of bone (ID 295, 1756), cognitive function (ID 296), fertility and reproduction (ID 297, 300), reproductive development (ID 298), muscle function (ID 299), metabolism of fatty acids (ID 302), maintenance of joints (ID 305), function of the heart and blood vessels (ID 306), prostate function (ID 307), thyroid function (ID 308), acid-base metabolism (ID 360), vitamin A metabolism (ID 361) and maintenance of vision (ID 361) pursuant to Article 13 of Regulation (EC) No 1924/2006 on request from European Commission. EFSA Journal 2009;7(9):1229, 34 pp. doi:10.2903/j.efsa.2009.1229 Available at http://www.efsa.europa.eu/en/efsajournal/pub/1229

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2009g. Scientific Opinion on the substantiation of health claims related to copper and protection of DNA, proteins and lipids from oxidative damage (ID 263, 1726), function of the immune system (ID 264), maintenance of connective tissues (ID 265, 271, 1722), energy yielding metabolism (ID 266), function of the nervous system (ID 267), maintenance of skin and hair pigment (ID 268, 1724), iron transport (ID 269, 270, 1727), cholesterol metabolism (ID 369), and glucose metabolism (ID 369) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 on request from the European Commission. EFSA Journal 2009;7(9):1211, 21 pp. doi:10.2903/j.efsa.2009.1211 Available at http://www.efsa.europa.eu/en/efsajournal/pub/1211

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2009h. Scientific Opinion on the substantiation of health claims related to folate and blood formation (ID 79), homocysteine metabolism (ID 80), energy-yielding metabolism (ID 90), function of the immune system (ID 91), fustion of blood vessels (ID 94, 175, 192), cell division (ID 193), and maternal tissue growth during pregnancy (ID 2882) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 on request from the European Commision. EFSA Journal 2009;7(9):1213, 22 pp. doi:10.2903/j.efsa.2009.1213 Available at http://www.efsa.europa.eu/en/efsajournal/pub/1213

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2009i. Scientific Opinion on the substantiation of health claims related to iron and formation of red blood cells and haemoglobin (ID 249, ID 1589), oxygen transport (ID 250, ID 254, ID 256), energy-yielding metabolism (ID 251, ID 1589), function of the immune system (ID 252, ID 259), cognitive function (ID 253) and cell division (ID 368) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 on request from the European Commission. EFSA Journal 2009;7(9):1215, 20 pp. doi:10.2903/j.efsa.2009.1215 Available at http://www.efsa.europa.eu/en/efsajournal/pub/1215

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2009j. Scientific Opinion on the substantiation of health claims related to vitamin D and maintenance of bone and teeth (ID 150, 151, 158), absorption and utilisation of calcium and phosphorus and maintenance of normal blood calcium concentrations (ID 152, 157), cell division (ID 153), and thyroid function (ID 156) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 on request from the European Commission. EFSA Journal 2009;7(9):1227, 19 pp. doi:10.2903/j.efsa.2009.1227 Available at http://www.efsa.europa.eu/en/efsajournal/pub/1227

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2009k. Scientific Opinion on the substantiation of health claims related to lactase enzyme and breaking down lactose (ID 1697, 1818) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 on request from the European Commission. EFSA Journal 2009; 7(9):1236, 13 pp. doi:10.2903/j.efsa.2009.1236 Available at http://www.efsa.europa.eu/en/efsajournal/pub/1236

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2009l. Scientific Opinion on the substantiation of a health claim related to Uroval® and urinary tract infection. EFSA Journal 2009; 7(12):1421, 8 pp. doi:10.2903/j.efsa.2009.1421 Available at http://www.efsa.europa.eu/en/efsajournal/pub/1421

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2010a. Scientific Opinion on the substantiation of a health claim related to fermented milk containing Lactobacillus casei DN-114 001 plus yoghurt symbiosis (Actimel®), and reduction of Clostridium difficile toxins in the gut of patients receiving antibiotics and reduced risk of acute diarrhoea in patients receiving antibiotics pursuant to Article 14 of Regulation (EC) No 1924/2006. EFSA Journal 2010;8(12):1903, 17 pp. doi:10.2903/j.efsa.2010.1903 Available at http://www.efsa.europa.eu/en/efsajournal/pub/1903

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2010b. Scientific Opinion on the substantiation of health claims related to lactulose and decreasing potentially pathogenic gastro-intestinal microorganisms (ID 806) and reduction in intestinal transit time (ID 807) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2010;8(10):1806, 15 pp. doi:10.2903/j.efsa.2010.1806 Available at http://www.efsa.europa.eu/en/efsajournal/pub/1806

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2010c. 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. EFSA Journal

2010;8(10):1763, 18 pp. doi:10.2903/j.efsa.2010.1763. Available at http://www.efsa.europa.eu/en/efsajournal/pub/1763

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2010d. Scientific Opinion on the substantiation of health claims related to vitamin D and normal function of the immune system and inflammatory response (ID 154, 159), maintenance of normal muscle function (ID 155) and maintenance of normal cardiovascular function (ID 159) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2010;8(2):1468, 17 pp. doi:10.2903/j.efsa.2010.1468 Available at http://www.efsa.europa.eu/en/efsajournal/pub/1468

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2010e. Scientific Opinion on the substantiation of a health claim related to Lactobacillus casei strain Shirota and maintenance of the upper respiratory tract defence against pathogens by maintaining immune defences pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Journal 2010;8(10):1860, 15 pp. doi:10.2903/j.efsa.2010.1860 Available at http://www.efsa.europa.eu/it/efsajournal/pub/1860

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2010f. Scientific Opinion on the substantiation of health claims related to wheat bran fibre and increase in faecal bulk (ID 3066), reduction in intestinal transit time (ID 828, 839, 3067, 4699) and contribution to the maintenance or achievement of a normal body weight (ID 829) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2010;8(10):1817, 18 pp. doi:10.2903/j.efsa.2010.1817 Available at http://www.efsa.europa.eu/it/efsajournal/pub/1817

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2011a. 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. EFSA Journal 2011;9(6):2167, 19 pp. doi:10.2903/j.efsa.2011.2167 Available at http://www.efsa.europa.eu/en/efsajournal/pub/2167

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2011b. Scientific Opinion on the substantiation of health claims related to proanthocyanidins from cranberry (Vaccinium macrocarpon Aiton) fruit and defence against bacterial pathogens in the lower urinary tract (ID 1841, 2153, 2770, 3328), "powerful protectors of our gums" (ID 1365), and "heart health" (ID 2499) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2011;9(6):2215, 18 pp. doi:10.2903/j.efsa.2011.2215 Available at http://www.efsa.europa.eu/en/efsajournal/pub/2215

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2011c. Scientific and technical guidance for the preparation and presentation of an application for authorisation of a health claim (revision 1). EFSA Journal 2011;9(5):2170, 36 pp. doi:10.2903/j.efsa.2011.2170 Available at http://www.efsa.europa.eu/en/efsajournal/pub/2170

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2011d. Scientific Opinion on the substantiation of health claims related to Lactobacillus rhamnosus GR-1 (ATCC 55826) in combination with Lactobacillus reuteri RC-14 (ATCC 55845) and defence against vaginal pathogens by increasing the proportion of lactobacilli and/or decreasing the proportion of potentially pathogenic bacteria and/or yeasts (ID 945) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2011;9(6):2232, 15 pp. doi:10.2903/j.efsa.2011.2232 Available at http://www.efsa.europa.eu/en/efsajournal/pub/2232

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2011e. Guidance on the scientific requirements for health claims related to gut and immune function. EFSA Journal 2011;9(4):1984, 12 pp. doi:10.2903/j.efsa.2011.1984 Available at http://www.efsa.europa.eu/en/efsajournal/pub/1984

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2011f. Scientific Opinion on the substantiation of health claims related to Bifidobacterium longum BB536 and improvement of bowel regularity (ID 3004), normal resistance to cedar pollen allergens (ID 3006), and decreasing potentially pathogenic gastro-intestinal microorganisms (ID 3005) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2011;9(4):2041, 18 pp. doi:10.2903/j.efsa.2011.2041 Available at http://www.efsa.europa.eu/en/efsajournal/pub/2041

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2011g. Scientific Opinion on the substantiation of a health claim related to ProteQuine® and increasing suppressed concentrations of secretory IgA and reducing the risk of influenza and common cold pursuant to Article 14 of Regulation (EC) No 1924/2006. EFSA Journal 2011;9(4):2128, 10 pp. doi:10.2903/j.efsa.2011.2128 Available at http://www.efsa.europa.eu/en/efsajournal/pub/2128

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2011h. Scientific Opinion on the substantiation of a health claim related to ProteQuine® and bovine lactoferrin and increasing suppressed concentrations of secretory IgA and reducing the risk of common cold with sore throat pursuant to Article 14 of Regulation (EC) No 1924/2006. EFSA Journal 2011;9(4):2129, 10 pp. doi:10.2903/j.efsa.2011.2129 Available at http://www.efsa.europa.eu/en/efsajournal/pub/2129

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2011i. Scientific Opinion on the substantiation of a health claim related to Bimuno® GOS and reducing gastro-intestinal discomfort pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Journal 2011;9(12):2472, 13 pp. doi:10.2903/j.efsa.2011.2472 Available at http://www.efsa.europa.eu/en/efsajournal/pub/2472

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2011j. Scientific Opinion on the substantiation of health claims related to activated charcoal and reduction of excessive intestinal gas accumulation (ID 1938) and reduction of bloating (ID 1938) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2011;9(4):2049, 15 pp. doi:10.2903/j.efsa.2011.2049 Available at http://www.efsa.europa.eu/it/efsajournal/pub/2049

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2011k. Scientific Opinion on the substantiation of health claims related to rye fibre and changes in bowel function (ID 825), reduction of post-prandial glycaemic responses (ID 826) and maintenance of normal blood LDL-cholesterol concentrations (ID 827) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2011;9(6):2258, 18 pp. doi:10.2903/j.efsa.2011.2258 Available at http://www.efsa.europa.eu/en/efsajournal/pub/2258

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2011l. Scientific Opinion on the substantiation of health claims related to oat and barley grain fibre and increase in faecal bulk (ID 819, 822) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2011;9(6):2249, 13 pp. doi:10.2903/j.efsa.2011.2249 Available at http://www.efsa.europa.eu/en/efsajournal/pub/2249

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2011m. Guidance on the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health. EFSA Journal 2011;9(12):2474, 13 pp. doi:10.2903/j.efsa.2011.2474 Available at http://www.efsa.europa.eu/en/efsajournal/pub/2474

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2011n. Scientific Opinion on the substantiation of claims on meat or fish and the improvement of non-haem iron absorption (ID 1223) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2011;9(4):2040, 14 pp. doi:10.2903/j.efsa.2011.2040 Available at http://www.efsa.europa.eu/en/efsajournal/pub/2040

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2011o. Scientific Opinion on the substantiation of health claims related to fats and "function of the cell membrane" (ID 622, 2900, 2911) and normal absorption of fat-soluble vitamins (ID 670, 2902) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2011;9(6):2220, 15 pp. doi:10.2903/j.efsa.2011.2220 Available at http://www.efsa.europa.eu/en/efsajournal/pub/2220

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2011p. Scientific Opinion on the substantiation of a health claim related to beta-palmitate and increased calcium absorption pursuant to Article 14 of Regulation (EC) No 1924/2006. EFSA Journal 2011;9(7):2289, 16 pp. doi:10.2903/j.efsa.2011.2289 Available at http://www.efsa.europa.eu/en/efsajournal/pub/2289

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2012a. Guidance on the scientific requirements for health claims related to appetite ratings, weight management, and

blood glucose concentrations. EFSA Journal 2012;10(3):2604, 11 pp. doi:10.2903/j.efsa.2012.2604 Available at http://www.efsa.europa.eu/en/efsajournal/pub/2604

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2012b. Scientific Opinion on the substantiation of health claims related to a combination of Lactobacillus gasseri PA 16/8, Bifidobacterium bifidum M 20/5 and Bifidobacterium longum SP 07/3 and maintenance of upper respiratory tract defence against pathogens (ID 931, further assessment) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2012;10(6):2718, 15 pp. doi:10.2903/j.efsa.2012.2718 Available at http://www.efsa.europa.eu/en/efsajournal/pub/2718

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2012c. Scientific Opinion on the substantiation of health claims related to dried plums of „prune" cultivars (Prunus domestica L.) and maintenance of normal bowel function (ID 1164, further assessment) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2012;10(6):2712, 17 pp. doi:10.2903/j.efsa.2012.2712 Available at http://www.efsa.europa.eu/en/efsajournal/pub/2712

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2012d. Scientific Opinion on the substantiation of a health claim related to *Saccharomyces cerevisiae* var. *boulardii* CNCM I-3799 and reducing gastro-intestinal discomfort pursuant to Article 13(5) of Regulation (EC) no 1924/2006. EFSA Journal 2012;10(7):2801, 9 pp. doi:10.2903/j.efsa.2012.2801 Available at http://www.efsa.europa.eu/en/efsajournal/pub/2801

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2013a. Scientific Opinion on the substantiation of a health claim related to Yestimun® and defence against pathogens in the upper respiratory tract pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Journal 2013;11(4):3159, 12 pp. doi:10.2903/j.efsa.2013.3159 Available at http://www.efsa.europa.eu/en/efsajournal/pub/3159

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2013b. Scientific Opinion on the substantiation of a health claim related to proanthocyanidins in Urell® and reduction of bacterial colonisation of the urinary tract by inhibition of the adhesion of P-fimbriated E. coli to uroepithelial cells pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Journal 2013;11(7):3326, 10 pp. doi:10.2903/j.efsa.2013.3326 Available at http://www.efsa.europa.eu/en/efsajournal/pub/3326

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2013c. Scientific Opinion on the substantiation of a health claim related to hydroxyanthracene derivatives and improvement of bowel function pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Journal 2013;11(10):3412, 12 pp. doi:10.2903/j.efsa.2013.3412 Available at http://www.efsa.europa.eu/en/efsajournal/pub/3412

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2013d. Scientific Opinion on the substantiation of a health claim related to a combination of Bifidobacterium longum LA 101, Lactobacillus helveticus LA 102, Lactococcus lactis LA 103 and Streptococcus thermophilus LA 104 and reducing intestinal discomfort pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Journal 2013;11(2):3085, 9 pp. doi:10.2903/j.efsa.2013.3085 Available at http://www.efsa.europa.eu/en/efsajournal/pub/3085

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014a. Scientific Opinion on the substantiation of a health claim related to Bimuno® GOS and reducing gastro-intestinal discomfort pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Journal 2014;12(7):3756, 13 pp. doi:10.2903/j.efsa.2014.3756 Available at http://www.efsa.europa.eu/en/efsajournal/pub/3756

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014b. Scientific Opinion on the substantiation of a health claim related to beta-galactosidase from Streptococcus thermophilus and reduction of gastrointestinal discomfort pursuant to Article 14 of Regulation (EC) No 1924/2006. EFSA Journal 2014;12(10):3841, 8 pp. doi:10.2903/j.efsa.2014.3841 Available at http://www.efsa.europa.eu/en/efsajournal/pub/3841

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014c. Scientific Opinion on the substantiation of a health claim related to Pacran® and defence against bacterial pathogens in the lower urinary tract pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Journal

2014;12(5):3656, 11 pp. doi:10.2903/j.efsa.2014.3656 Available at http://www.efsa.europa.eu/en/efsajournal/pub/3656

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014d. Scientific Opinion on the substantiation of a health claim related to a combination of Bifidobacterium longum LA 101, Lactobacillus helveticus LA 102, Lactococcus lactis LA 103 and Streptococcus thermophilus LA 104 and reducing intestinal discomfort pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Journal 2014;12(5):3658, 10 pp. doi:10.2903/j.efsa.2013.3658 Available at http://www.efsa.europa.eu/en/efsajournal/pub/3658

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014e. Scientific Opinion on the substantiation of a health claim related to CranMax® and reduction of the risk of urinary tract infection by inhibiting the adhesion of certain bacteria in the urinary tract pursuant to Article 14 of Regulation (EC) No 1924/2006. EFSA Journal 2014;12(5):3657, 11 pp. doi:10.2903/j.efsa.2014.3657 Available at http://www.efsa.europa.eu/en/efsajournal/pub/3657

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2015a. Outcome of a public consultation on the discussion paper for the revision of the guidance on the scientific requirements for health claims related to gut and immune function. EFSA supporting publication 2015:EN-758. 117 pp. Available at http://www.efsa.europa.eu/en/supporting/pub/758e

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2015b. Scientific Opinion on the substantiation of a health claim related to "native chicory inulin" and maintenance of normal defecation by increasing stool frequency pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Journal 2015;13(1):3951, 12 pp. doi:10.2903/j.efsa.2015.3951 Available at http://www.efsa.europa.eu/en/efsajournal/pub/3951

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2015c. Scientific Opinion on the substantiation of a health claim related to β-galactosidase from Kluyveromyces lactis in Colief® and a reduction of gastrointestinal discomfort pursuant to Article 14 of Regulation (EC) No 1924/2006. EFSA Journal 2015;13(7):4187, 13 pp. doi:10.2903/j.efsa.2015.4187 Available at http://www.efsa.europa.eu/en/efsajournal/pub/4187

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2015d. Scientific opinion on lactitol and the maintenance of normal defecation: evaluation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Journal 2015;13(10):4252, 12 pp. doi:10.2903/j.efsa.2015.4252 Available at http://www.efsa.europa.eu/en/efsajournal/pub/4252

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2015e. Scientific Opinion on the substantiation of a health claim related to Bifidobacterium bifidum CNCM I-3426 and defence against pathogens in the upper respiratory tract pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Journal 2015;13(5):4094, 9 pp. doi:10.2903/j.efsa.2015.4094 Available at http://www.efsa.europa.eu/en/efsajournal/pub/4094

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2016. General scientific guidance for stakeholders on health claim applications. EFSA Journal 2016;14(1):4367, 38 pp. doi:10.2903/j.efsa.2016.4367 Available at http://www.efsa.europa.eu/en/efsajournal/pub/4367

Harber MJ and Asscher AW, 1985. Virulence of urinary pathogens. Kidney Int, 28, 717-721.

Hyman PE, Milla PJ, Benninga MA, Davidson GP, Fleisher DF and Taminiau J, 2006. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology, 130, 1519-1526.

Irvine EJ, Whitehead WE, Chey WD, Matsueda K, Shaw M, Talley NJ and Veldhuyzen van Zanten SJ, 2006. Design of treatment trials for functional gastrointestinal disorders. Gastroenterology, 130, 1538-1551.

Ronald A, 2003. The etiology of urinary tract infection: traditional and emerging pathogens. Dis Mon, 49, 71-82.

Shamir R, St James-Roberts I, Di Lorenzo C, Burns AJ, Thapar N, Indrio F, Riezzo G, Raimondi F, Di Mauro A, Francavilla R, Leuchter RH, Darque A, Huppi PS, Heine RG, Bellaiche M, Levy M, Jung C, Alvarez M and Hovish K, 2013. Infant crying, colic, and gastrointestinal discomfort in early

childhood: a review of the evidence and most plausible mechanisms. J Pediatr Gastroenterol Nutr, 57 Suppl 1, S1-45.

Standing Committee on the Food Chain and Animal Health, 2007. Guidance on the implementation of Regulation (EC) No 1924/2006 on nutrition and health claims made on foods – Conclusions of the Standing Committee on the Food Chain and Animal Health, 14 December 2007. Available at http://ec.europa.eu/food/safety/docs/labelling_nutrition_claim_reg-2006-124_guidance_en.pdf

Veldhuyzen van Zanten SJ, Talley NJ, Bytzer P, Klein KB, Whorwell PJ and Zinsmeister AR, 1999. Design of treatment trials for functional gastrointestinal disorders. Gut, 45 Suppl 2, II69-77.

## Abbreviations

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| GI | gastrointestinal |
| IBS | irritable bowel syndrome |
| ID | identification number |
| IgA | immunoglobulin A |
| IgE | immunoglobulin E |
| NDA | EFSA Panel on Dietetic Products, Nutrition and Allergies |
| UTI | urinary tract infection |