TECHNICAL REPORT

Outcome of a public consultation on the Draft Opinion of the EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA) on a guidance on the scientific requirements for health claims related to gut and immune function¹

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SUMMARY

The European Food Safety Authority (EFSA) carried out a public consultation to receive input from the scientific community and all interested parties on a draft guidance document on the scientific requirements for the substantiation of health claims related to gut and immune function, prepared by the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) and endorsed by the Panel for public consultation at its Plenary meeting on 8-10 September 2010. The draft guidance document is based on the experience gained with the evaluation of health claims, and is aimed at further assisting applicants in preparing and submitting their applications for the authorisation of health claims. The written public consultation for this document was open from 28 September 2010 to 22 October 2010, and the document was also discussed, together with the comments received during the public consultation, at a technical meeting with experts in the field on 2 December 2010 in Amsterdam. EFSA received comments from 58 interested parties including applicants for health claims, non-governmental organisations, industry organisations and academia. EFSA and its NDA Panel wish to thank all stakeholders for their very useful contributions. The current report summarises the outcome of the public consultation, including a brief summary of the comments received and of how the comments were addressed. The NDA Panel prepared an updated version of the guidance document taking into account the questions/comments received. This document was discussed and adopted at the NDA Plenary meeting on 26-28 January 2011, and is published in the EFSA Journal.

¹ On request from EFSA, Question No EFSA-Q-2010-01541, issued on 25 March 2011.
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Outcome of a public consultation on a draft guidance on the scientific requirements for gut and immune function claims

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BACKGROUND AS PROVIDED BY EFSA

Regulation (EC) No 1924/2006 harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. According to the Regulation, health claims should 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 the scientific substantiation of health claims, since 2007. Most recently, a briefing document on the scientific evaluation of health claims was published for consultation in April 2010, followed by a technical meeting with experts from the food industry, Member States and the European Commission in Parma, in June 2010.

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

TERMS OF REFERENCE AS PROVIDED BY EFSA

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

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

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

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

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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
**CONSIDERATION**

1. **Introduction**

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 developed a draft guidance document on the scientific requirements for the substantiation of health claims related to gut and immune function. In line with EFSA’s policy on openness and transparency, and in order for EFSA to receive comments from the scientific community and stakeholders on its work, EFSA engages in public consultations on key issues. Accordingly, the draft guidance document, which should be read in conjunction with the general guidance document on the evaluation of Article 13.1, 13.5 and 14 health claims, was published on the EFSA website for comments (28 September 2010 to 22 October 2010), and formed the basis for discussion, together with the comments received during the public consultation, at a technical meeting with scientific experts in the field on 2 December 2010 in Amsterdam. The NDA Panel prepared an updated version of the guidance document, taking into account the questions/comments received. The updated guidance document was discussed and adopted at the NDA Plenary meeting of 26-28 January 2011, and is published in the EFSA Journal. EFSA is committed to publishing the comments received during the public consultation, as well as a short report on the outcome of the consultation, also taking into account the comments received at the technical meeting of 2 December 2010.

2. **Screening and evaluation of comments received**

2.1. **Comments received**

EFSA has received comments from 58 interested parties including applicants for health claims, non-governmental organisations, industry organisations and academia. A summary of the comments received is given below, and all written comments received are listed in the Appendix. Comments related to policy or risk management aspects were considered to be outside the scope of the consultation, and are not covered in this report. Some comments were considered to be too detailed and technical to be covered in a guidance document, for example comments on experimental design and methods, statistical analysis or exhaustive lists of appropriate outcome measures for claimed effects. Some of the comments may need to be considered in the context of a specific application for health claims, and are difficult to be covered in a guidance document. It should be noted that the 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. Health claims are often technically complex and unique, and it is not possible for the NDA Panel to predict all potential claims, including appropriate outcome measures. Some of the comments have been taken up in the general guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims.

2.2. **Nature of specific comments**

The main issues raised in the comments received were the following:

2.2.1. **Bowel function**

- Changes in bowel function: what is the meaning of “within the normal range”? 

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7 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.

8 EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2011. Guidance on the scientific requirements for health claims related to gut and immune function. EFSA Journal, 9(4):1984, 12 pp.
- Is reduced diarrhoea a beneficial physiological effect? And should diarrhoea be included in the overall description of bowel function.
- Extrapolation from studies on children to the general population.
- Stool consistency as an appropriate outcome measure.
- Can more than one outcome measure be considered to substantiate a specific claim, for example for stool frequency?
- Appropriateness of the use of (validated) questionnaires.

2.2.2. Gastro-intestinal development
- Proposal for a claim on promoting normal development of digestion, intestinal barrier function, immune system for infants/young children.

2.2.3. Gastro-intestinal discomfort
- Are Irritable Bowel Syndrome (IBS) patients (adults or children) an acceptable study group?
- Are there study groups other than IBS patients to support a claim for the general population?
- Is reducing gastro-intestinal discomfort a beneficial physiological effect in young children?
- What outcome measures are acceptable, for example, are quality of life questionnaires acceptable?
- What are appropriate validation requirements for questionnaires for the purpose of the study?

2.2.4. Gastro-intestinal microbiota
- What constitutes a beneficial microbiota, for example, can an increase in numbers of bifidobacteria or lactobacilli be considered as a beneficial physiological effect per se in subgroups of the general population, for example, infants or the elderly? Some disagreements were expressed that increased bifidobacteria or lactobacilli were not considered beneficial physiological effects per se.
- Whether gastro-intestinal outcome measures such as intestinal permeability, pH, and short-chain fatty acid production can be considered in themselves as a beneficial physiological effect. Could these gastro-intestinal markers be considered supportive in combination with clinical outcomes, or could they be considered as a risk factor for an infection outcome?
- What is an appropriate cut-off level at which a reduction of the numbers of relevant pathogens would be meaningful? What constitutes a minimum infective dose, and whether any statistically significant reduction of pathogenic microorganisms can always be linked to a beneficial physiological effect?
- Can a claim on defence against pathogens be substantiated by clinical outcome measures only, for example traveller’s diarrhoea without a measurement of pathogens?
- Some comments with respect to the list of groups of microorganisms which are considered pathogenic.
- Is the restoration of a disturbed microbiota considered as a beneficial physiological effect?
- Outcomes for function claims and disease risk reduction claims related to gastro-intestinal microbiota.

2.2.5. Digestion/absorption of nutrients
- Not only improvement of absorption should be considered but also reduced absorption of nutrients.
- Clarify the sentence that digestion/absorption of a nutrient is only considered beneficial where absorption is a limiting factor for the maintenance of an adequate status of the nutrient.
- Can only increased bioavailability of a nutrient be considered a beneficial physiological effect?

2.2.6. Function of the immune system

- Structure of this section is complicated and immunity as protection against infections and allergies should be better separated. Defence against tumour cells should be included.
- Can immunological markers be used to substantiate a function claim if supported by a concomitant clinical outcome?
- For a function claim on immune defence against pathogens is it sufficient to measure the clinical endpoint with concomitant immunological markers? Need the immunological markers be assessed in the same study?
- Does EFSA only accept maintenance of immune function claims or also claims for an improved function of the immune system?
- Can maintenance of a normal immune function be extended to an improvement of an impaired immune system (e.g. in the elderly), and can evidence provided for a restoration of immunological markers be sufficient to substantiate a claim on immune function?
- Which methods are appropriate to assess the incidence of infections?
- Does an outcome measure like enhanced antibody titres in response to a vaccination substantiate a claim on defence against pathogens outside the vaccination context?
- Why isn’t a reduction in the number and severity of infections sufficient to substantiate a claim for improved immune response?

2.2.7. Reducing a risk factor for infection or allergy

- Can disease risk reduction claims also be based on infection endpoints?
- Is there a need to identify a risk factor for allergy risk reduction claims?
- What could be an appropriate risk factor to substantiate disease risk reduction claims related to allergies?
- Can some immunological markers (e.g. sIgA) be considered as independent predictors of a disease risk related to infection, and would this replace the need to demonstrate a reduction in disease risk?
- How can a decreased risk factor be a good thing if caused by food constituent x, but not if caused by food constituent y?

2.2.8. Reduction of inflammation

- Clarify the statement that whether or not reduction of inflammatory markers is considered beneficial would depend on the context in which the claim is made.
- To give guidance on potential markers of chronic inflammation.
2.3. Panel consideration of comments received

EFSA has reviewed all comments carefully and has updated the guidance on the scientific requirements for gut and immune function health claims accordingly, which is now published in the EFSA Journal.

2.3.1. Bowel function

The revised guidance document further clarifies appropriate outcome measures, that more than one outcome measure can be considered to substantiate a specific claim if outcome measures are interrelated, and that patients with functional constipation are an appropriate study group to substantiate claims on bowel function for the general population, including children. More clarification has been provided on the meaning of changes in bowel function within the normal range. The document also clarifies that diarrhoea may be used as an outcome measure for other claims.

2.3.2. Gastro-intestinal development

The discussion at the technical meeting of 2 December 2010 revealed that there are still open questions as to what constitutes normal development, a beneficial effect, the age of the target group, and the reference group. Therefore, it was considered that this potential claimed effect should not yet be covered in the guidance document. In addition, to date the Panel has only very limited experience with the evaluation of these claims.

2.3.3. Gastro-intestinal discomfort

The revised guidance document now clarifies appropriate outcome measures for the claimed effect, that questionnaires which are developed according to general validation principles and are appropriate for the purpose of the study are required, and that validated general quality of life questionnaires alone are insufficient as outcome measures. It also highlights that IBS patients or subgroups of IBS patients are generally considered an appropriate study group to substantiate claims on gastro-intestinal discomfort for the general population (adults and children).

2.3.4. Gastro-intestinal microbiota

The revised guidance document contains a new section on defence against pathogens, and clarifies that for claims related to defence against pathogens appropriate outcome measures are clinical outcomes related to gastro-intestinal infections. If the outcome measure was the reduction of specific pathogens, the relevance of such a reduction should be justified, for example, by the magnitude of reduction or by evidence for a reduction in clinical outcomes related to infections accompanying the reduction in pathogens/toxins. It was also made clear that an observed increase in the number of any group of microorganisms needs to be accompanied by evidence for a beneficial physiological or clinical outcome, and that these criteria apply to both adult and infant/children populations. It is also emphasised in the document that other outcome measures such as reduction of intestinal permeability or pH are not beneficial physiological effects per se, but may provide evidence on the mechanisms and biological plausibility of a claim related to defence against pathogens. The list of groups of microorganisms which are considered to be pathogenic was slightly amended. A possible beneficial physiological effect related to the restoration of a disturbed microbiota needs to be assessed on a case-by-case basis, based on the evidence provided. As the Panel has not yet evaluated such a claim, this outcome measure is not covered in the guidance document.

A separate section on reducing a risk factor for infection was introduced into the guidance document, and it was clarified that for reduction of disease risk claims related to gastro-intestinal infections, it is considered that the presence of pathogens or toxins in the gastro-intestinal tract is associated with the

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9 EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2011. Guidance on the scientific requirements for health claims related to gut and immune function. EFSA Journal, 9(4):1984, 12 pp.
development of infections, and relevant reductions of specific pathogenic microorganisms or their toxins (supported by the magnitude of the reduction or by evidence of a reduction of clinical outcomes related to infection) in the gastro-intestinal tract are considered beneficial physiological effects in the context of reducing a risk factor for gastro-intestinal tract infections.

2.3.5. Digestion/absorption of nutrients
The document clarifies that whether improved digestion is considered a beneficial physiological effect may depend on the consequences of impaired digestion, for example, the effect of undigested nutrients in the gastro-intestinal tract. The revised document further explains that improved nutrient absorption is only considered beneficial where absorption is a limiting factor for the maintenance of adequate status of the nutrient and where the absorbed nutrient can be utilised. For claims related to reduced absorption of nutrients (e.g. cholesterol), these should be considered in the context of reduced blood concentrations of these substances.

2.3.6. Function of the immune system
A separate chapter for function claims related to resistance to allergens has been introduced into the guidance document. The guidance clarifies that for claims related to immune defence against pathogens the same outcome measures may be used to substantiate claims as the ones related to defence against pathogens, together with concomitant changes in relevant immunological parameters, preferably shown in the same studies. The guidance now explains that for claims on maintaining immune function in population groups at risk of immunosuppression (confirmed by symptoms and/or markers), studies in those subjects showing an improvement of the same symptoms and/or immune markers may be appropriate. The document also spells out that stimulation of protective antibody titres as measured by increased numbers of individuals attaining protective levels could be used to substantiate a claim on immune defence against pathogens. For allergy risk reduction claims the document clarifies that if it can be shown that an alteration of a (immunological) marker(s) is accompanied by 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.

2.3.7. Reducing a risk factor for infection or allergy
Separate sections on reducing a risk factor for infection, and on reducing a risk factor for allergy, were introduced in the guidance document, and the role of a “risk” factor in a disease risk reduction claim was explained (see also clarification provided in sections 2.3.4 and 2.3.6). Except for factors for which changes are generally predictive of the development of a disease, the extent to which a change in a factor is beneficial in the context of a reduction of disease risk claim needs to be considered on a case-by-case basis.

2.3.8. Reduction of inflammation
The guidance document now explains that the reduction of markers of inflammation is not in itself a beneficial physiological effect, but that altering levels of markers of inflammation might indicate a beneficial physiological effect, if it can be demonstrated for a specific dietary intervention that altering the levels of inflammatory markers is accompanied by a reduced incidence of a disease.
GLOSSARY AND ABBREVIATIONS

IBS  Irritable Bowel Syndrome
sIgA  Secretory IgA
APPENDIX

FULL LIST OF COMMENTS RECEIVED ON THE DRAFT OPINION OF THE EFSA PANEL ON DIETETIC PRODUCTS, NUTRITION, AND ALLERGIES (NDA) ON A GUIDANCE ON THE SCIENTIFIC REQUIREMENTS FOR HEALTH CLAIMS RELATED TO GUT AND IMMUNE FUNCTION

This list contains the comments submitted to EFSA via the public consultation held from 28 September 2010 to 22 October 2010. Comments submitted by individuals in a personal capacity are presented anonymously. Comments submitted formally on behalf of an organisation appear with the name of the organisation.

| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
|--------------|--------------|--------------|
| AESGP - Association of the European Self-Medication Industry | General comments | Lines 142-145: “Whether the design and quality of the studies allow scientific conclusions to be drawn for the substantiation of the claim. The evaluation takes into account the hierarchy of evidence as described in the EFSA guidance (ref), e.g. intervention studies generally provide stronger evidence than observational studies”

Comment: “Allow scientific conclusions” seems to refer to standards for development principles for interventional studies. There is a need to clarify the interventional standard allowing conclusions to be drawn. |
The Association of the European Self-Medication Industry (AESGP) welcomes the publication of guidance documents in the area of scientific substantiation of health claims, as this is certainly helpful to better understand the set of rules applicable to the assessment of applications for Article 13.5 and Article 14 health claims. However, the nature itself of the evaluation process and the need to assess each application on a case by case basis implies that guidance documents can not answer all the questions/issues faced by applicants.

Therefore, AESGP feels that it would be advisable to encourage the introduction of a procedure mirroring the existing Community consultation for the authorization of medicinal products. Many of the difficulties currently encountered by applicants could indeed be overcome by establishing Scientific Advice Meetings with the European Food Safety Authority to provide applicants with the possibility to discuss their data packages upfront and make an informed judgment concerning all aspects of relevance for an application.

Membership of AESGP believes that several sections of the draft “Guidance on the scientific requirements for health claims related to gut and immune function” could be further developed (also by means of concrete examples); specific passages where more detailed indications would be welcome are highlighted in the comments to the chapters/sections.

In general, the guidance allows for several undefined markers to be accepted for different claims and outcomes (and allows for these to be evaluated on a case by case basis). Applicants would benefit from a clear definition of the types of markers that will be acceptable for health claims submissions. By way of example:

Does the NDA Panel believe there are specific markers that should be used for specific outcomes, or does the Panel have a general list of markers to address incidences of upper respiratory infections or gastrointestinal disturbances?

Will there be different markers for reduction of pathogens, immunity and inflammation?

Finally, it would be helpful if the guidance document could provide greater clarity on the criteria applicable to claims related to children development and health. The current version of the document discusses maintenance and improvement of a function but does not provide enough details on development of the function itself (in the context of Article 14 health claims referring to children’s development and health).
| ORGANISATION                                      | CHAPTER TEXT                          | COMMENT TEXT                                                                 |
|--------------------------------------------------|---------------------------------------|------------------------------------------------------------------------------|
| AESGP - Association of the European Self-Medication Industry | 3.1 Claims on bowel function          | Comment: It would be helpful to provide examples of “generally accepted methods” (line 168) |
|                                                  |                                       | Questions:                                                                  |
|                                                  |                                       | - While considering claims on bowel function, the guidance document refers only to claims on constipation: what about claims on loose stool? |
|                                                  |                                       | - Should the type of population to be involved into human studies for constipation be selected according diagnostic criteria or to be defined by the patient feelings? |
|                                                  |                                       | - What does the NDA Panel consider as a normal range for bowel function? On which parameters? |
|                                                  |                                       | - Can the NDA Panel confirm that appropriate outcome measures are mechanistic activity studies (transit time) and/or human studies (based on symptoms)? |
|                                                  |                                       | - What does stool bulk mean? Weight? Bristol stool form scale?               |
| AESGP - Association of the European Self-Medication Industry | 3.2 Claims on gastrointestinal discomfort | Comment: It would be helpful to specify in the guidance the recommended duration of use for the human studies. It is also not clear what is regarded by the NDA Panel as a global severity score –does it correspond to abdominal pain and/or bloating or to each symptom separately? |
### AESGP - Association of the European Self-Medication Industry

| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
|--------------|--------------|--------------|
| 3.2 Claims on gastrointestinal discomfort | General remarks: This chapter widely describes medical conditions rather than symptoms of "gastrointestinal discomfort". Terms like "abdominal pain/cramp" are suitable to illustrate symptoms to be treated with medicinal products and AESGP doubts whether they are appropriate to describe the objective of health claims (it should be avoided to provide information about health functions of food that would attribute medicinal properties to food). The last paragraph should be deleted, as Irritable Bowel Syndrome (IBS) is not an occasional discomfort in healthy people but a disease with chronic character. This chronic character is a precondition for the diagnosis of IBS (at least 3 days per month in the last 3 months, according to Longstreth et al., Gastroenterology 2008;130:1480-1491) which is a crucial difference to occasional gastric discomfort in healthy people.
In addition, there is increasing evidence that in a considerable proportion of IBS patients subclinical inflammatory changes are involved in the etiology of this disease, and that these changes are lacking in healthy persons (Collins et al., Gut 2001 49:743-745; Barbara et al., Gut 2002 51:i41-i44. Delvaux. Gut 2002 51:i61-i67; Liebregts et al. Gastroenterology 2007 132:913-920). As there may therefore be a distinct pathophysiological difference between at least a considerable proportion of IBS patients and healthy people with occasional gastrointestinal discomfort, it seems to be questionable (also from a pharmacological point of view) whether results from IBS patients can be transferred to the general, healthy population. In parallel to the case of § 4.2 (Claims on inflammation) a transfer of data from clinically ill patients to the general population would attribute clinical symptoms of a disease to this healthy population, thereby assuming that the foodstuff under consideration has medicinal properties (which can only be attributed to medicinal products). As a consequence, reference to IBS should not be included here and the last paragraph should be deleted. |
| 3.3 Claims on oral and gastrointestinal microbiota | Lines 201-202: “There is a distinction in evaluation of effects on pathogenic or toxicogenic microorganisms for function claims and for disease reduction claims”
Comment: It would be helpful to have clarification and examples for both function claims and disease reduction claims. |
| 3.3 Claims on oral and gastrointestinal microbiota | Line 200: “Generally, a decrease by less than 1 log value is not considered meaningful”
Comment: It would be helpful to have a definition of what is/would be considered meaningful with relation to human health. |
| ORGANISATION                                                                 | CHAPTER TEXT                                                                 | COMMENT TEXT                                                                                                                                                                                                 |
|------------------------------------------------------------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| AESGP - Association of the European Self-Medication Industry                | 3.3 Claims on oral and gastrointestinal microbiota                           | Lines 196-199: “Appropriate outcome measures of the claimed effect in human studies include reduction of numbers of pathogenic microorganisms or their toxins in stools or other suitable samples. The composition of microbiota in the gastrointestinal tract show great variability. Therefore, a microbiologically relevant reduction of pathogens, which is sustained over time in the same study group, should be demonstrated”  
Comment: It seems very challenging to conduct human trials that can demonstrate a microbiologically relevant reduction of pathogens which is sustained over time. |
| AESGP - Association of the European Self-Medication Industry                | 3.3 Claims on oral and gastrointestinal microbiota                           | Comment: The difference between data needed to support a disease risk reduction claim and data needed to support claims related to maintaining normal defence against pathogens could be further clarified. |
| AESGP - Association of the European Self-Medication Industry                | 3.3 Claims on oral and gastrointestinal microbiota                           | Question: It is not clear which claims on gastrointestinal microbiota the guidance refers to: microbiologic ones (“restores gastrointestinal microbiota”) or clinical ones (“helps to prevent antibiotic-induced intestinal microbiota disequilibrium [frequently diagnosed by diarrhoea]”, “helps to prevent travellers intestinal microbiota disequilibrium caused by pathogenic bacterial agents)? As there is no correlation between the number of pathogenic microorganisms or the presence of toxins and the symptoms, we suggest focusing on symptoms. |
| AESGP - Association of the European Self-Medication Industry                | 3.4 Claims on digestion/absorption of nutrients                              | Lines 246-248: “To assess lactose digestion, studies in susceptible populations, defined either by clinical symptoms or by lactase genotyping, with appropriate assessment of symptoms, and/or measurement of breath hydrogen and methane are required”  
Question: How objective are the symptoms indicating a health disturbance, whereas the measurement of lactase genotyping seems very stringent? Would the data interpretation be limited to the population that has been genotyped? |
| AESGP - Association of the European Self-Medication Industry                | 4.1 Claims on the function of the immune system                              | Lines 285-286: “Stimulation of protective antibody titres could be used to substantiate a health claim on the function of the immune system related to defence against pathogens”  
Comment: It would be helpful to have clarification on what is needed to demonstrate stimulation of protective antibody titres. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
|--------------|--------------|--------------|
| AESGP - Association of the European Self-Medication Industry | 4.1 Claims on the function of the immune system | Lines 277-278: “Clinical as well as laboratory measures are preferentially shown in the same intervention studies”
Comment: As this implies an interventional setting with invasive approaches (e.g. blood collection, allergy testing: skin-prick test, allergen exposure etc.), the feasibility and appropriateness of such proposals should be discussed. It could be acknowledged that an interventional scheme might be of importance for proof-of-concept studies – but not considered as mandatory for claim substantiation on broader scale study basis. |
| AESGP - Association of the European Self-Medication Industry | 4.1 Claims on the function of the immune system | Lines 268-273: “Outcome measures of the claimed effect in human studies include incidence of infection (e.g. in upper respiratory tract, gastrointestinal tract, urinary tract, etc.) and reduction of numbers of pathogens for claims related to defence against pathogens, and incidence of allergic manifestations for claims related to response to allergens. However, since the incidence of infection may not necessarily represent an effect on the immune system, for claims involving the immune system, appropriate evidence of a concomitant change in immunological parameters needs to be provided”
Question: It is not fully clear how to substantiate incidence of immune function claims – if the target is the general, healthy population, shall applicants measure changes in immunological parameters among it and complement them with measures on incidence of infection? |
| AESGP - Association of the European Self-Medication Industry | 4.1 Claims on the function of the immune system | Lines 268-273: “Outcome measures of the claimed effect in human studies include incidence of infection (e.g. in upper respiratory tract, gastrointestinal tract, urinary tract, etc.) and reduction of numbers of pathogens for claims related to defence against pathogens, and incidence of allergic manifestations for claims related to response to allergens. However, since the incidence of infection may not necessarily represent an effect on the immune system, for claims involving the immune system, appropriate evidence of a concomitant change in immunological parameters needs to be provided”
Comment: It would be helpful to have clarification on the concomitant change in immunological parameters. |
| AESGP - Association of the European Self-Medication Industry | 4.2 Claims on reduction of inflammation | Lines 301-304: “Whether or not reduction of inflammatory markers is considered beneficial would depend on the context in which the claim is made (i.e., the health benefit of reducing inflammatory responses and the appropriateness of the markers used for the assessment of the effect would have to be considered on a case-by-case basis).”
Comment: It would be helpful to clarify this statement, also by means of concrete example(s). |
| AESGP - Association of the European Self-Medication Industry | 4.2 Claims on reduction of inflammation | AESGP would like to point out that inflammatory disorders are pathological findings and claims on reduction of inflammation would illicitly attribute medicinal properties to foodstuffs. This chapter should therefore be deleted. |
| ORGANISATION               | CHAPTER TEXT          | COMMENT TEXT                                                                                                                                 |
|---------------------------|-----------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Alliance for Natural Health| 3.1 Claims on bowel function | Line 163: The draft guidance mentions constipation as a disorder of normal bowel function, but does not discuss loose stools. The latter should be included.  
Line 164: Reduced faecal bulk is discussed as being associated with constipation. However, there is considerable overlap in terms of faecal bulk between normal subjects and those with constipation, as noted by Cummings et al., 2004/PASSCLAIM. This should be clarified in the draft guidance.  
Line 164: Although the draft guidance mentions diverticular disease as a potential sequela of constipation, it is not the only one. An extremely important omission – which was noted by Cummings et al., 2004/PASSCLAIM – is colorectal cancer, the most common form of non-sexual cancer in both male and females in Europe, which should be included in the guidance document. It should be noted that both diverticular disease and colorectal cancer are posited as sequelae of low stool weight.  
Line 165: It is somewhat misleading to state that “changes in bowel function within the normal range might be considered beneficial”, since certain beneficial effects are associated with changes that could be considered to lie outside the normal range. For example, for most EU populations, an increase in mean daily stool weight of 50% would be beneficial in terms of reduced colon cancer risk and changes that bring transit time within the normal range are also considered beneficial (Cummings et al., 2004/PASSCLAIM). This situation has implications for both Article 13 (health claims other than those relating to reduction of disease risk or children’s development/health) and Article 14 (health claims relating to reduction of disease risk or children’s development/health) health claims.  
Line 167: Among the appropriate outcome measures should be included diary-recorded quality/appearance of stool (Cummings et al., 2004/PASSCLAIM).  
Line 168: For the sake of clarity, the "generally accepted methods” mentioned here should be defined.  
Reference  
Cummings JH, Antoine J-M, Azpiroz F, Bourdet-Sicard R, Brandtzaeg P, Calder PC, et al. PASSCLAIM: Gut health and immunity. Eur J Nutr 2004;43(Suppl. 2):I1/118–I1/173. |
| ORGANISATION               | CHAPTER TEXT                           | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|---------------------------|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Alliance for Natural Health | 3.1 Claims on bowel function           | Line 163: The draft guidance mentions constipation as a disorder of normal bowel function, but does not discuss loose stools. The latter should be included. Line 164: Reduced faecal bulk is discussed as being associated with constipation. However, there is considerable overlap in terms of faecal bulk between normal subjects and those with constipation, as noted by Cummings et al., 2004/PASSCLAIM. This should be clarified in the draft guidance. Line 164: Although the draft guidance mentions diverticular disease as a potential sequela of constipation, it is not the only one. An extremely important omission – which was noted by Cummings et al., 2004/PASSCLAIM – is colorectal cancer, the most common form of non-sexual cancer in both male and females in Europe, which should be included in the guidance document. It should be noted that both diverticular disease and colorectal cancer are posited as sequelae of low stool weight. Line 165: It is somewhat misleading to state that “changes in bowel function within the normal range might be considered beneficial”, since certain beneficial effects are associated with changes that could be considered to lie outside the normal range. For example, for most EU populations, an increase in mean daily stool weight of 50% would be beneficial in terms of reduced colon cancer risk and changes that bring transit time within the normal range are also considered beneficial (Cummings et al., 2004/PASSCLAIM). This situation has implications for both Article 13 (health claims other than those relating to reduction of disease risk or children’s development/health) and Article 14 (health claims relating to reduction of disease risk or children’s development/health) health claims. Line 167: Among the appropriate outcome measures should be included diary-recorded quality/appearance of stool (Cummings et al., 2004/PASSCLAIM). Line 168: For the sake of clarity, the "generally accepted methods” mentioned here should be defined. |
| Alliance for Natural Health | 3.2 Claims on gastrointestinal discomfort | Line 181: The draft guidance recognition of IBS as a relevant study population to support claims aimed at the general population is commendable. However, there is no universally recognized definition of irritable bowel syndrome (IBS), which may present problems with regard to extrapolating study results in IBS patients to the general population. |
### Outcome of a public consultation on a draft guidance on the scientific requirements for gut and immune function claims

| ORGANISATION                  | CHAPTER TEXT                                                                 | COMMENT TEXT                                                                                                                                                                                                 |
|-------------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Alliance for Natural Health   | 3.3 Claims on oral and gastrointestinal microbiota                            | Line 188: The draft guidance should consider that increasing the levels of bowel microorganisms from the lower end of their normal range toward the upper limit of normal might be a beneficial effect. This may be particularly true for disturbances in the bowel microbiota following antibiotic therapy. Lines 189 and 192: Although they have the same meaning, use of the terms “toxicogenic” and “toxinogenic”, should be made consistent to aid clarity of the guidance. Line 200: For clarity, use of the term “generally” should be avoided in this case by defining the situations in which a decrease in pathogen by less than 1 log value is considered meaningful. Line 204: The draft guidance should be amended to recognize the fact that, since vaccines have been approved for market based on studies that demonstrated reduced incidence/duration of infections, a similar level of evidence should apply to health claims made under Articles 13 and 14. Lines 226–235: A focus of the draft guidance on human intervention studies risks unnecessarily excluding other forms of evidence, such as epidemiological studies. It is entirely possible that health claims could be supported by examining symptom severity or duration of infection in populations exposed to a nutrient and comparing them with populations that lack such exposure. |
| Alliance for Natural Health   | 3.4 Claims on digestion/absorption of nutrients                               | ADDITIONAL AREAS TO BE INCLUDED AFTER SECTION 3.4 AND BEFORE SECTION 4 Stomach acidity pH plays a crucial role in a normally functioning digestive tract. Hypochlorhydria is a widespread problem even in healthy people and especially in the elderly. It leads to malabsorption of proteins and other nutrients. Hypochlorhydria may also lead to bacteria overgrowth in the intestine. Supporting a healthy pH should be regarded as a beneficial physiological function. References: Christiansen PM. The incidence of achlorhydria and hypochlorhydria in healthy subjects and patients with gastrointestinal diseases. Scand J Gastroenterol. 1968; 3(5): 497-508. Kassarjian Z, Russell RM. Hypochlorhydria: A Factor in Nutrition Annual Review of Nutrition; 9: 271-285. Holt PR, Russell RM. Chronic gastritis and hypochlorhydria in the elderly. 1993. CRC Press. Bile quality and release Bile quality and its timely release into the duodenum is essential for healthy function of the GI tract and proper absorption of fats and other nutrients. Fatty acids in the lumen of the duodenum stimulate endocrine cells to release the hormone cholecystokinin (CCK). CCK stimulates contractions in the smooth muscle of the gallbladder. As well, CCK causes relaxation of the sphincter of Oddi, allowing bile release into the duodenum. Acidic chyme in the lumen of the duodenum stimulates other endocrine cells to release the hormone secretin. Secretin stimulates duct cells in the liver to release bicarbonate into the bile. Accordingly CCK and secretin should be recognised as useful biomarkers for healthy bile function. References: Maton PN, Selden AC, Chadwick VS. Large and small forms of cholecystokinin in human plasma: measurement |
| ORGANISATION                  | CHAPTER TEXT                                      | COMMENT TEXT                                                                                                                                                                                                 |
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| Alliance for Natural Health  | 3.4 Claims on digestion/absorption of nutrients  | Line 240: While the draft guidance makes specific reference to problems caused by the deficiency of one enzyme, namely lactase, many suffer deficiencies in protein, carbohydrate and fat digestion linked to inadequate endogenous or exogenous intake of other enzymes, including those that are grouped as protease, peptidase, amylase, lipase, invertase. Cellulase and others. Foods or food constituents that contribute to healthy levels of these and other digestive enzymes should be regarded as beneficial and should be amenable to function or disease risk reduction claims. |
| Alliance for Natural Health  | 3.4 Claims on digestion/absorption of nutrients  | Line 250: Clarity of the document would be improved by clarifying or avoiding the term “generally” regarding absorption of non-haem iron in the human intestine.                                                                 |
|                              |                                                  | Line 254: The draft guidance refers to “generally accepted methods” of measuring iron absorption, but it would be useful to list them in the interests of clarity.                                                      |
| ORGANISATION          | CHAPTER TEXT                                              | COMMENT TEXT                                                                 |
|----------------------|-----------------------------------------------------------|-----------------------------------------------------------------------------|
| Alliance for Natural Health | 4.1 Claims on the function of the immune system         | COMMENTS ON SECTION 4.1                                                      |
|                      |                                                           | Lines 287-292: It is of great concern to us that the draft guidance suggests that immune system markers can only be used as supporting evidence for a claim. This is inconsistent with the view, drawn from the controversial area of vaccination, that “stimulation of protective antibody titres” may be used to substantiate immune function (lines 285-6). Assuming that a particular alteration in the expression or amount of an immune marker or signalling chemical can be associated with enhanced immune system function, such markers should be able to be used to support immune system claims. Any claim, on a case-by-case basis, could be qualified according to the degree of evidence available to support it. It would make sense, where possible, to divide these markers according to whether they relate to the innate or cell-mediated immune system. Innate immune markers would therefore include antimicrobial peptides, lysozymes, non-specific leukocytes, macrophages, specific interleukins, NF-kB, T-cells, Th1/Th2 cytokine ratios, etc. An increasing body of research is pointing to the vital role of the gut in immune modulation. There are a vast array of biomarkers associated with the gut microbiota that have not been included in the guidance. Included in the biomarker list should be toll-like receptors, such as TLR-2, TLR-4 and TLR-5. See extensive references in a paper review paper published through Nature Reviews in September 2010: Eberl G. A new vision of immunity: homeostasis of the superorganism. Mucosal Immunol. 2010; 3(5): 450-60. |

analyze & realize ag | General comments                                           | First of all I would like to thank you for the publication of the draft guidance. This paper contains a lot of very concrete information on EFSA’s requirements for clinical trials to substantiate claims related to gut and immune function. This information is very important for stakeholders planning a submission of a respective health claim. We have been longing for this kind of specific information! It will be helpful to obtain similar guidelines for other health claims as well. |
| ORGANISATION          | CHAPTER TEXT                             | COMMENT TEXT                                                                                                                                                                                                 |
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| analyze & realize ag  | 4.1 Claims on the function of the immune system | Under paragraph 4.1. about claims on the function of the immune system, it is stated in line 268-273 that: “Outcome measures of the claimed effect in human studies include incidence of infection (e.g. in upper respiratory tract, gastrointestinal tract, urinary tract, etc.) and reduction of numbers of pathogens for claims related to defence against pathogens, and incidence of allergic manifestations for claims related to response to allergens. However, since the incidence of infection may not necessarily represent an effect on the immune system, for claims involving the immune system, appropriate evidence of a concomitant change in immunological parameters needs to be provided (see section 3.3).”  
I do not agree with this statement. As it was argued in the PASSCLAIM publication on gut health and immunity (Cummings et al., 2004), changes in immune parameters may not necessarily translate into improved host defence. The authors state “It is not clear whether the wide variation in in vivo and ex vivo functional responses among apparently healthy individuals results in variable susceptibility to infection….Ultimately, a change in susceptibility to, or severity of, infectious disease is the outcome of greatest significance” Changes in immune parameters may not be relevant because there may be excess capacity in some immune functional responses and a further increase would not lead to improved immune function (Cummings et al., 2004). On the other hand, there may be an improved immune function without measurable changes in the immune parameters, since these parameters are subject to large individual variations due to a number of factors, such as nutrient status, age, hormonal status, stress, exercise, alcohol consumption, smoking, just to name a few (Cummings et al., 2004). Therefore, changes in immune parameters may be masked by individual variations, and not be detectable in a human clinical trial, although a reduction of number and duration of infections is observed. Would EFSA in this case reject a claim on immune function? How would EFSA explain a reduction in number and severity of infections if not by an improved immune response? Does it make sense to demand a battery of measurements, if the relevance for the intended claim is questioned even by experts (see Cummings et al., 2004)? I would very much appreciate, if you would evaluate my concerns and comment on it. |
| ORGANISATION                  | CHAPTER TEXT                                      | COMMENT TEXT                                                                                                                                 |
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| apl. Prof. University Mainz  | 4.1 Claims on the function of the immune system | **1.1.** EFSA should follow same principles in claims according to article 13.1 as well as 13.5 and 14. At present equality of criteria for evidence is not applied as can be seen from the decision on vitamin D and immune function: For a claim “contributes to normal function of the immune system” EFSA sees sufficient evidence based on 3 review articles. In these articles the authors refer to animal trials and epidemiological data mainly. There is evidently no data based on pivotal human trials in the target population of healthy subjects in Europe. The authors of the reviews see “promising” data, but not final evidence on immune function of vitamin D and still unclear mechanisms and even paradoxical results. Therefore a cause-effect relationship is still to be shown. The purpose of the Health Claim Regulation (see preamble) is protection of the consumer and promotion of innovations by the industry. Favouring non-innovative generic claims and impeding innovations is in contrast of the purpose of the regulation. **1.2.** The opinion statement by EFSA should be more refined and transition time lines extended based on such refined statements: The present situation shows that a more refined process of decision making is mandatory to prevent major economic damage to European companies and to prevent the false impression of the consumer that there is no evidence at all for major categories of functional foods. In case of a 90% probability for efficacy (p<0.10) a pending procedure might be more adequate and less harmful for the companies than a no decision. In such a case a transition time line of use of claims might be a solution. In this transition time of 3-5 years the evidence may be provided by appropriate confirmative trials which would be reassessed by EFSA. **1.3.** Risk Reduction Claims should be enabled based on Relative Risk (in case of lacking risk factor) Claims on Risk Reduction should be permitted based on Relative Risk (RR), since the wording risk reduction is sufficiently cautious to prevent consumers from too far fetching promises. **Question 1:** Can a body function claim “enhances immune defence” or “strengthens immune defence” be based on antibody response to a pathogen in a vaccination trial alone or only in conjunction with supporting evidence by outcomes of infections related to such pathogens? **Question 2:** Can a body function claim “enhances immune defence” or “strengthens immune defence” be based on NK cell counts or NK cell activity or NK activity index (NK cell count multiplied with activity) according to H. Bruunsgaard, Exp. Gerontol. 37(2001)127-136) - during infection, - only in the healthy state, - within incubation time when assessed in conjunction with later infection outcome? Can this evidence be provided by different studies, where one/some are dedicated to NK cell function and others to infection outcome? **Question 3:** Is the following sufficient, to show cause-effect relationship: Efficacy of a probiotic strain shown for enhancement of antibody response to an influenza vaccine; Or is further mechanistic evidence required, although the EMEA is accepting antibody response as sufficient measure to assess protection against the pathogen against which the antibodies are directed (e.g. in case of influenza vaccination)? If so, is evidence for a shift of the Th1/Th2 ratio to Th1 response in human PBMC by the same product/probiotic strain in vitro sufficient, based on the fact that it is known that enhancement of Th1 response results in an increase in IgG production by B cells (Calder, J. Nutr. (Suppl.),2007; Winkler et al. J. Nutr. (Suppl.)(2007); etc.).
Outcome of a public consultation on a draft guidance on the scientific requirements for gut and immune function claims

| ORGANISATION          | CHAPTER TEXT                              | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| apl. Prof. University Mainz | 4.3 Claims on reducing a risk factor for infections or allergy | The following should be defined more precisely:  
1: Can risk reduction claims be based on infection endpoints such as relative risk (RR) of infection as assessed by incidence of infection? Claims on Risk Reduction should be permitted based on Relative Risk (RR), since the wording risk reduction is sufficiently cautious to prevent consumers from too far fetching promises.  
2: Will a decrease in IgA after physical stress be accepted as risk factor for respiratory infections? (See Nieman et al., J.S.M.P.F., 2006)  

| Barry Callebaut           | 3.3 Claims on oral and gastrointestinal microbiota | lines 186 to 188: Does this mean that a probiotic effect can not be supported simply by an increase of the number of beneficial bacteria e.g. Bifidobacteria and Lactobacilli? An increase in Bifidobacteria can be health beneficial in elderly persons.  
Bifidobacteria are numerically important colonic species that can occur in adults in excess of 10EXP10 per gram dry weight in faeces (Finegold et al. 1983). In conjunction with the shifts observed in the genus Bacteroides, the decline in beneficial Bifidobacteria numbers is one of the most marked changes in the elderly gut, with a number of studies confirming these reductions (Mitsuoka et al. 1974; Benno et al. 1992; Mitsuoka 1992; Gavini et al. 2001; Hopkins et al. 2001; Woodmansey et al. 2004). Taken in conjunction with reduced species diversity, such changes indicate a decline in the stability of this population in the ageing colonic ecosystem. A wide range of bifidobacterial species are found in infants and young adults, however, in the elderly population, species diversity is reduced to one or two dominant organisms, in particular Bifidobacterium adolescentis or the phenotypically similar Bifidobacterium angulatum and Bifidobacterium longum (Mitsuoka et al. 1974; Gavini et al. 2001; He et al. 2001; Hopkins and Macfarlane 2002). One suggestion used to explain the decline in bifidobacterial species diversity in elderly people is reduced adhesion to the intestinal mucosa, although it is not clear if this is because of changes in the bacteria, or in the chemical composition and structure of colonic mucus (Ouwehand et al. 1999; He et al. 2001). Such a decline could result in a reduced functionality and immune responsiveness in the gut, and an increased susceptibility to gastrointestinal infections.  
Changes at species level of such a nutritionally important sub-population could have considerable consequences for the elderly host, because of alterations in metabolic activities, and for other bacteria in the ecosystem that rely on a complex cross-feeding network within the gut.  
Dietary probiotics delivery is one of the possible strategies to counteract these changes, to bring more species diversity and increase the number of beneficial bacteria like Bifidobacteria in ageing people. (E.J. Woodmansey, 2007, Intestinal bacteria and ageing)  

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| ORGANISATION                  | CHAPTER TEXT       | COMMENT TEXT                                                                                                                                                                                                 |
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| Barts and the London School  | General comments   | EFSA needs to clarify the benchmarks for claim substantiation. Section 2.2 is clearly written in a way that suggests data are undergoing peer-review for quality by the panel. While this may be the case for commercially sensitive data (although experts outwith the panel will be needed), for published works which have already undergone peer-review, it is not acceptable for members of the panel to weigh the evidence and decide on its quality and importance. This seems to be an attempt to mimic regulatory bodies for medicines, but these are foods. If one begins with the proper null hypothesis that a food should have no effect, then demonstration of a statistically significant effect should be sufficient for the claim to be allowed. A second outcome of the review by the panel of published data is that it creates uncertainty and confusion. If there are no clear guidelines, but it is left up to the panel's discretion, no food manufacturer will know how many studies to do and what level of proof is needed. This will have the effect of discouraging research on the health benefits of foods, and have the exact opposite effect that the legislation was designed to bring. Who is going to spend 1 million euro on a clinical study, which even if it gives a positive result, can be second-guessed after publication and a claim based on the paper denied? |
| of Medicine                  | 4. Immune system   | The section on the immune system is generally not helpful and seems to have been constructed without reference to article 13.5 and 14. In the first paragraph of 4.1, lines 260-262, the confusion is compounded by mixing up immunity as a protective against against infections, with inappropriate immunity as manifest by allergies. Sections 4.2 then talks about inflammation in a broad and unhelpful sense and 4.3 goes on about risk reductions for infections and allergy. these are completely different things and combining them only confuses the issue. Lines 308-311 are a good example of confusion. Is EFSA really saying that a human intervention study which shows that a food had a beneficial effect is only supportive evidence, but that a change in a risk factor is needed? It is worth remembering that the Finnish studies which claimed that probiotics given to mother and then her baby could prevent the development of eczema showed no reduction in markers of allergy in the children. This part of the document could benefit from several worked examples in immunology and infection where EFSA could make it very clear what kind of evidence they are looking for. Thus if a food could reduce serum IgE from 400 units to 200 units, is that a risk reduction? Even though we know that it will have no effect on allergies. |
4.1 Claims on the function of the immune system

Line 285 and 286 suggest that boosting of antibody titers could be used to substantiate a health benefit claim against pathogens. The question which immediately arises from this statement is whether the claim can be used to substantiate an effect against all pathogens, a class of pathogens, or the pathogen against which the vaccine was designed to protect. Common sense says that the last case should be adopted. Lines 268 to 273 have an important omission. Undue focus has been made on reductions in incidence of infections and pathogen numbers. A consistent finding in many probiotic studies is that taking the product shortens the duration of symptoms. The immune system is there to allow recovery from infection and quicker recovery is a meaningful clinical endpoint and indicative of an effect on the immune system. Whether this correlates with a biomarker of resistance is an unacceptably high hurdle to cross since it is extremely well established that protective immunity is multi-factorial and cellular immunity is very hard to measure. It is also shows a rather narrow understanding of the immune response. Pathogen numbers are one determinant of infection, but for the individual, the symptoms are caused by the host response to the pathogen. For example, taking paracetamol to relieve the symptoms of a cold makes people feel better, but does not reduce viral load.

BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS

General comments

The BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS welcomes the initiative of the NDA panel to address issues like

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

in order to clarify the requirements for substantiation of health claims.

These clarifications should also be seen as an opportunity to reduce the number of borderline cases. Indeed, clear criteria for the substantiation of health claims clearly differentiating them from therapeutic indications, could be a major help for the competent authorities in evaluation borderline cases. Consequently the BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS was surprised to see to rationale followed by the NDA. This rationale, although aiming at clarifying the requirements for health claim substantiation, seems on certain levels quite confusing because it would seem not to take into account restrictions emerging from legislation concerning other fields than food (supplements) and health claims.

From legislation on clinical trial for example, it is clear that when a clinical trial (as defined in the Directive 2001/20/EC) is conducted, the product used therein is clearly an investigational medicinal product. As food supplements are supposed to have a nutritional or physiological effect, these effects would normally not be deductible from a clinical trial. Moreover food supplements aim at supplementing a normal diet, which is difficultly associative to the notion of a clinical trial.

Another factor to be taken into account is that in a lot of these trials the investigated endpoint is clearly therapeutical, a fact which also contributes to the product’s status being medicinal.

The BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS acknowledges the fact that
indeed the wording “clinical trial” is not used in the document but considers that “(human) studies” would include these trials. (which is, indeed, reflected in the data as introduced by the Member States)
As a general remark, the BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS would like to draw attention to the fact that health claims can only be made for product categories as foreseen in the Regulation 1924/2006 and that the greatest care should be given to the use of data obtained by means of studies done with products that are not part of one of these categories.

Beneficial physiological effect

101. The BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS would welcome a clear definition a “physiological effect” and “beneficial physiological effect” in relation to “modification of a physiological function” and “correction of a physiological function”, notions that are integral part of the medicinal product’s definition.

107: the “improvement” of a function can by no means be the fact that pathological status is returned to normal. Moreover, the normal status is to be defined in this context.

BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS wonders to which extend this “improvement” is a modification of a physiological function?

Studies/outcome measures appropriate for substantiation of claims

136: “whether the studies have been carried out with the food/constituent for which the claim is made.”

BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS considers, as already mentioned, that the definition of an investigational medicinal product should be taken into account in this context.

167: “Appropriate outcome measures of the claimed effect in human studies include transit time, frequency of bowel movements, stool bulk.”

BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS considers that these outcome measures can be influenced by the use of substances that have a pharmacological effect => extrapolation to products that are not supposed to have pharmacological effects is therefore inadmissible.
| ORGANISATION                                      | CHAPTER TEXT                        | COMMENT TEXT                                                                 |
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| BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS | 3.2 Claims on gastrointestinal discomfort | 177. BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS is surprised to see that the NDA panel would consider data emerging from a “clinical trial” or “human study” investigating the “effect” of a product in patients with IBS to be transposable to the general population. It is stated (179) that “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.” The physiological status of an IBS patient is not comparable to that of a healthy subject and other factors linked to the disease are likely to influence the outcome of the studies done in this patient population. Diseases like IBS have indeed an impact on the general status of the body and can lead to conditions not comparable to the ones found in healthy subjects. The proposed methodology would suppose transposing data from ill patients to healthy subjects which makes no sense. |
| BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS | 3.3 Claims on oral and gastrointestinal microbiota | 191: “The Panel considers that reducing the numbers of specific pathogenic microorganisms in these ecosystems is a beneficial physiological effect.” 194: “reducing the numbers of specific pathogenic microorganisms or their toxins in these ecosystems is considered a beneficial physiological effect in the context of reducing a risk factor for infection.” 205. “However, clinical outcomes (e.g. number of episodes of infection, severity of symptoms, or duration of infection such as indicated by diarrhoea diagnosed as infection-related using specific criteria), demonstrated in human intervention studies could be supportive of the claimed effect related to pathogens.” Concerning the cited paragraphs (191/194/205), BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS considers that “the abnormal presence of pathogenic or toxicogenic microorganisms in the intestine (189)” clearly indicates that the aim of these claims is, by “reducing the numbers of specific pathogenic microorganisms(191)” to transform a pathological state into a normal physiological state, which is out of the scope of the food supplement definition. |
| BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS | 3.4 Claims on digestion/absorption of nutrients | 240. BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS would like to underline the fact that Lactose intolerance is classified by WHO as a disease (E73 – ICD10). |
| ORGANISATION                                | CHAPTER TEXT                        | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS | 4.1 Claims on the function of the immune system | 272: “appropriate evidence of a concomitant change in immunological parameters needs to be provided”
BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS considers immunological effects leading to modification of a physiological function (immune system) as being an integral part of the definition of a medicinal product
284: “For that reason vaccines are usually produced with adjuvants, so that the majority of recipients of vaccines attain sufficient titres to be protected. Stimulation of protective antibody titres could be used to substantiate a health claim (sic) on the function of the immune system related to defence against pathogens.”
BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS considers it inappropriate to evaluate effects of substances given as adjuvant when administering a medicinal product into a general effect (in absence of this medicinal product)

| BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS | 4.2 Claims on reduction of inflammation | “…reduction of inflammation” is a therapeutic indication. 294: “Inflammation is a non-specific physiological response to tissue damage that is mediated by the immune system.” 300: “reducing levels of markers of inflammation might indicate a beneficial physiological effect.” BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS considers that when an underlying cause of inflammation is present, it would be a health hazard to reduce the level of inflammation markers without medical supervision. Inflammation responses are complex immunological processes and influencing these in any manner might pose serious health risks (cancer, HIV, auto immune diseases,….) BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS therefore considers this section largely out of scope for health claims.

| BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS | 4.3 Claims on reducing a risk factor for infections or allergy | BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS considers the section concerning allergies only relevant for food related allergies.
BELGIAN FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS considers the comments made on the section as referred to in lines (191/194/205), are equally applicable on the section dedicated to the infection risk reduction.

| Beneo Institute | 3. Gastro-intestinal tract | Key points
- Scientific judgements within Europe need to be consistent, e.g. in the context of fibres there is a clear regulatory statement that fermentation is a beneficial physiological effect, whereas in this guidance document it is considered as supportive evidence, only.
- Scientific judgement should consider other scientific opinions that have been peer reviewed by expert in the field.

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| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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|              | Re: Fermentation as physiological effect | The Guidance documents so far considers fermentation only as supportive evidence in the context of the gastrointestinal flora. However, fermentation is an acknowledged beneficial physiological effect for fibres in total as defined and endorsed in 2008/100/EC, Rec.5: “Fibre [...] has one or more beneficial physiological effects such as: decrease intestinal transit time, increase stool bulk, is fermentable by colonic microflora, reduce blood total cholesterol, reduce blood LDL cholesterol levels, reduce postprandial blood glucose, or reduce blood insulin levels.” The health relevance has been reviewed and confirmed by several panels, including recently EFSA in its document on DRVs on dietary fibre (EFSA Journal 2010; 8(3): 1462). The current document confirms a beneficial effect for bowel regularity, explicitly transit time and stool bulk, and EFSA has in a different context also acknowledged the beneficial effects of lower total and lower LDL cholesterol. In order to be consistent through European Regulations as well as scientific opinions, the same should apply to all effects that in other contexts are beneficial, i.e. reduction of postprandial glucose and insulin (not a subject of the guidance document under discussion) as well as the fermentability by the colonic flora. Otherwise, it would be confusing and misleading to the consumer that an effect that is considered as beneficial and officially acknowledged in one, but not another context by the same panel. |
|              | Re: Gastro-intestinal functions and considerations of other scientific expert panels | The views expressed by the NDA panel in this document on gut and immune functions are based on their criteria set up for the evaluation of Health Claims in the EU. This includes apparently also the views on whether an effect is a beneficial physiological effect. It should be noted that these views are not uniformly shared among scientists worldwide. This is in particular the case for body function claims (e.g. in the USA only disease risk reduction claims are evaluated following similar criteria). We would like to point out that it is not the (nutritional) science that has changed for these body functions, but it is the criteria that have changed into pharmacological and study-by-study stand-alone assessments. This needs to be clarified to the outside as otherwise, it falsely implies that it was industry who may have misled the consumer. Specifically, gastrointestinal function claims that are not directly disease-related or classical stool-related bowel functions are consolidated by science as well and supported by academic scientists worldwide, e.g. microbiota-associated functions. Moreover, there are earlier publications by scientific expert panels, e.g. the EU-funded PASSCLAIM project on gut and immunity (Cummings et al., 2004, Eur. J. Nutr. (Supp2) 43: II/118-II/173). This opinion is not taken into account but disagrees with the current document in several regards. Scientific reasons of the NDA panel are missing. Hence, views expressed by the NDA panel shall be backed up by scientific data and put into perspective that here same criteria for pharmacological and nutritional endpoints are applied. |
| ORGANISATION                  | CHAPTER TEXT     | COMMENT TEXT                                                                                                                                                                                                 |
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| Beneo Institute, Wormser Str. 11, D-67283 Obrigheim/Pfalz | General comments | L60: Which claimed effects are beneficial physiological effects  
Judgements whether effects are beneficial to health are fundamental; Art.13 applications focussed on the substantiation of cause/effect relationship, not the effect itself. Consequently, when an effect was hitherto dismissed as not beneficial, this was because the evidence for the effect itself was not provided together with the claim application.  
This differs in the current guidance document when the NDA is explicitly asked which claimed effects are beneficial physiological effects in general. If effects are dismissed out of the context of specific applications as non beneficial - as in this draft Guidance - the impact of such judgement is much more substantial and requires a scientific credence that is not provided in this document (lacks scientific references).  
A view of the NDA on "beneficial physiological effects" without valid scientific argumentation cannot be presented to the outside as absolute and must not appear as generally accepted scientific evidence  
L101: Assessing beneficial physiological effects  
There are several recent panel publications that have also been subject to peer review by experts in the field and have expressed different views on the relevance of certain effects than the NDA. One example is the prebiotic effect that is supported by a large scientific community which is simply not mentioned. Other examples are the views on fermentation, immunological and inflammatory markers as supportive evidence, only. For e.g. cholesterol, it took decades of intense scientific discussions to reach today’s level of acceptance as marker. However, even for cholesterol there is no common agreement whether it is total, LDL-, HDL-chol or their ratio what is more meaningful and all only give an indication for the probability to get a CV complication rather than to be predictive. Many subjects live well with high levels without CVD. Nevertheless, for risk/benefit balance, cholesterol is accepted as appropriate. We do not question this, but want to point out that it took more than one document to come to this stage: Products were on the market long before a consensus on cholesterol was achieved.
The cholesterol example also shows that consensus on such markers cannot be based on intervention studies alone. It requires an integrated approach including associations and observations from impaired and healthy status. Claims with smaller health implications that clearly demonstrate a physiological effect, but lack proof in a clinical sense (e.g. normal gut flora vs. pathogens) require a different approach to assess "beneficial". These are claims targeted for markers of possible physiological effects, but not aimed at a disease, i.e. authentic "health-related" messages. In these regards, the document lacks true guidance and compiles previous views, only. Solutions and explanations in an accepted scientific manner are needed.  
In order to allow progress in a way that consumers can benefit from advances in developing areas of nutrition - taking account of the nature of nutritional science as a holistic science in contrast to pharmocology as a targeted science - a broad scientific consultation among experts should be opened whether effects are beneficial. This should address EFSA’s gaps and respect other scientific consensus, references and peer views. Such an approach should find credible consensus for beneficial physiological effects based on expert knowledge and reflecting today’s possible standard  
L100: Assessment of benefit |
EFSA J. 2010 p.1673 defines benefit in relation to probability: How is ensured that this definition is consistently applied to HC as well, particularly "probability"? How is risk (consumer misleading) vs. benefit (probability of effect) balanced?

Scientific judgements within Europe need to be consistent, e.g. in the context of fibres there is a clear regulatory statement that fermentation is a beneficial physiological effect, whereas in this guidance document it is considered as supportive evidence, only.

Scientific judgement should consider other scientific opinions that have been peer reviewed by expert in the field.

Re: Fermentation as physiological effect
The Guidance documents so far considers fermentation only as supportive evidence in the context of the gastointestinal flora. However, fermentation is an acknowledged beneficial physiological effect for fibres in total as defined and endorsed in 2008/100/EC, Rec.5:

Fibre [...] has one or more beneficial physiological effects such as: decrease intestinal transit time, increase stool bulk, is fermentable by colonic microflora, reduce blood total cholesterol, reduce blood LDL cholesterol levels, reduce postprandial blood glucose, or reduce blood insulin levels.

The health relevance has been reviewed and confirmed by several panels, including recently EFSA in its document on DRVs on dietary fibre (EFSA Journal 2010; 8(3): 1462).

The current document confirms a beneficial effect for bowel regularity, explicitly transit time and stool bulk, and EFSA has in a different context also acknowledged the beneficial effects of lower total and lower LDL cholesterol. In order to be consistent through European Regulations as well as scientific opinions, the same should apply to all effects that in other contexts are beneficial, i.e. reduction of postprandial glucose and insulin (not a subject of the guidance document under discussion) as well as the fermentability by the colonic flora. Otherwise, it would be confusing and misleading to the consumer that an effect that is considered as beneficial and officially acknowledged in one, but not another context by the same panel.

Re: Gastro-intestinal functions and considerations of other scientific expert panels
The views expressed by the NDA panel in this document on gut and immune functions are based on their criteria set up for the evaluation of Health Claims in the EU. This includes apparently also the views on whether an effect is a beneficial physiological effect. It should be noted that these views are not uniformly shared among scientists worldwide. This is in particular the case for body function claims (e.g. in the USA only disease risk reduction claims are evaluated following similar criteria).

We would like to point out that it is not the (nutritional) science that has changed for these body functions, but it is the criteria that have changed into pharmacological and study-by-study stand-alone assessments. This needs to be clarified to the outside as otherwise, it falsely implies that it was industry who may have misled the consumer.
| ORGANISATION                  | CHAPTER TEXT | COMMENT TEXT                                                                                                                                                                                                 |
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| Beneo Institute, Wormser     | 3.2 Claims on| Specifically, gastrointestinal function claims that are not directly disease-related or classical stool-related bowel functions are consolidated by science as well and supported by academic scientists worldwide, e.g. microbiota-associated functions. Moreover, there are earlier publications by scientific expert panels, e.g. the EU-funded PASSCLAIM project on gut and immunity (Cummings et al., 2004, Eur. J. Nutr. (Suppl2) 43: II/118-II/173). This opinion is not taken into account but disagrees with the current document in several regards. Scientific reasons of the NDA panel are missing. Hence, views expressed by the NDA panel shall be backed up by scientific data and put into perspective that here same criteria for pharmacological and nutritional endpoints are applied. |
| Str. 11, D-67283 Obrigheim/Pfalz | gastrointestinal discomfort | Lines 175ff: We welcome the clarification of the panel that subjective perceptions are in principle be entitled for a beneficial physiological effect and to open the possibility to explore such effects in people suffering from functional bowel disorders. We have, however, comments regarding the request for "validated" subjective global symptom severity questionnaires in a stringent way: - So-called validated questionnaires are either designed to distinguish between diseases and sites of the intestine tract. These cannot be used for global symptoms, but may contain some useful elements. - The other questionnaires that claim to be validated are usually disease-specific and may not completely fit a particular study population. Even if IBS subjects are chosen for assessing an effect, often, sub-sets are the appropriate panel (e.g. with/without diarrhea; suffering in particular from bloating or abdominal pain etc.). In this case, a selection of relevant questions from well-established questionnaires would be more scientifically appropriate. In some cases, language adaptations are necessary in order to allow the assessment in panels in countries in which the typical scientific phrases are not common as well as their translation back into English. As another complicating factor, strict validation requires "responsiveness", i.e. means that a positive and negative control are available which - given the nature of functional bowel disorders as without defined clinical measurable symptoms, resembles a chicken/egg principle. For these reasons - there are certainly more - "validated" should to be attenuated/ameliorated into "scientifically appropriate questionnaires for the study panel and the disorder under investigation". As up to now, gastrointestinal disorders have been appreciated as beneficial physiological effect but without a positive causal-effect relationship - one reason being the use of a non-validated questionnaire. It can be speculated that the available "validated" questionnaires are inappropriate for studying the health effects of nutrients on gastrointestinal disorders. The EFSA should be more open in these regards to allow other scientific approaches as well. |
Irrespective that it is difficult to precise a normal GI microbiota composition, characteristics that such microbiota should have, can be defined as outlined already by Gibson&Roberfroid (1995):
- a predominantly saccharolytic energy metabolism
- high short chain fatty acid production
- little, if any peptolytic energy generation
- low ammonia, amines, phenols, putrefactants
- no formation of sulphides
- additional benefits from secondary metabolism
- absence of pathogenicity/toxigenicity
- low inflammatory properties
- no association with disease or impaired biosis, disturbed GI conditions associated with lower levels

Based on these characteristics and known properties, bifidobacteria and lactobacilli (possibly apart from other less researched saccharolytic microbes) are regarded as valid markers in the scientific community - recently (2010) endorsed by Gibson etal. and Roberfroid etal who state "The prebiotic effect is now a well established scientific fact. The more data are accumulating, the more it will be recognised that such changes in the microbiota's composition, especially increase in bifidobacteria, can be regarded as a marker of intestinal health".

Both publications have been subject of peer review and have thus been approved by many scientists. Neither are we aware that they have been challenged by other scientists in the research area (in fact the contrary is true). We thus query about the arguments why EFSA counteracts this apparently broadly accepted scientific evidence.

The prebiotic concept aims to support a stable flora that would be of benefit under situations where normobiosis is threatened (infections, antibiotic-associated diarrhoea, ageing, bottle-feeding); this just one aspect. It is certainly equally important that the healthy flora contributes to a gut content that carries a lower toxic burden to the host and may even be important for contributing to energy metabolism of the colonic epithelium. A focus on pathogens would only consider one (pathogenic or medical) aspect. A focus on pathogens would aim at disease risk reduction, whereas the use of beneficial markers would allow intended enhanced structure function claims.

A reduction of 1 log shall not be meaningful: In the context of foodborne pathogens, this opinion is puzzling as microbiologists are reluctant to define minimum effective doses for infectious microbes above 1. We query whether it would be ethical/possible to demonstrate an effectiveness that would be close to absence: The current proposal implies that a food ingredient needs to be as effective as a designed therapeutic antibiotic.

Overall, limiting beneficial functions of the gut microflora to pathogen reduction and thereby deny the importance of "just" harmful, innocuous and in particular beneficial microbes is not shared by a large community of scientific experts in the field and writes off at least two decades of peer reviewed published gut microbial research. This will
**SUMMARY**

Outcome of a public consultation on a draft guidance on the scientific requirements for gut and immune function claims.

| ORGANISATION             | CHAPTER TEXT                        | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| Beneo Institute, Wormser | 3.4 Claims on digestion/absorption of nutrients | lead to pre-empt the consumer to benefit from products that have been on the market for years. L232ff: Supportive evidence. EFSA views lower intestinal permeability, short chain fatty acid formation and pH as supportive evidence, only. The importance of an intact physical and functional barrier was emphasised for example by Cummings etal. (2004). There is also a common understanding among scientists that short chain fatty acids are important nutrients for the gut epithelium and systemic health. We also question why a lower intestinal permeability is not considered as exclusively beneficial? This implies that normal gut leakage has a physiological function instead of being considered as a weak point in the body’s barrier (reference?). Lines 255/256: What is specifically meant that an improved nutrient absorption is only considered beneficial where absorption is a limiting factor for the maintenance of adequate status of the nutrient? One can speculate that irrespective of dietary recommendations, subjects have sub-adequate intakes and any improved bioavailability can only be considered as positive for said individual.  

| Beneo Institute, Wormser | 4.1 Claims on the function of the immune system | The document considers that maintenance of a normal immune function is a physiological effect and incidences of infections or allergic manifestations together with concomitant changes in immunological parameters, are in principle appropriate. This appears to be plausible. Markers of the immune system alone may be considered as supportive. However, we also noted that several vitamins and minerals were positively viewed for effects on the immune system. An example is folate (ID 91). The only reference provided in the respective opinion relate to in vitro effects on T lymphocytes, i.e. markers that can only be considered as supportive. Another reference for the basis for the conclusion, that a cause and effect relationship has been established between the dietary intake of folate and a normal function of the immune system (EFSA Journal 2009; 7(9): 1213 has not been provided. The referenced opinions on folate as a nutrient by IoM and SCF did not look at this specific health function. Key point For transparency reasons, the guidance document should be supplemented with scientific judgements/justifications for those vitamin and mineral claims targeted at the immune function (and how cause and effect relationship was considered to be established.). Current references provide only markers that are supportive or are based on studies that cannot be considered as representative for the general population (e. g. vitamin E and immune defence and tuberculosis). Markers that are only considered as supportive in the present guidance document, were in the context of certain vitamins and minerals in fact the only scientific reference to support a claim (e.g. folate and immunity). This displays varying standards of assessment without rationale. To the consumer it is not obvious that the criteria applied to
| ORGANISATION                        | CHAPTER TEXT                  | COMMENT TEXT                                                                                                                                 |
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| Beneo Institute, Wormser Str. 11, D-67283 Obrigheim/Pfalz | 4.2 Claims on reduction of inflammation | Chronic inflammation is an area of growing concern. This concern is based on inflammatory markers that are also measured in disease status. In view of lacking better markers, it can be assumed that these are of the highest possible standards today and as such should be appreciated in order to allow advances in the respective area. If such markers are not acknowledged, no advances in research will be possible - to the disadvantage of the consumer. |
| Biofortis                           | 3.1 Claims on bowel function | In addition to outcomes which should be appropriate, the method of evaluation is important to guarantee the relevance of the data.  What methods are accepted for the evaluation of transit time, frequency of bowel movement or stool bulk? Is it interesting to introduce the notion of responder (i.e person who reports improvement)? Stool frequency and consistency are usually assessed using the Bristol Stool Scale. How data should be analysed? Considering stool consistency, should we use the raw data or create a quantitative score which represents the deviation to the normal (Normal = BSS score of 3-4)? |
### ORGANISATION | CHAPTER TEXT | COMMENT TEXT
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Biofortis | 3.2 Claims on gastrointestinal discomfort | Considering gastrointestinal discomfort and namely IBS, most of international guidelines recommend defining responder.  
* Is this relevant to substantiate a claim to define a responder or should we use a continuous score?  
* How a responder should be defined? Many authors recommend to use the SGA (Symptom Global Assessment) question. What is the opinion of the Panel on this particular point?  

Biofortis | 3.3 Claims on oral and gastrointestinal microbiota | Are molecular biology methods relevant to count microorganisms in biological samples or are cultures the only accepted method?  
What molecular biology methods are validated and accepted by the Panel?  

Biofortis | 4.1 Claims on the function of the immune system | Outcomes measures of a claimed effect related to the function of the immune system should include incidence of infection and appropriate evidence of a concomitant change in immunological parameters. Should these outcomes be assessed in the same clinical study or may they be assessed separately but studies presented together in the health claim dossier?  

British Nutrition Foundation | General comments | 2.1 Beneficial physiological effects Aspects of this section are helpful but others require more elaboration in my opinion. For example in the penultimate paragraph it would be helpful to have a discussion about disease as a gradual process compared to a clinical entity, in order to establish more clearly the transition between a healthy population and a diseased one for a particular functional effect. For example, people with the “functional bowel disorder” IBS are considered to be an appropriate study group for claims intended for the general population (lines 177-182) – are there other examples that could be provided?  

British Nutrition Foundation | General comments | Thank you for the opportunity to comment on this paper. It has been interesting to see a compilation of the approaches taken to date in the areas of gut and immune heath, and given the publicity EFSA’s work is attracting, I commend the NDA on finding time to initiate this particular piece of work. I am hopeful that this is the first step in opening up the discussion on complex areas such as these (and drawing in additional specific expertise) and at the same time providing further guidance that can be used by food operators working in this area. I am a public health nutritionist with a broad range of interests, rather than specialist in either microbiology or immunology, and my comments are made in this context.  
There appears to be a difference in the approaches taken in the various sections; for example, the bowel function section compared to later ones. Noting that these are particularly challenging areas to untangle, I suggest it would be helpful to the wider community if the level of detail in the text were to be made more consistent and justification for the approaches taken provided (e.g. as links to the relevant opinions, or via provision of key scientific references in the text). In other words, it would be helpful to understand why particular relationships were supported (perhaps as
| ORGANISATION               | CHAPTER TEXT                                      | COMMENT TEXT                                                                                                                                                                                                 |
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| British Nutrition Foundation | 3.1 Claims on bowel function                      | Compared with the extent of comment in later sections (e.g. 3.3), there is very limited substantiation here. For example, it would be useful to clarify what the normal range of bowel function is considered to be, and whether or not the implication here is that there is evidence to support the contention that constipation or indeed transit time or reduced faecal bulk are considered independent risk factors for specific diseases. |
| British Nutrition Foundation | 3.2 Claims on gastrointestinal discomfort         | I agree that the ability of a food to reduce gastrointestinal discomfort such as bloating or cramps may be regarded as beneficial to the individual but the justification for accepting this is not detailed. I would imagine that more detail on this would be helpful for those companies considering claims in this area. |
| British Nutrition Foundation | 3.3 Claims on oral and gastrointestinal microbiota | I am not a microbiologist (though I have had an interest in pro- and prebiotic research for some time) but was surprised to see the balance in the document regarding pathogenic bacteria versus reference to other (non-pathogenic) bacterial components of the gut flora, given that the latter make up the bulk of the gut flora most of the time (the build up of pathogens in the colon would usually presumably be very temporary as they would be eliminated via diarrhoea). Furthermore, I was under the impression that relatively small numbers of pathogens could be retained in the gut without ill effect and have assumed that this is related to the overall balance of the colonic flora among other things. I accept that it is not possible to define the exact numbers of the different bacterial groups that constitute a normal microbiota, which would in any case presumably vary considerably between individuals and with age for example, but for decades now, well respected experts in the field such as Roberfroid and Gibson have published, in peer reviewed journals, characteristics of a healthy gut flora derived from their own research and the research of others, which I recall include aspects such as SCFA production, low ammonia production, and characteristic energy metabolism among a number of others. I was surprised to see that no reference is made to these characteristics, which seem to have become the bedrock of the work conducted by expert scientists working in this well established field, or to the case studies) as well as why other proposed relationships were found to be wanting. |
Outcome of a public consultation on a draft guidance on the scientific requirements for gut and immune function claims

| ORGANISATION             | CHAPTER TEXT               | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                 |
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| British Nutrition Foundation | 3.4 Claims on digestion/absorption of nutrients | Lines 255-6: I suggest the text here is too broad as inadequate status tends to be concentrated in certain subgroups within a population e.g. older people, women of child bearing age, and I assume the situation is likely to vary from one European country to another depending on food policies, the level of dietary inequalities and the like. Iron is given as the example but presumably this could apply to other nutrients e.g. B12 in elderly people. |
| Cargill                  | General comments            | a) Line 107: “For function claims, a beneficial effect may relate to maintenance or improvement of function”. According to our understanding, this would imply that “a beneficial effect” would be an increase of a beneficial effect/marker: like, stimulation of beneficial bacteria for function claims on the intestinal microbiota or, stimulation of protective antibody titers for function claims on the immune system. It appears however, that this approach is not entirely in line with the view of the NDA panel – which is to our perception more focused on decreasing markers of “disease” rather than to improve beneficial functioning in the case for function claims. Such an additional distinction would make it clearer to differentiate function claims from disease risk reduction claims. To our perspective it is not clear from the document what/where exactly the distinction between the two types of claims lies (apart from the wording of the claims).  

b) Line 108-110: “For reduction of disease risk claims, ‘beneficial’ refers to whether the claimed effect relates to the reduction of a risk factor for the development of human disease (not reduction of the risk of the disease). And (…), risk factor is an independent predictor of risk and (…) relationship with disease is biologically plausible”. It is not clear whether a reduction in risk factor (e.g. decrease in pathogenic bacteria) is by its own sufficient to make a disease risk reduction claim or whether this should be accompanied by clinical evidence, e.g. less severity or duration of episodes of disease (like infections, allergies). |
We do acknowledge that this type of set-up: focusing on risk factors rather than on clinical outcomes is of relevance when considering chronic diseases (like diabetes, cardiovascular disease, cancer). However, in case when clinical outcomes can be measured (duration/severity of illness) one might question whether such an association with a risk factor is still necessary.

| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Cargill      | 3.1 Claims on bowel function | a) Line 167-168: Outcome measures: “include transit time, frequency of bowel movements, stool bulk”. Suggestion to include: consistency of the stools. Consistency of the stools is related to the water content, which is around 70-80%. Constipated subjects generally pass harder stools with a water content of less than 70%. In general, as daily stool weight increases, stools become softer and less well formed. Particularly, it is the hardness and dryness of stools that is thought to cause discomfort on defecation (Cummings et al. 2004 Eur J Clin Nutr 43: II/118-173). Consistency of the stools (e.g. increased softness) could be considered as an outcome measure. Consistency is usually recorded in a diary after visual inspection (Bristol Stool Form Scale) or measured by physical analysis of water content.

b) Suggestion to consider subjects with functional constipation as appropriate study group.
Functional constipation has been defined according to the Rome III Diagnostic Criteria on the basis of occurrence of straining, lumpy or hard stools, number of defecations per week, etc. Segmental contraction and propulsive activities are affected by endocrine, metabolic and environmental factors. Frequency of defecation is high in infancy and becomes less frequent during ageing. Environmental influences affecting colonic motility are stress, eating patterns/dietary intakes and physical activity. Due to the many influential factors, high inter- and intra-individual variation exists in the levels of colonic motility (Wyman et al. 1978 Gut 19: 146-150). Episodes of low motility and in some cases of (temporary) incontinence can occur also in healthy people. Functional constipated subjects could be considered as appropriate study group to support claims on bowel function intended for the general population. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Cargill      | 3.2 Claims on gastrointestinal discomfort | Line 175-176: Outcome measures include “validated subjective symptom severity questionnaire”. Symptom severity questionnaires are targeted towards patients, e.g. dyspepsia and irritable bowel disease. The discriminate validity of the Functional Digestive Disorders Quality of Life questionnaire (FDDQL) has been shown by the more severe the functional digestive disorder appears to be, the more impaired the quality of life is. Also, validity has been supported by the correlation found between FDDQL and SF-36 questionnaire scales for more general measures of well-being (Chassany et al. 1999 Gut 44:527-533). For other questionnaires, e.g. Gastrointestinal Symptom Rating Scale modified for IBS patients (GSRS-IBS), validity has been tested against several disease specific health-related quality of life questionnaires showing good correlation (incl. FDDQL) (Wiklund et al. 2003 Scand. J. Gastroenterol. DOI: 10.1080/00365520310004209). It is however unclear yet what the criteria are for the NDA panel to consider a questionnaire to be appropriately “validated” to substantiate claims on gastrointestinal discomfort in healthy people. |
| Cargill      | 3.3 Claims on oral and gastrointestinal microbiota | c) Line 226: “For claims related to “maintaining normal defense against pathogens in the gastrointestinal tract” (which would constitute a function claim), the text indicates that similar outcome measures should be applied, e.g. (...) reduction of numbers of pathogenic microorganisms (...) or toxins (...) as well as clinical outcomes (e.g. number and duration of episodes of infection, etc.). This would imply that the same (level of) evidence is necessary for function claims and disease risk reduction claims. This is not clear. Therefore we would emphasize the importance of differentiating between the evidence needed for function claims and disease risk reduction claims for the gastrointestinal microbiota. In this respect, increasing the levels of health promoting bacteria could be considered a beneficial physiological effect to substantiate a function claim related to the improvement of normal defense against pathogens in the gastrointestinal tract. d) Line 211: The “non-exhautive list of groups of microorganisms that are considered pathogenic or toxicogenic”. Food-borne pathogens do normally not reside in the gastrointestinal tract of the general healthy population. Would pre-screening for individuals who are carriers for these organisms still be considered as representative for the general population? Would the NDA consider it acceptable to test in different regional populations where food borne illness is more prevalent despite differences in the background diet of such regions when compared to Western diets? e) Line 232: For claims “to maintaining normal defense against pathogens in the gastrointestinal tract”, effects on “intestinal permeability can be assessed in human studies, such outcomes are themselves insufficient for the substantiation of the claim. In order for a pathogen to invade and translocate to extra-intestinal tissues, it has to pass the epithelial barrier. The intestinal lining epithelial cells serve as a barrier that prevents invasion and translocation of microorganisms and is modulated by specific tight junctions present between epithelial cells and regulate paracellular permeability. The integrity of the intestinal barrier is essential for human health and impacted by stress, chronic inflammation and the use of drugs like antibiotics. In this respect, strengthening the epithelial barrier function could be considered a beneficial physiological effect to substantiate a functional claim related to the improvement of normal defense against pathogens in the gastrointestinal tract. The Cr-EDTA test as an example is considered a valid marker to assess intestinal barrier function. NOTE: the our knowledge the Draft |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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|              |              | guidance on gut and immune claims does not address the issue of oral microbiota (as given in the above toolbox of this webpage). |
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| Cargill      | 3.3 Claims on oral and gastrointestinal microbiota | a) Line 186-188: In brief, the evidence available today is not considered convincing to the NDA panel that “increasing the number of specific microorganisms or any group of microorganisms is in itself a beneficial physiological effect”, whereas “reducing the numbers of specific pathogenic microorganisms is”. According to our interpretation however, a reduction in the levels of pathogens/toxins would not contribute to the maintenance or improvement of a function, but rather as earlier stated, serve as a risk factor to indicate to reduce the risk for developing disease (and hence referring to a disease risk reduction claim). We would therefore suggest considering an increase in the levels of health promoting bacteria a beneficial physiological effect to substantiate a function claim on the gastrointestinal microbiota (e.g. maintenance of normal defense against pathogens in the gastrointestinal tract).

Increasing the levels (/activities) of health promoting bacteria (> 1 log cfu/g and sustained over time), mainly of the genus Bifidobacterium, have been shown to exert beneficial physiological effects in the human body. This is demonstrated by the considerable body of evidence on the differences in the composition of the microbiota (high levels of bifidobacteria) between formula fed and breast fed infants (the latter being considered as having a ‘healthy’ microbiota). Amongst the many functions bifidobacteria and lactobacilli have, is the creation of a non-permissive environment for pathogenic bacteria in the large bowel. This can be induced by metabolic shifts (production of anti-microbial substances, nutrient depletion) and/or occupying ecological niches of virulent micro-organisms restricting their abundance in the colonic microbiota (Servin, 2004 FEMS Microbiology Rev. 28: 405-440).

In addition, healthy bacterial groups are characterized by a beneficial metabolism to the host through their SCFA formation (creating a saccharolytic environment in the gut), absence of toxin production, formation of defensins and vitamin synthesis. Also, their cell wall is devoid of lipopolysaccharides or other inflammatory mediators (i.e. mainly Gram positive) (Roberfroid et al. 2010 Brit J Nutr 104: S1-63) creating a more beneficial environment in the intestinal tract.

b) Line 190-200/203: (...) The NDA panel considers a reduction in presence of pathogenic microorganisms (...) toxins (...) a beneficial physiological effect (...) for substantiating disease risk reduction claims. A decrease by less than 1 log cfu/g value is not considered meaningful and (...) decrease should be sustained over time.

The NDA panel considers a reduction in presence of pathogens of less than 1 log cfu/g not meaningful however it is unclear whether such changes are against baseline or placebo interventions. Changes in the levels of pathogenic microorganisms of this magnitude upon dietary interventions have been observed in some cases (Rafter et al. 2007 AJCN 85: 488-496) however, the exact cut-off at which level beneficial effects can be assumed is according to our knowledge unclear. In addition, the numbers of persons being colonized with pathogenic microorganisms after intervention in the study group against placebo could be an outcome of interest as well for predicting the risk of disease.
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Cargill      | 4.1 Claims on the function of the immune system | a) Line 268-271: Outcome measures “include the incidence of infections for claims related to defense against pathogens”. And, “incidence of allergic manifestations for claims related to response to allergens”.

The use of the term “incidence” as an outcome measure is not clear. Particularly, given that the text (general considerations, page 5 line 2) states that “for reduction of disease risk claims the claimed effects relates to the reduction of a risk factor for the development of a human disease (and not reduction of the disease)”. Incidence is a measure of the risk of developing a new condition (disease) within a specified period of time. This refers, however, to the development of disease itself.

b) Line 276-278: For claims on the ‘functioning of the immune system’ and ‘risks for allergic manifestations’ the text states that “this needs to include physician diagnosed allergies, immunologic nature of the allergies to be corroborated with appropriate measures. Clinical as well as laboratory measures (…)”.

As is done in the case of possible outcome measures for infection (severity of symptoms, episodes of infection, etc.) with a concomitant reduction in a risk factor (e.g. pathogens) we would be supportive of including such advice also for allergic manifestations, e.g. on potential outcome measures for infection (severity of symptoms, episodes of infection, etc.) with a concomitant reduction in a risk factor (e.g. pathogens) as well as acknowledged risk factors (concomitant change in immunological parameter). An example for a clinical measure could be the SCORing Atopic Dermatitis scale (SCORAD) which is a clinical tool for assessing the severity of atopic dermatitis.

c) Line 279-286: For claims on ‘functioning of the immune system’ higher vaccination responses is listed as a beneficial outcome as measured by increased numbers of individuals achieving protective status or higher increments of antibody titers. Many vaccines are multi-valent and individuals may respond to some of the included antigenic variants (ex. Flu strains) and not others. It is suggested that an increase in the number of antigenic variants to which the individual responds should also be considered a beneficial outcome as regards resistance to infection.

Cargill | 4.2 Claims on reduction of inflammation | Line 293-304: We would suggest the NDA panel to further provide guidance on potential markers of chronic inflammation to be considered of providing supportive evidence for claims substantiation in this area. Given the importance of chronic inflammation in the etiology/development of chronic disease (e.g. associated to the obese phenotype) evidence in this field is rapidly emerging and for some markers at an advancing stage.
## Outcome of a public consultation on a draft guidance on the scientific requirements for gut and immune function claims

| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
|--------------|--------------|--------------|
| Chr. Hansen A/S | General comments | Chapter 2.2 Studies/outcome measures appropriate for substantiation of claims  
Page 5, line 151-2: Extrapolating between populations:  
Studies should be performed in a study group representative of the population group for which the claim is intended (page 5, line 151-2). Can results from e.g. infection studies in children (who have a higher incidence of infection) be used as evidence to claim beneficial effects in the general (healthy) population? Can results from other subpopulations with higher infection risk such as elderly, athletes or people under stress be used to extrapolate to the general population? |
| Chr. Hansen A/S | 3. Gastro-intestinal tract | Page 6, line 165-6, 174: Duration of beneficial physiological effects:  
According to the draft guideline changes in bowel function and reduction of GI discomfort are considered beneficial physiological effects (page 6, line 165-6, 174). Should these changes be demonstrated in short term studies (e.g. 4 weeks treatment), or will it be necessary to show long term sustained effects (e.g. 6 months), and/or to perform studies with short term repeated cycles of use (as described in CPMP/EWP/785/97) in order to obtain a GI health claim? |
| Chr. Hansen A/S | 3.2 Claims on gastrointestinal discomfort | Page 6, line 175-6: Validated tools:  
According to the guideline endpoints should be measured with validated tools (page 6, line 175-6). If tools validated in an IBS population are modified as necessary for use in the general population, will these be considered sufficiently validated?  
Page 6, line 177-182, and page 6, line 175-6: Outcome measures for GI discomfort:  
According to the draft guideline an IBS population can be used as study population for claims intended for the general population (page 6, line 177-182). Furthermore, gastrointestinal discomfort should according to the guideline be measured with validated subjective global symptom severity questionnaires (page 6, line 175-6).  
For IBS studies, the recommended primary endpoint is ‘satisfactory relief’ or ‘adequate relief’ and not symptom scores (refer to Rome III, The Functional Gastrointestinal Disorders. 3rd edition 2006 and CPMP/EWP/785/97). Will a global assessment of relief of discomfort be acceptable for substantiation of a claim in the general population? |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Chr. Hansen A/S | 3.3 Claims on oral and gastrointestinal microbiota | Page 7, line 198-9: Gastrointestinal microbiota: A microbiologically relevant reduction of pathogens should be sustained over time (page 7, line 198-9). How should a sustained reduction over time be demonstrated (time frame for sustained reduction and/or number of repeated measurements)? Page 7, line 200: Meaningful decrease in pathogens Generally a decrease of less than 1 log value is not considered meaningful (page 7, line 200). Does that mean that a decrease of 1 log value or more is considered meaningful? Is it possible to provide a reference for assessing 1 log value as relevant? Page 7, line 228-32: Duration and severity of infections: Which methods are considered appropriate to assess duration and severity of infections (page 7, line 228-32)? Must all infection assessments (presence, severity, duration) be performed by a health care professional with the consequence that all subjects must be in contact with a health care professional on a daily basis as soon as symptoms appear? Would it be possible to describe this in a section specifically relating to the immune system? |
| Chr. Hansen A/S | 4.1 Claims on the function of the immune system | Page 8, line 263: ‘Maintain’ or ‘improve’ claims related to the immune system: The draft guideline states that for functional claims a beneficial effect may relate to maintenance or improvement of a function (page 4, line 107). Regarding claims on the function of the immune system only ‘maintaining a normal immune function’ is mentioned as a beneficial effect (page 8, line 263). Does that mean that only ‘maintain’ claims will be accepted for immunity? Or can a claim for ‘improvement of immune function’ be accepted? Can a study demonstrating stimulation of protective antibodies after a vaccine (page 9, line 285-286) substantiate a claim such as ‘improves function of the immune system’? Page 8, line 268: Incidence of infections: Which methods are considered appropriate to assessing incidence of infection (page 8, line 268)? Will clinical study data based on incidence of infection self-reported by subjects be accepted? Or must presence of infection be evaluated by a health care professional (as for allergies page 8, line 275-6)? Is it necessary to confirm the presence of infection by collecting a sample and determine the pathogen (i.e. virus type for UTI)? Page 8, line 268-270: Lowering of numbers of pathogens: Is it necessary to show both reduced incidence of infection and reduction in number of pathogens in e.g. the upper respiratory tract (or urinary tract) for a function claim related to defence against pathogens (page 8, line 268-270)? How will it be possible to show a reduction of pathogens related to respiratory infections as the general population does not have a basal level of pathogens (e.g. rhinovirus) that can be reduced? Which methodologies should be used to show lowering of pathogens related to infections (e.g. upper respiratory tract, urinary tract, GI tract etc.)? Page 8, line 268: Infection study: Measuring an outcome such as incidence of infection (page 8, line 268), can be performed in infection studies based on natural exposure to pathogens by free-living subjects however, such a study requires large numbers of subjects and is very season dependent as infection incidence varies a lot. Will studies with an experimental exposure (e.g. inoculation of all subjects with rhinovirus cold) be accepted as substantial evidence for a claim related to defence against pathogens? |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Page 8, line 271-3: Immune markers and clinical endpoints:  
The draft guidance states (page 8, line 271-3) that in addition to a reduction in infection incidence an appropriate evidence of a concomitant change in immunological parameters needs to be provided. Showing both clinical effects and effects on immune markers in the same study will lead to very complex study designs. Can a health claim be approved if based on two different studies showing effects on immune markers, and clinical endpoints, respectively?  
Which immunological parameters (ref page 8, line 273) are considered appropriate for evidence of an effect on the immune system?  
Page 9, line 279-286: Vaccination studies:  
The draft guideline (page 9, line 279-286) states that 'stimulation of protective antibody titres could be used to substantiate a health claim on the function of the immune system related to defence against pathogens'. Does that mean that in the specific case where a vaccination model has been used to demonstrate effects on the immune response to a challenge, a study demonstrating clinical efficacy (e.g. reduced incidence of infection, and a change in immunological parameters) is not required, but the claim can be substantiated solely on evidence from a vaccine study?  
Chr. Hansen A/S  
4.3 Claims on reducing a risk factor for infections or allergy  
Page 9, line 312: Risk factor for infections:  
In the draft guideline only the presence of pathogens is mentioned as a risk factor for claims related to infections (page 9, line 312). A low level of secretory IgA has in some studies been associated with an increased risk of respiratory infections (see e.g. Gleeson M. Mucosal immune responses and risk of respiratory illness in elite athletes. Exerc Immunol Rev 2000;6:5-42). If a significant increase in sIgA levels can be shown, will this be considered sufficient to claim 'reduce risk of infection' because the risk factor 'low level of sIgA' is reduced?  
Committee for Human Medicinal Products (CHMP), European Medicines Agency  
3.1 Claims on bowel function  
Line 167 Measurements of transit time (radiological assessment) as outcome are questioned. It is recommended that only stool frequency and stool consistency are measured as outcome.  
Committee for Human Medicinal Products (CHMP), European Medicines Agency  
3.1 Claims on bowel function  
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| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Committee for Human Medicinal Products (CHMP), European Medicines Agency | 3.2 Claims on gastrointestinal discomfort | Line 170 and 177  The inclusion of pain as something associated with food in absence of a IBS diagnosis is questioned. Likewise, it is unlikely that a dietetic product would be efficacious in relieving pain. Along the same lines, IBS should not be included among possible claims, but central to the diagnosis of IBS is abdominal pain. IBS is not physiological and not a risk factor for disease. Subjects with IBS are according to definition patients and not healthy population which should be the target for these products. The recommendations are in addition in conflict with the current European guideline on drug development in IBS. Line 175  One could question the recommendation for a GSA endpoint. (This endpoint for studies in IBS has been heavily critised and was the focus of a meeting arranged by the ROME foundation in 2009 which included regulators (incl EMA), academia and industry. A follow-up conference on outcome measures in IBS is planned in 2011 (again EMA participation is expected).) However, for a physiological claim for a food supplement, the endpoint could perhaps be used. |
| Committee for Human Medicinal Products (CHMP), European Medicines Agency | 3.3 Claims on oral and gastrointestinal microbiota | Line 186 and 192  We would tend to disagree. Probiotics are commonly used to reduce the frequency of antibiotic-associated diarrhea and there is some scientific support for this. In our opinion, AAD is more relevant for this document compared with the claim of reducing the risk of (clinical) GI infection by reducing number of pathogens in the colon. When does an infection become an infection? Line 191  Can pathogenic bacteria be reduced by food supplements? Ev reword to increase proportion of non-pathogen bacteria (probiotics) Line 218  Helicobacter pylori does not belong to this list. It is difficult to imagine that any food could affect this bacteria located as sole surviving microorganism in the acidic stomach environment. |
| Committee for Human Medicinal Products (CHMP), European Medicines Agency | 3.4 Claims on digestion/absorption of nutrients | Line 240  Considering the wide range in prevalence of lactose intolerance I would suggest rewording the sentence accordingly, e.g. "between 4-60% of the population...". There is an "of" in Line 241 that should be deleted. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Dairy & Food Culture Technologies | General comments | “Applications for claims that specify target groups other than the general (healthy) population are the subject of ongoing discussions with the Commission and Member States with regard to their admissibility.” What do you mean by "other than the general (healthy) population"? Does this mean non-"healthy" people? e.g. people with symptoms, but perhaps not a diagnosed disease? Or people with a disease whose symptoms could be helped with a food? |
| Danisco | 3.1 Claims on bowel function | Changes in bowel function within the normal range might be considered beneficial. This statement would be difficult to defend as a change from normal to normal would not be expected to have an additional health benefit. This way of thinking is in line with opinions released by EFSA earlier. Changing bowel functions from out side the normal range to inside the normal range could be considered beneficial. |
| Danisco | 3.1 Claims on bowel function | “Changes in bowel function within the normal range might be considered beneficial physiological effects.” What is meant with “within the normal range”? Should this be interpreted as changing from normal to normal is a benefit? |
| Danisco | 3.1 Claims on bowel function | Dialogue. An opportunity for a dialogue between EFSA and the applicant, before submission of the dossier, would allow the applicant to produce a dossier of high quality. High quality dossiers should be beneficial to EFSA, as less time would be needed for review of the dossier. - In part 2 of the health claims dossiers, information on Stability and Bioavailability should be given. It would be useful if EFSA would issue a simple guidance on how stability and bioavailability should be recorded, similar to what EFSA has provided for the Characterization of microorganisms. Rows 142-150 discuss design and quality of studies. A generic guidance to such studies would be useful, e.g. is only double-blind, placebo controlled cross-over studies considered pertinent? How many subjects are needed in a study to be considered a pertinent study? Can a claim be based on one study? Or should there be at least two studies, one that show and effect, and a 2nd study to confirm the effect? - Rows 151-156 discuss study groups. What constitutes “general population”? Can results in a study group with children of 4-10 years, be extrapolated to a “general population”? |
| Danisco | 3.3 Claims on oral and gastrointestinal microbiota | The document has a very black and white view or "pathogenic and toxigenic" microbes. It does not take into account that certain "pathogens" at low levels my have a beneficial function. Their levels and activity should maybe be controlled rather then eradicated. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Danisco      | 3.3 Claims on oral and gastrointestinal microbiota | Clostridium difficile can be toxigenic or not. The non-toxigenic strains are probably not or much less pathogenic than the toxigenic strains. Such a distinction should be made, similar as for Clostridium perfringens. |
| Danisco      | 3.3 Claims on oral and gastrointestinal microbiota | Generally, a decrease by less than 1 log value is not considered meaningful. That maybe true although this would be more a rule of thumb rather than a a statement based on scientific evidence. More over, a reduction by 1 log or more does not have to be a health benefit either. Certain "pathogenic or toxigenic" strains are present as part of the normal microbiota at low levels (normal range); reducing those levels by 1 log or more is unlikely to have a health benefit. On the other hand, an ill person carrying high levels of a pathogen may not be helped by a reduction of 1 log. More relevant would be to reduce pathogens to a level (break point) below where they can be expected not to contribute to disease. That will be different for different pathogens, patient groups, etc. and it may not even be know for most pathogens. But that would be the only way to say that a reduction is meaningful from a health perspective. A reduction below a certain level is meaningful, not the magnitude of the reduction as such. |
| Danisco      | 3.3 Claims on oral and gastrointestinal microbiota | Row 200 discusses microbiologically relevant reduction of pathogens. The decrease by at least 1 log value is not supported by any scientific data. The term is too general and should be more specific to the type of microorganisms: Clostridium difficile vs toxicogenic Clostridium difficile. Furthermore, a reduction may be irrelevant if initial levels are high; the subject may still be colonised with sufficient pathogens to become/remain ill. On the other hand, when levels are already very low, further reductions may not have any relevance either. What really counts is reducing levels of potential pathogens to levels below where they can cause disease; this probably is pathogen and target dependent, and may not even be known. Finally, EFSA does not consider that "potential pathogens" may have a beneficial function at low levels. |
| Danisco      | 4.1 Claims on the function of the immune system | line 286 "heath" should be "health" |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Danisco      | 4.1 Claims on the function of the immune system | 4.1 Claims on the function of the immune system |

Rows 287-292 discuss markers of the immune system. A number of markers are listed that is considered, by EFSA, as supportive evidence. What is needed, according to EFSA, to validate such a marker so that the marker could be used as an indication on a health benefit, such as the antibody titre discussed in the paragraph above.

Line 286; health should be health

‘For that reason vaccines are usually produced with adjuvants, so that the majority of recipients of vaccines attain sufficient titres to be protected. Stimulation of protective antibody titres could be used to substantiate a health claim on the function of the immune system related to defence against pathogens.’

It is uncertain that a further increase in antibody titre provides more protection. Even if it would, it would need to be indicated how much; which is probably vaccine dependent.
| ORGANISATION                | CHAPTER TEXT      | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| Danish Dairy Board Brussels | General comments | 1) We understand that the food/constituent must be sufficiently defined and characterised. According to this we assume that this means that the different strains can be taxonomically classified to strain level and to belong to a specific species by biochemical or molecular genetic methods. In addition, the number of bacteria of each of the individual strains must be quantitated in the product used in the intervention trial. It is also preferable if the strains have been identified to survive the transport through the gut and thus can be found in faecal samples.  
2) Composition of food/constituent in pertinent studies  
From the EFSA document prepared for the conference in PARMA June 1 2010 we understand that pertinent studies must be done with the food/constituent that the claim is made. For products containing multiple strains we assume this means that the studies have to be done with the combination of the different strains and not with one strain at a time. It is those studies with the appropriate combination that are the pertinent studies and the basis for a claim application  
3) Additional studies e.g. on mechanisms  
Studies on mechanisms behind an effect can be added to an application. This means that if studies have been done on the combination of strains in model systems or if such studies have been done on the strains separately and not the combination those studies can be used to point out a possible mechanism. However those mechanistic studies are not compulsory for the application and approval of a health claim.  
4) A rational for the role of each constituent relevant to the claimed effect should be provided  
Here we assume the following issues are rationales for the use of multiple probiotic strains e.g. Lactobacilli and Bifidobacteria have different niches in the gut environment. Meta analyses have shown that some individual strains have effects and also generally combinations have been seen to have effects. In addition to this we assume that EFSA may be interested in studies on individual strains, however since the strains may influence the properties of each other the studies on individual strains are of less importance.  
Concerning studies/outcomes measures appropriate for substantiation of claims we would like a clarification or examples on lines 153-156. Please give some examples on requirements that are need to make an extrapolation from the study group to the target group  
Concerning claims on bowel function and gastrointestinal comfort the guidelines are clear and we find them in line with general opinions among scientists on what is beneficial and can be studied. |
| Danish Dairy Board Brussels | 3.1 Claims on bowel function |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
### Danish Dairy Board Brussels

**3.3 Claims on oral and gastrointestinal microbiota**

Concerning claims on gut microbiota and immune function we have a general remark i.e. we think that true endpoints looking at reduction in incidence, duration and severity of infections needs to be evaluated as very important factors for health claims. In the sections describing this area, possible markers are given a very high impact. We want to point out the many markers in this area are still not very clearly defined and established. By giving the markers a too strong impact on the possibility to get claims and giving the true endpoints only a secondary importance we are worried that this will considerable influence the possibility to get claims despite the fact that good intervention studies have been done.

Concerning the gut microbiota the panel considers reduction of the number of pathogenic microorganisms a beneficial physiological effect. We agree that this can be the case, however it is common that healthy persons are carrying pathogenic or potential pathogenic microorganisms without any symptoms. It is thus questioned by us and in the scientific society whether the reduction of pathogenic organisms is a good marker for risk reduction. We question the line 203-208 stating that the reduction in incidence or duration of infections is not an evidence of risk reduction but that the reduction of pathogenic organisms is. We are in strong favour that the true endpoints showing the reduction in incidence and duration should be evaluated as very strong evidence for the influence of probiotics on infection. We therefore also think it is reasonable to give a possibility for claims on reduction of risk for infection based only on true endpoints and not always with a requirement on immune markers or numbers of pathogenic organisms. Of cause this requires good placebo controlled double blind randomised with significant results, as is thru for all claims.

### Danish Dairy Board Brussels

**4.1 Claims on the function of the immune system**

Concerning claims on gut microbiota and immune function we have a general remark i.e. we think that true endpoints looking at reduction in incidence, duration and severity of infections needs to be evaluated as very important factors for health claims. In the sections describing this area, possible markers are given a very high impact. We want to point out the many markers in this area are still not very clearly defined and established. By giving the markers a too strong impact on the possibility to get claims and giving the true endpoints only a secondary importance we are worried that this will considerable influence the possibility to get claims despite the fact that good intervention studies have been done.

### Danish Dairy Board Brussels

**4.2 Claims on reduction of inflammation**

Concerning claims on reduction of inflammation we would like a clarification or examples on lines 301-304. Please give some examples on what inflammatory markers that are acceptable for claims on inflammation reduction.
| ORGANISATION | CHAPTER TEXT         | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| DANONE       | General comments     | Danone warmly welcomes EFSA’s initiative to provide additional guidance to applicants for the substantiation of health claims. We however acknowledge that the draft guidance is not intended to be an exhaustive list of acceptable beneficial effects and studies/outcome measures and is mostly based on the already issued evaluations. The draft guidance therefore does not fulfil the industry need to have clear views of beneficial effects/studies and outcome measures. The industry requests a consultation process between the panel and either industrial experts or scientific investigators before the beginning of a scientific programme or a dossier submission. The guidance does not consider physiological specificities of newborns for which functions, like digestive processes, intestinal barrier function and immune function have not been developed to their full capacity. Danone needs a clear statement in the guidance that promoting the normal development/maturation of these functions is considered a beneficial physiological effect and that the development of these functions in breastfed infants can be taken as a reference. We would welcome clear guidance regarding the age categorization in infants/children. For adult populations, clarification is required on the definition of appropriate study groups: - Can populations with symptoms (glucose intolerance, insulin resistance, hypertension, allergy,…) be part of the general population? - Would a study be pertinent when performed on subjects with a pathology unrelated to the claimed effect but which increases their susceptibility to the disease/function impairment mentioned in the claim (e.g. a product effect on respiratory infection in a subject with asthma)? The functional benefit of a food in the area of gut health and immunity is very complex because one specific function can be evaluated by several appropriate outcome measures. Further clarification is needed on how the Panel is evaluating the overall consistency of the food effect. The hierarchy of evidence is already published (EFSA journal 2007 530, 1-44), but we need clarification on how the panel is weighing evidence obtained in human intervention trials: - How does the panel consider a study with a neutral main outcome but with positive statistically significant secondary outcome measures that are appropriate for claim substantiation? - How is the panel assessing the relevance of the magnitude of the effect taking into account that we are dealing with food for general population? - Is a single high quality human study sufficient to substantiate a claim if supported by other evidence such as mechanisms, epidemiological data or similar findings with other similar foods? - Is a meta-analysis designed to substantiate a claim considered more pertinent than the individual studies? We believe that scientific data supporting the biological plausibility of the effect has to be taken into account in the weighing of the evidence, even if mechanisms of actions are not elucidated. The importance of biological plausibility hardly appears in the panel’s opinions on gut health and immunity area whereas they are meaningful parts of the overall consistency of the food effect. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| DANONE       | 3.1 Claims on bowel function | - We ask for additional clarification on the following aspects to allow applicants to understand EFSA’s requirement for demonstrating a beneficial effect of food on bowel function:  
- In 163-165: Diarrhoea and constipation are both part of the spectrum of bowel habit and are equally important concerns at the population level. Diarrhoea is associated with shorter transit times, more frequent bowel movements, increased faecal bulk and softer stools and is the counterpart.  
- Can the Panel confirm the inclusion of diarrhoea to the overall description of bowel function?  
- Can the panel define what is the “normal range” of normal bowel function?  
- In 162-165: For infants and young children (from 0 to 3 years old), functional constipation and functional diarrhoea are gastrointestinal problems that commonly occur. Constipation is more common in formula fed infants compared to breast fed infants and there is a difference in transit time between breast- and formula fed infants.  
- Can the Panel please confirm that the change in bowel function is a relevant physiological effect for infants and young children and whether a change in bowel function towards values that are seen in breastfed infants can be interpreted as changes within the normal range?  
- In 167-168: For adults and children (from 3 to 18 years old), no information is given on population(s) which is/are considered as appropriate study group(s).  
- We therefore ask confirmation on the appropriateness of the following study groups for claims on bowel function in the general population: children and adults with functional constipation, children and adults with functional diarrhoea, subjects with colonic diverticulosis and elderly people.  
- In addition can the Panel please confirm whether people with alterations of a single appropriate outcome measure (e.g. people with slow transit time or with low bowel movement frequency), whatever their health condition, are considered as an appropriate study group?  
- We would like to have the confirmation that the Panel refers to the accepted diagnostic criteria for functional bowel disorders (i.e. generally accepted diagnostic criteria such as Rome criteria) for defining the different sets of appropriate populations.  
- In 167-168: Other generally accepted list of appropriate outcome measures can be used for bowel function. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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|              | - Does the panel accept measures such as stool consistency (Bristol Stool form scale for example), bowel movement difficulty and feeling of incomplete evacuation, measured with validated questionnaires? |
|              | - Validated overall subjective assessment of bowel habits (e.g. satisfaction with bowel habits) is another generally accepted method to assess bowel function. Does the panel accept validated overall subjective assessment of bowel habits as appropriate? |
|              | - Considering the multiple outcome measures associated with bowel function, we ask the Panel to specify the number of outcome measures needed to demonstrate a beneficial effect on bowel function (e.g. is a change of one single outcome measure sufficient to substantiate an effect on bowel function)? |
Outcome of a public consultation on a draft guidance on the scientific requirements for gut and immune function claims

| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
|--------------|--------------|--------------|
| DANONE       | 3.2 Claims on gastrointestinal discomfort | - We welcome the confirmation of three important considerations for claim on gastrointestinal discomfort: - In 174: reducing GI discomfort is considered as beneficial physiological effect. - In 175-176: validated subjective global symptom severity questionnaire(s) are appropriate outcome measures. - In 179-182: the continuum of GI discomfort between healthy people and IBS is recognised and in consequence, scientific evidence obtained in IBS are relevant for a claim in the general healthy population. - We believe that clarifications on the following points will help to improve the understanding of EFSA requirements for claim on gastrointestinal discomfort: - In 170-173: For infants and young children (from 0 to 3 years old), symptoms of gastrointestinal discomfort frequently occur as the various gastrointestinal functions are not fully developed during the first months of life. The symptoms will cause discomfort for the infant and will be a source of concern for parents, which can result in distress, lack of sleep, fatigue and feelings of despair. - In 174: Does the panel consider that reducing gastrointestinal discomfort is a beneficial physiological effect for infants and young children? - In 175-176: Does the panel consider the frequency and/or severity of colics (using generally accepted diagnostic criteria such as Rome) as appropriate outcome measures of the claimed effect in this population? - In 170-173: For children (from 3 to 18 years old), no information is given with regards to the appropriate study groups. Does the panel consider that IBS children are also considered as an appropriate study group for generally healthy children? Does the Panel consider that children with functional abdominal pain are also considered as an appropriate study group for generally healthy children? - In 175-176: Other generally accepted measures apart from severity can be used to evaluate gastrointestinal discomfort (e.g. symptom frequency questionnaires, overall assessment of GI discomfort/comfort, adequate or satisfactory relief of IBS symptoms; specific dimensions of quality of life questionnaires): Does the panel confirm that those kind of questionnaires are acceptable? Will the panel accept new appropriately validated questionnaires developed in the coming years? In 175-176: Digestive symptoms (abdominal pain, bloating, flatulence, abdominal bloating/distension, borborigmy) are important components of gastrointestinal discomfort. Changes in either frequency, severity or bother from a single digestive symptom are considered as appropriate measures: does the panel agree that this kind of evidence can be considered as part of the overall reduction of GI discomfort? - For food, no specific guidelines exist, especially for IBS (e.g. responder definition). We believe that the determination of the thresholds considered beneficial for human health for food requires specific recommendation. Can the Panel please address this issue in the guidance? - Multiple appropriate measured outcomes can be used to assess improvement of GI discomfort (e.g. overall assessment of GI discomfort as main outcome; questionnaire on symptoms frequency as secondary outcome). As we are looking for a functional effect of food, multiple appropriate outcomes reflect a beneficial physiological effect. Therefore, we think that the value of a study as a source of data substantiating a claimed effect based on primary criteria has to be balanced by the effect on secondary appropriate outcomes. - Can the panel also confirm that secondary appropriate outcomes can be meaningful for the value of a study in the food area? |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| DANONE       | 3.3 Claims on oral and gastrointestinal microbiota | Most of this section is not related to microbiota but to pathogens, mainly those which contaminate foods and are not normal gut inhabitants, such as Salmonella spp and Shigella spp. No reference is made to microbiota composition or modification and resistance to infection, which does not open any way for claims on gut microbiota. -The reduction of pathogens in the gastrointestinal (GI) tract (or the reduction of toxin) is recognised as a suitable marker to demonstrate a health benefit. A decrease of more than 1 log is proposed as a threshold. Although this provides an objective measure, this level is questionable. In rotavirus infections, probiotics could be effective without strong reduction of shedding. For other pathogens like Shigella spp, which can cause dysentery at 10^-100 cells, a one log reduction would mean nothing. -A major function of the gut microbiota is to prevent colonization by potential pathogens, through competition with such invading pathogens for ecological niches and production of inhibitory metabolites and antimicrobial substances. Therefore Danone seeks confirmation that not only the reduced number of specific pathogens but also a reduced ratio is an appropriate outcome measure to substantiate the maintenance of a normal defence against pathogens. The panel provided a non-exhaustive list of groups of intestinal microorganisms considered as pathogenic or toxicogenic. Could the panel provide a list of excluded pathogens, as well as a list of relevant pathogens occurring in respiratory, urinary and vaginal tracts? Could the duration needed to ascertain that the reduction of pathogens is sustainable be defined? -Despite the statement in ln 186-188, Danone considers that, in a population of infants and young children, increasing or decreasing the ratio of specific bacterial groups, including lactobacilli and/or bifidobacteria (towards a composition of the microbiota of breastfed infants), reflects a modulation of the overall composition of the ecosystem, which can be meaningful to health. The biochemical activity of this complex ecosystem generates healthy as well as potentially harmful compounds. Danone seeks confirmation that a modulation resulting in a decrease of putrefactive bacteria and undesirable end products such as ammonia and sulfate gases is beneficial for human health. -Several studies have reported that the microbiota varies between healthy individuals and those with immune related disorders such as inflammatory bowel disease. As an example, several studies have reported that increase in anti-inflammatory bacteria, such as Faecalibacterium prausnitzii, a common gut commensal, or decrease in the toxin-producing Clostridium spp were correlated with decreased risk of inflammatory disorders. Could this type of risk factor reduction be recognized in the future and what is missing today to demonstrate it? -The Panel sees both reduction of numbers of pathogens or their toxins AS WELL AS clinical outcomes demonstrated in human intervention studies as appropriate outcome measures for claims related to maintaining normal defence against pathogens in the GI tract. Danone seeks confirmation that a claim related to maintaining normal defence against pathogens can be substantiated by ONLY clinical outcomes in human intervention studies OR ONLY reduction of pathogens or their toxins. In addition, in case the pathogen itself is not detectable, is a beneficial effect on the clinical outcomes sufficient to substantiate a claim related to maintaining normal defence against pathogens? -Other microbiota than gut microbiota is not discussed in the draft document unlike in previous documents. The arguments given for gut microbiota should be extended to other body sites where microbiota contributes to health. |
| ORGANISATION | CHAPTER TEXT           | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                                          |
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| DANONE       | 3.4 Claims on digestion/absorption of nutrients | The panel is considering only one part on digestion/absorption of nutrients, i.e. improvement of absorption. It is as important to consider also REDUCTION of absorption of nutrients as potential claims. Three examples can illustrate the potential: reduction of absorption of dietary cholesterol, reduction of absorption of oxalate, and reduction of speed of absorption of glucose. Does the panel agree with these as being beneficial effects?  
- Similarly, iron absorption is a risk factor for hemochromatosis, and any dietary factor that can reduce iron absorption should be eligible for an article 14 claim for those at higher risk of hemochromatosis accordingly.  
- The rationale for “beneficial effect” should be established by comparison with the average capacity of digestion/absorption of nutrients of the average targeted population.  
- The example of lactose malabsorption is focusing on symptoms, and it is interesting that alleviation of these symptoms is considered as a beneficial effect. This is reinforcing the concept that dietary improvement of gut dysfunctions expressed as common complaints or symptoms is included in the scope of improvement of the gut’s functions.  
- Finally, maintenance of adequate status is one logical beneficial effect, but modulation of digestion/absorption of nutrients can also be a critical factor to modulate the effect of a given nutrient on some functions. Therefore the effect on absorption can be the rationale for a claim on different beneficial effects beyond maintenance of adequate status. |
| DANONE       | 4. Immune system       | The Panel indicated that some markers (lymphoid subpopulations number, lymphocytes proliferative responses, phagocytosis, natural killer cells activity and others) may be considered as supportive evidence, in as much as they are proposed as mechanism of the effect (ln 287-292). The Panel seems thus to consider these markers insufficient to substantiate a claim on immune function by themselves. The above list of markers mainly concerns the innate immune function which is the first immune defence involved in case of infection. The questions are:  
- Can the innate immune response to infection be considered a function for a 13.5 claim if supported by concomitant beneficial effects on clinical outcomes?  
- In this case, would a marker measured in the incubation period of infection or during infection (e.g. Natural Killer cell activity/cell count) be considered appropriate to substantiate a body function, namely the immune response to infection?  
- The Panel indicated that the incidence of infection may not necessarily represent an effect on the immune system and appropriate evidence of a concomitant change in immunological parameters needs to be provided (ln 268-273). Danone seeks information from the Panel for which specific cases, incidence of infection does not represent an effect on the immune system. Also, what is meant precisely by « appropriate » evidence?  
In addition, very often one study is dedicated to one primary objective in order to substantiate a certain effect. Accordingly in the present case, one study may be dedicated to a body function (immune function) and another to a clinical outcome (incidence of infection). This raises the following questions:  
- Would the Panel accept evidence on body function and clinical outcome in case it is provided by two separate studies? If not, either the clinical outcome or the body function will have to be defined as multiple primary/secondary parameters in one study which would increase the sample size required. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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|              |              | - In case of combined investigation of disease outcome and immune functions parameters in a same study, we assume that both must be considered of equal importance whatever their position as primary or secondary criteria. However, does the immune function need to be the primary parameter or is it accepted as secondary parameter to substantiate a body function claim? The infectious disease endpoint would usually be defined as the primary parameter since it statistically requires a higher sample size than a body function. |
|              |              | - The combined investigation in one study would imply an adapted strategy of adjustment for multiple comparisons on clinical outcomes and on function markers or risk factors. Does the Panel confirm this position? |
|              |              | - The Panel stated that allergic manifestations are caused by undesired immune responses to environmental allergens while on the other hand the Panel requests corroboration of the immunologic nature of these allergies. Can the Panel therefore explain in which cases it is possible to deny the immunologic nature of physician diagnosed allergic manifestations which were done according to generally recognised and validated methods (e.g. Hanifin and Rajka criteria, ARIA guidelines)? |
| DANONE       | 4.1 Claims on the function of the immune system | The Panel indicated that stimulation of protective antibody titres could be used to substantiate a health claim on the function of the immune system related to defence against pathogens (line 279-286). This raises the following questions: |
|              |              | - Do enhanced antibody titres to antigens of a specific pathogen contained in vaccine substantiate a claim on the function of the immune system related to the defence against natural infection by this pathogen outside the vaccination context? |
|              |              | - To which vaccines do the validated cut off values of vaccination mentioned refer to? |
|              |              | - Can the following two phrases: “increased numbers of individuals attaining protective levels” or “increments in titres in groups of individuals” be used independently and therefore is each one alone sufficient to sustain a claim on the function? |
|              |              | EFSA required that claims on ‘natural defences’ be clearly defined regarding the specific aspect of immune function that is the subject of the claim (In 266-267). Our question is: how specific must the claim on immune function be? For instance, in case of antibody response to specific vaccine, would it be claimed an enhancement of: immune defence, adaptive immunity or defence against pathogens? |
|              |              | The Panel also indicated that outcome measures of the claimed effect include reduction of numbers of pathogens for claims related to defence against pathogens (ln 268-270). The questions are as follows: |
|              |              | - Is the reduction of pathogens intended as reduction of commensal pathogens or reduction of pathogens in the course of related infection? |
|              |              | - For a 13.5 claim, can the reduction of pathogens load in the course of infection be considered as a function, that is able to reduce the occurrence and/or severity and/or duration of the associated disease? |
|              |              | - Is it acceptable to claim on effect against pathogens with demonstrated beneficial effect only on clinical outcomes of an infection such as incidence/duration/severity? |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| DANONE       | 4.3 Claims on reducing a risk factor for infections or allergy | The Panel explained that The decision on whether or not The alteration of a risk factor is considered to be beneficial in The context of a reduction of disease risk claim depends on The extent to which it is established that The risk factor is an independent predictor of disease risk. Can The Panel please clarify what kind of substantiation is required to prove that a risk factor is an independent predictor of disease risk? - in addition, Danone seeks confirmation that in order to substantiate a claim on reducing a risk factor, it is not required to show an effect on clinical outcome as long as The risk factor is confirmed to be an independent predictor of disease risk and The relationship of The risk factor to The development of The disease is biologically plausible. - The Panel confirmed The presence of pathogens as a risk factor for claims related to infections. Could The Panel provide a positive list of immune parameters considered as risk factors? Danone specifically seeks confirmation whether or not The following markers (as suggested by PASSCLAIM) are accepted by EFSA as risk factor for infections: The amount of pathogens in The course of infection, low specific antibody response to vaccines, levels of total or specific secretory immunoglobulin a and markers of mucosal barrier functional integrity. - Also no confirmed risk factors were mentioned for claims related to allergy. Could The Panel provide a positive list of immune makers considered as risk factors related to allergy? Danone specifically seeks confirmation whether or not levels of total or specific IgE (as suggested by PASSCLAIM) Can be considered risk factor for allergy? |
Outcome of a public consultation on a draft guidance on the scientific requirements for gut and immune function claims

| ORGANISATION | CHAPTER TEXT          | COMMENT TEXT                                                                 |
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| EHPM         | General comments      | "2. General considerations”                                                 |
|              |                       | "2.1. Beneficial physiological effect”                                       |
|              | Line 103: We believe that the draft document fails to address the question why the effect is judged beneficial or not. It is our view that a judgment of whether a health effect is beneficial can only be made after the assessment of all the evidence. |
|              | Line 119 & 123: The Regulation does not limit health claims to the healthy normal population and any group, including subjects with a disease, must be eligible as the target population for the health claim. We believe it is also appropriate to remove the example of joint health and osteoarthritis patients as this is a draft guidance on gut and immune health only and no proper technical debate on the joint health function has taken place yet. |
|              | "2.2. Studies/outcome measures appropriate for substantiation of claims” |
|              | Line 132: Instead of "human studies", we believe that "human data" is the correct term to be used. The Nutrition and Health Claims Regulation refers to "generally accepted scientific evidence" and thus human studies are not "central" for substantiation of health claims. EFSA should take into account the totality of the available evidence, not only human studies. |
|              | Line 144: Please note that the reference is missing in the document. |
|              | Line 147: We strongly believe that listing the elements that, with reasonable certainty, would be acceptable and identifying these elements that would certainly not be acceptable, would be extremely useful for applicants. |
|              | Line 158: We believe that if a health claim is not in line with the findings of the studies, EFSA should preferably provide a proposal for a suggested rewording of the claimed effect in line with the evidence available, rather than keeping the effect as stated and disqualifying the studies as inappropriate. |
|              | Line 159: For the gut and immune health topic, such experts consultations may be helpful to base opinions on a broader basis than only the views of the experts of the NDA panel. In that sense we welcome the technical meeting that will be held on 2 December 2010. |
### General comments

**General comment 1:**
EHPM welcomes the opportunity to have a fundamental discussion on the scientific requirements for the substantiation of health claims related to gastrointestinal tract and immune system. We also welcome the fact that the approach of the NDA Panel in this specific field is further detailed and that the draft guidance has been open to public consultation and will further be discussed by scientific experts at the technical meeting held on 2 December 2010. We however regret that no opportunity is given to discuss the general principles in the same level of detail (general principles as laid down in the draft briefing document for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims). General principles may need to be adapted depending on the comments received during this public consultation.

**General comment 2:**
EHPM is of the opinion that this useful opportunity, to discuss fundamental aspects of a specific health topic, comes very late in the claims assessment process. It is therefore only achieving its aim of being useful for applicants if:
1) no further assessments would take place until the document has been finalised, and
2) applicants have had the chance of revising their (already submitted) application in line with these EFSA guidelines.

**General comment 3:**
We observe that the document contains many scientific statements or points of view without scientific references. We feel that references to generally accepted scientific evidence as published in peer review journals, as is customary in scientific discussions, would be appropriate.

**General comment 4:**
We observe that one important topic linked to gut and immune health is missing in this draft document: diarrhea. We would appreciate if this issue could be added into the draft guidance document.

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**SUMMARY**

Line 13: It would be very useful to include a list (even if non-exhaustive) of beneficial effects and studies/outcome measures that are acceptable according to the EFSA NDA Panel. For SMEs, especially, this would be very helpful and concretely achieve the aim of assisting them in preparing their applications for the authorisation of health claims. This would increase the clarity of this guidance document.

**BACKGROUND AS PROVIDED BY EFSA**

Line 46: It should be noted that while the Regulation refers to the "highest possible standard", this does not necessarily mean the highest standard per se. If the standard adopted is not achievable unless all research of the past decades is done again, then this may be the highest standard, but certainly not the highest possible standard. We strongly feel the document and the way in which claims are assessed should better reflect the current state of research.

**ASSESSMENT** - "1. Introduction"

Line 92 & 93: It is strange that reference to "experience gained to date with the evaluation of health claims" in this
specific field is made, without even giving examples of claims throughout the text. All opinions that are relating to gut health and immune function to date have been negative (except for vitamins and minerals). We believe that it would be very helpful to include specific examples of claims that have been assessed and elaborate on the reasons why the substantiating evidence was judged to be insufficient or not supportive of the claimed effect. We would even question if the experience of the Panel with the evaluation of health claims in this field is a valid ground for such scientific views and statements. We believe that references from "generally accepted scientific evidence" (as stated in the Nutrition and Health Claims Regulation) would be far more appropriate.

| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| EHPM         | 3. Gastro-intestinal tract | "3. Gastro-intestinal tract" |
|              |              | General comment on Sections 3 and 4: |
|              |              | In sections 3 and 4 more information is required on the degree of evidence necessary in terms of the duration & numbers of persons studied. |
|              |              | It would also be helpful to have advice on suitable controls in studies to minimise bias and overcome the issue of blinding. |
|              |              | Advice on the number of outcome measures required is also needed, for instance for section 3.1. |
| EHPM         | 3.1 Claims on bowel function | "3.1. Claims on bowel function" |
|              |              | • More advice is needed on what are the acceptable study groups. For example will data in constipated subjects be viewed as pertinent data to substantiate a health claim? |
|              |              | • It would be helpful to give guidance on how many of the appropriate outcome measures EFSA would like to see data for – i.e. is it acceptable to have good data on just one of these measures, or is EFSA looking for data on all of these measures, or something in between. |
|              |              | • More information would be helpful about EFSA views on subjective data in this area – can this be used to substantiate a claim, or would this only be considered as supporting data? |
|              |              | • Are subject-reported data on stool frequency considered as objective or subjective evidence, and is this a sufficiently strong end point to substantiate the claim? |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| EHPM         | 3.2 Claims on gastrointestinal discomfort | "3.2. Claims on gastrointestinal discomfort"
We note that the appropriate outcome measures are based on subjective data.
Line 180: We welcome the fact that patients with IBS (Irritable Bowel Syndrome) are considered as an appropriate study group for claims intended for the general population. |
| EHPM         | 3.3 Claims on oral and gastrointestinal microbiota | "3.3. Claims on gastrointestinal microbiota"
Line 211: The list of food-borne micro-organisms are mostly linked to traveler’s diarrhea. However, the reference to diarrhea is unfortunately missing from this document and we would like to ask EFSA to include claims in relation to diarrhea in this guidance document. |
| EHPM         | 3.4 Claims on digestion/absorption of nutrients | "3.4 Claims on digestion/absorption of nutrients" More advice would be helpful in relation to situations where absorption is a limiting factor for nutrient status. It would be helpful to have information about the acceptability of using particular population sub-groups, and particularly in relation to medical conditions e.g. situations of poor B12 absorption in older people. |
| EHPM         | 4. Immune system | General comments on the Section 4 "Immune System":
The immune system is maintaining health by really sophisticated ‘network’ comprising many different players who interact with each other to such extent not yet fully understood and therefore we would expect that for such health category some ‘grading of evidence’ should be naturally possible since the limited knowledge can not be conclusive.
The grading of health claims could be arranged in similar way as the US FDA deals with so called ‘Qualified Health Claims’, for example in case of EPA/DHA case:
"Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. One serving of [name of food] provides [x] grams of EPA and DHA omega-3 fatty acids. [See nutrition information for total fat, saturated fat and cholesterol content.]
http://www.cfsan.fda.gov/~dms/lab-qhc.html." |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| EHPM | 4.1 Claims on the function of the immune system | 4.1. "Claims on the function of the immune system"
We believe that this section is particularly complicated and would benefit from a summary table.
We have noticed some inconsistency: between lines 279 and 286, the principles of vaccination are described. This is completely out of reach of foods bearing health claims and strictly limited to medicines. |
| EHPM | 4.2 Claims on reduction of inflammation | 4.2. "Claims on reduction of inflammation"
Line 297: If these markers are insufficient for a change in inflammatory response and do not indicate a beneficial effect per se, we would like to ask EFSA to further clarify which biomarkers would been considered as acceptable. |
| ERNA (European Responsible Nutrition Alliance) | General comments | Line 159: It would be good to hear how the NDA panels consults experts from various disciplines as such is not documented. We believe that the best people qualified to provide a consensus-based appraisal of the state of the art in a specific field of health are the experts in this field, who meet at symposia, present and discuss their work and can provide a balanced view of how strong a consensus is. This is particularly relevant in cases where the effects of long recognized substances, e.g. glucosamine, lutein, beta-carotene, etc have been rejected by EFSA. Also in the field of gut and immune health such consensus consultations may be helpful to base opinions on a broader basis than only the views of the experts of the NDA panel.
Nevertheless, the technical meeting of 2 December will be the first time EFSA openly consults other experts in the field and we warmly welcome this. We hope that the discussions and views expressed at that meeting may provide information on the extent that the statements and views of the NDA panel constitute generally accepted standards in this specific field of health. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| ERNA (European Responsible Nutrition Alliance) | General comments | Line 158: It would be interesting to know how the NDA panel arrives as the conclusion of what is generally accepted in the relevant research fields. The criticism on the quality and design of many peer reviewed published studies points to a discrepancy between EFSA’s opinion and that of experts in the field. Furthermore, applying today’s standards may reflect a state of science that is not met by earlier studies that nevertheless still may contribute scientific findings in support of the claimed effect. It should also be observed that many of the published studies have not been performed with the intention that they would serve one day for the substantiation of a claim on a food product and this will also most probably be the case for future research. The scientific conclusions of the authors are based on the outcome variables selected, not the inverse. If a health claim is not in line with the findings of the studies, we would expect EFSA to provide a proposal for a suggested rewording of the claimed effect in line with the evidence available, rather than keeping the effect as stated and disqualifying the studies as inappropriate. |
| ERNA (European Responsible Nutrition Alliance) | General comments | Line 155: Even if not exhaustive, it would be very helpful as guidance to provide a listing of those target populations that would be acceptable and those that would not as representative of the normal population. |
| ERNA (European Responsible Nutrition Alliance) | General comments | Lines 148-150: This sentence would require some further clarification, as it is not clear how this is in reality applied. Does it mean that for reproducibility reasons two or more independent but similar studies are needed? In order to be publishable, scientific publications require new research and are very reluctant to publish duplication. It is our understanding that the consistency of the evidence should in the first place come from an assessment of the totality of evidence available, including observational and experimental work. Reproducibility can only be addressed where the evidence allows such assessment. It should not be an automatic prerequisite for each claimed effect. |
| ERNA (European Responsible Nutrition Alliance) | General comments | Line 147: The NDA panel states that there is no pre-established formula as to how many or what type of studies are needed to substantiate a claim. We observe however that what has been submitted to date has not resulted to any gut or immune function claims getting a positive opinion (except for some vitamins and minerals). There seem therefore to be a general understanding of the formula that is not sufficient to accept a claimed effect. This element is key for clarity to companies wanting to submit claims applications with a reasonable chance of having the claim approved. A guidance that is not able to provide more clarity of these elements is of little value. It would therefore already be a start to list the elements that with reasonable certainty would be acceptable and to identify these elements that would certainly not be so. A certain pragmatism relating to the possibilities and limitation of nutritional research as opposed to pharmaceutical research would also be welcomed. |
| ERNA (European Responsible Nutrition Alliance) | General comments | Line 144: There is a reference missing in the text. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| ERNA (European Responsible Nutrition Alliance) | General comments | Line 142: It may be legitimate that the EFSA NDA panel addresses the design and quality of studies. However, we observe from opinions published that the conclusions of the NDA panel often are at odds with those of the peer review process. Indeed, design and quality of studies are always evaluated during the peer review process prior to publication in a scientific Journal. Furthermore, criticism or divergent views on the conclusions that the authors of the original research draw, is usually shared directly with the authors or is published as comments or letters to the editor. While in some cases criticism from the NDA panel is justified, it would be expected that this is shared with the authors and submitted to scientific peers to enable an appropriate right of defense and further scientific discussion. This is especially the case where the design and quality of original publications is criticized and the credibility of this work is undermined in EFSA opinions. We would like to ask EFSA to reflect on the broader implications of their approach. |
| ERNA (European Responsible Nutrition Alliance) | General comments | Line 136: In line with the above, the right terminology would be ‘whether the evidence relates to’, not ‘whether the studies have been carried out with’. |
| ERNA (European Responsible Nutrition Alliance) | General comments | Line 133: In line with the above, the right terminology would be ‘evidence’, not ‘studies’. |
| ERNA (European Responsible Nutrition Alliance) | General comments | Line 132: The right terminology should be ‘human data’, not ‘human studies’. A focus only on studies is too limited and ignores the requirement to assess the totality of the available evidence. We would also like to observe that for article 13.1 applications, the Regulation does not require that human studies are central for the substantiation of health claims. The terminology used in the Regulation is ‘generally accepted scientific evidence’. |
| ERNA (European Responsible Nutrition Alliance) | General comments | Line 123: No fundamental debate has taken place on the relevance of osteoarthritic patients for claims relating to joint health and this view may subject to criticism. As this claim does not relate to gut and immune health, it is therefore best removed from this text and introduced for discussion at a relevant future thematic technical meeting. |
| ERNA (European Responsible Nutrition Alliance) | General comments | Line 119: It should be noted that the Regulation does not limit health claims to the healthy normal population and any group, including diseased people must be eligible as a target population for a health claim. |
| ERNA (European Responsible Nutrition Alliance) | General comments | Line 117: This phrase could benefit from examples to clarify what is meant by ‘The extent to which the reduction of a risk factor is beneficial in the context of a reduction of disease risk claim’. The requirement of a case-by-case basis is not very helpful as guidance. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| ERNA (European Responsible Nutrition Alliance) | General comments | Line 109: We feel that the focus on only the risk factor and not on the reduction of the risk of a disease is a narrow interpretation of the Regulation and does not present a logic scientific principle. If this is not considered by EFSA, it may lead to valuable health benefits not being accepted because of principle. The aim of reducing a risk factor is ultimately to reduce the disease risk. If evidence is presented, showing that the food intervention reduces the risk of the disease, it would be scientifically sound to accept this effect, even in cases where the biological mechanisms (and therefore the risk factor) is not known (as is often the case in the current state of scientific knowledge). Furthermore, there are situations where the risk factor in itself is the substance of the claimed effect (e.g. nutritional risk factors (low intake of a certain nutrient)). In such cases the requirement to show a reduction of the risk factor does not make sense. Clarity is therefore needed as how evidence relating to the reduction of a disease risk without the identification of a risk factor can be used to obtain a positive opinion. If the interpretation of the Regulation would not allow this, it is nevertheless legitimate for EFSA to highlight this aberration to the law maker. |
| ERNA (European Responsible Nutrition Alliance) | General comments | Line 103: The document focuses in great detail on whether an effect is beneficial or not, but fails to address the question why the effect is judged beneficial or not, i.e. no criteria nor justification for arriving at such a conclusion is presented. The judgment of whether a certain health effect is beneficial or not, is however a crucial step as if an effect is not considered as beneficial, the evidence for the health effect will not be considered in the first place. It is our view that a judgment of whether a health effect is beneficial can only be made after the assessment of all the evidence. Only if all evidence available is considered, a judgment can be given on the extent to which the observed effects are beneficial. This information may then be used, if relevant, to modify the wording of the claim in a way that would make it more in line with the evidence presented. We would suggest that in their opinions, EFSA provides more information to the European Commission on these considerations to allow for an informed decision to be taken. |
| ERNA (European Responsible Nutrition Alliance) | General comments | Line 97: There are no examples presented in the text. It would be very useful to illustrate the text with examples, elaborating on why in specific cases the evidence presented was not accepted by the NDA panel as (sufficient) proof of the claimed effect. |
| ERNA (European Responsible Nutrition Alliance) | General comments | Line 96: Such a list of beneficial effects and studies/outcome measures that are acceptable, even if non-exhaustive would be extremely useful to provide guidance and certainty to companies. |
| ORGANISATION                                      | CHAPTER TEXT | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                 |
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| ERNA (European Responsible Nutrition Alliance)   | General comments | Line 92: Scientific views and statements should be based on generally accepted scientific evidence as published in peer review journals. We would question if the experience of the panel with the evaluation of health claims in these areas is the only valid ground for such views or statements, especially since all claims assessed to date in relation to gut and immune function (except for vitamins and minerals) have been rejected with negative opinions. It would have been better to underpin and substantiate the views and statements with references from generally accepted scientific evidence. |
| ERNA (European Responsible Nutrition Alliance)   | General comments | Line 46: It should be noted that while the Regulation refers to the highest possible standard, this does not necessarily mean the highest standard per se. If the standard adopted is not achievable unless all research of the past decades is redone, then this may be the highest standard, but certainly not the highest possible standard. We strongly feel the document and the way in which claims are assessed should reflect better the current state of research. The document may of course provide recommendations for future research, but the approach should be sufficiently pragmatic to appreciate what science has already established, even in ways that may not have been optimal. |
| ERNA (European Responsible Nutrition Alliance)   | General comments | Line 14: It appears a bit strange that reference to examples is made, given that throughout the text no single example is presented and that all claims that are relating to gut health and immune function to date have been negative (except for vitamins and minerals). It would be very helpful and increase the usefulness of this guidance to include specific examples of claims that have been assessed and elaborate on the reasons why the substantiating evidence was judged to be insufficient or not supportive of the claimed effect. |
| ERNA (European Responsible Nutrition Alliance)   | General comments | Line 13: We feel that given the confusion that currently exists as to the expectations of the EFSA NDA panel on what is considered acceptable evidence, it would be extremely useful to include lists (even being non-exhaustive) of beneficial effects and studies/outcome measures that are acceptable. This would strongly increase clarity and would make that this document can be seen as concrete guidance, especially for (small and medium sized) companies that are looking to invest their sparse resources in the most efficient possible way. |
| ERNA (European Responsible Nutrition Alliance)   | General comments | Comment 8: Since to date no single claims in the area of pro- and prebiotics and immune and gut health has received a positive opinion, a fundamental question to address is if the approach taken by the NDA panel is appropriate to show such effects and if there is a genuine chance of ever having such a claim approved. We would very much welcome the vision of the NDA panel on this to be able to judge if investments on research in this area are still useful. It may also bee the adopted approach is simply too demanding for foodstuffs to comply with. We would appreciate if this element could be part of the discussion at the technical meeting, as it is quite fundamental. |
| ORGANISATION                                             | CHAPTER TEXT                      | COMMENT TEXT                                                                                           |
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| ERNA (European Responsible Nutrition Alliance)          | General comments                  | Comment 7: It would be recommended to clearly distinguish Part 3 (gut function) and 4 (immune function): Section from lines 226 to 235 can lead to confusion. |
| ERNA (European Responsible Nutrition Alliance)          | General comments                  | Comment 6: We note that many elements in this document are providing information on what is not considered as appropriate. It would be very helpful to focus on examples and elements that would be considered appropriate or sufficient for a valid and successful application. In this respect, examples of protocols and study designs for the substantiation of health claims related to gut and immune function would also be very useful. |
| ERNA (European Responsible Nutrition Alliance)          | General comments                  | Comment 5: We note that one important field is not included in the document: diarrhea. We would appreciate if this could be included in the document and the discussions of the technical meeting foreseen on 2 December to which we would like to share our expertise. |
| ERNA (European Responsible Nutrition Alliance)          | General comments                  | Comment 4: From a content point of view, we observe that the document contains many scientific statements without scientific references as substantiation. We feel it would have been appropriate to underpin each of the statements or points of view made by the NDA panel by references to generally accepted scientific evidence as published in peer review journals, as is customary in scientific discussions. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| ERNA (European Responsible Nutrition Alliance) | General comments | Comment 3: We also feel this opportunity to discuss fundamental aspects of a specific field of health, while extremely useful, comes very late in the process. It is therefore only achieving its aim of being useful for applicants if no further assessments would take place until the document has been finalised and applicants have had the chance of revising their (already submitted) application in line with these guidelines. |
| ERNA (European Responsible Nutrition Alliance) | General comments | Comment 2: We participated to the technical meetings EFSA has organized and would consider that the way in which the discussions took place were not optimal. A one-day workshop is short and in order to maximize the efficient use of time, we would suggest EFSA to address the topics one by one and have focused discussions (and not accumulate three different questions before addressing them together as in the last technical meeting). We would also suggest not to use a break-up group approach as this eliminates experts from parts of the discussion. |
| ERNA (European Responsible Nutrition Alliance) | General comments | Comment 1: We welcome the chance to have a fundamental discussion on the scientific principles underlying claims assessments in the field of gut and immune function. We regret however that no opportunity is given to discuss the general principles, as laid down in the draft briefing document for stakeholders on the evaluation of Article 13.1, 13.5 2 and 14 health claims, in the same level of detail. General principles may need to be adapted depending on the outcome of this consultation. |
| ERNA (European Responsible Nutrition Alliance) | 3.1 Claims on bowel function | Line 167: It would be very helpful, in addition to providing clarification on how these outcome measures are defined (transit time, frequency of bowel movements, stool bulk), if the NDA panel could also indicate that is the minimum degree of change that they would accept as biologically significant. |
| ERNA (European Responsible Nutrition Alliance) | 3.1 Claims on bowel function | Line 167: Would all of these outcomes need to be demonstrated or is one of them sufficient for the claim to be acceptable? |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| ERNA (European Responsible Nutrition Alliance) | 3.1 Claims on bowel function | Line 165: The NDA panel is of the opinion that changes in bowel function within the normal range might be considered beneficial physiological effect. No justification is given for this view. |
| ERNA (European Responsible Nutrition Alliance) | 3.1 Claims on bowel function | Line 165: We do not understand why only changes in bowel function within the normal range are considered and not changes that bring bowel functions back in normality. The fact that this would be considered as a medicinal effect is not an argument as it is well recognized that specific foods under EU law can be used for the dietary management of diseases, disorders or medical conditions. Furthermore, there are effects that are common for medicinal products and foods, e.g. the lowering cholesterol that is exemplified both by the use of medicinal products (HMG CoA reductase inhibitors, etc) and food components (e.g. specific fatty acids, phytosterols, etc). A reference to a normal range leads to the need of defining what this normal range is and what would constitute a significant and biologically relevant change to be acceptable. Consumer health is better suited by assessing the evidence underlying the observed health effect and on that basis then defining the usefulness of that effect than by rejecting effects from the start because of narrow definitions. |
| ERNA (European Responsible Nutrition Alliance) | 3.1 Claims on bowel function | Line 163: We note that while hard stools and constipation are explicitly considered, this is not the case with loose stools and diarrhea. We believe that also these aspects of bowel function and the effects foods can have on them, should be considered in this guidance paper. |
| ERNA (European Responsible Nutrition Alliance) | 3.2 Claims on gastrointestinal discomfort | Line 180: We welcome that patients with IBS are considered as an appropriate study group for claims intended for the general population. If the reasons for that is the lack of an organic cause and a higher frequency and greater severity of symptoms, this obviously also applies to other groups in other fields (e.g. higher susceptibility to episodes of infection in certain population groups, such as sporters and elderly people). This could be clarified in the document. |
| ERNA (European Responsible Nutrition Alliance) | 3.2 Claims on gastrointestinal discomfort | Line 175: It is advisable to clarify what is understood by validated questionnaires and provide clarification and examples, indicating what are the minimum requirements for acceptance. What also would need clarification is what level of improvement of symptoms / statistically significant difference, based on the results of such questionnaires would be acceptable for the claimed effect to receive a positive opinion. |
| ERNA (European Responsible Nutrition Alliance) | 3.2 Claims on gastrointestinal discomfort | Line 175: It would also be very helpful that the NDA panel explains what degree of change would be considered by the NDA panel as acceptable and how many of the different outcome measures investigated would need to improve before a claim in relation to gastrointestinal comfort can be accepted. This is especially relevant in relation to questionnaire based research since EFSA has appeared to put in one opinion a question as to clinical relevance of what it considers “a small difference (0.25 points on a scale from 1-7)” (EFSA opinion on LGG MAX (EFSA-Q-2008-444)) |
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ERNA (European Responsible Nutrition Alliance) | 3.2 Claims on gastrointestinal discomfort | Line 175: It would be very helpful to define what are the acceptable outcome measures for gastrointestinal comfort. The ones indicated in the document (distension/bloating, abdominal pain/cramp, borborygmi (rumbling) etc. appear non exhaustive and can be complemented with others (e.g. nausea, heartburn, fullness, vomiting, etc.).

ERNA (European Responsible Nutrition Alliance) | 3.3 Claims on oral and gastrointestinal microbiota | We note that on the comments submission page, section 3.3 is mentioning oral and gastrointestinal microbiota, whereas this section in the draft guidance paper only refers to gastrointestinal microflora. We therefore have not reflected on aspects related to oral microflora as this was not part of the document. We agree however that this aspect should be included in the discussions, as well as the microflora of other body cavities in so far as food claims are concerned.

ERNA (European Responsible Nutrition Alliance) | 3.3 Claims on oral and gastrointestinal microbiota | Line 232: It is not clearly argued why effects on intestinal permeability are not acceptable as proof to substantiate a claim relating to the maintenance of the normal defenses against pathogenic micro-organisms in the gut. The intestinal barrier and in particular an improvement of mucosal barrier function may even be more important for the prevention of infections than a reduction in the number of potential pathogenic bacteria in the intestine.

ERNA (European Responsible Nutrition Alliance) | 3.3 Claims on oral and gastrointestinal microbiota | Line 228: Could the NDA panel confirm that an increase in the number of beneficial microorganisms (Bifidobacteria/Lactobacilli) in addition to clinical outcomes also be acceptable as evidence related to maintaining normal defense against pathogens? If not, could the NDA panel explain why not?

ERNA (European Responsible Nutrition Alliance) | 3.3 Claims on oral and gastrointestinal microbiota | Line 228: We would welcome confirmation that clinical outcomes (frequency, number and duration of episodes of infection, severity of symptoms, …) are acceptable as indirect measures of the function of the immune system (Opinion on Yestimun (EFSA-Q-2008-667)).

ERNA (European Responsible Nutrition Alliance) | 3.3 Claims on oral and gastrointestinal microbiota | Line 228: For a claim related to the maintenance of the normal defense against pathogens, should the “by as well as” be understood as a requirement that a reduction of numbers of pathogenic microorganisms AND clinical outcomes together are required?

ERNA (European Responsible Nutrition Alliance) | 3.3 Claims on oral and gastrointestinal microbiota | Line 225: More guidance is needed on how such characterization is expected to be performed and which study protocols can be used to provide such information.
| ORGANISATION                        | CHAPTER TEXT                                              | COMMENT TEXT                                                                                                                                                                                                 |
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| ERNA (European Responsible Nutrition Alliance) | 3.3 Claims on oral and gastrointestinal microbiota          | Line 218: There seems to be a part of the sentence missing between the brackets.                                                                                                                                 |
| ERNA (European Responsible Nutrition Alliance) | 3.3 Claims on oral and gastrointestinal microbiota          | Line 211: The list of food-borne micro-organisms are mostly linked to traveller’s diarrhea. However, diarrhea is not covered by this paper. We would ask EFSA to include claims relating to the effect of food and food components in relation to diarrhea in this document. |
| ERNA (European Responsible Nutrition Alliance) | 3.3 Claims on oral and gastrointestinal microbiota          | Line 203: We would question this narrow interpretation of the Regulation which inverses cause and effect. The meaningful element for the consumer is undoubtedly the reduction in the incidence of infections, irrespective of the underlying mechanism. Knowledge of the mechanism is nice to have, but should not necessarily constitute an essential requirement for a claim to get a positive opinion. It is often not considered as a prerequisite for the adoption of function claims, so it should not be for reduction of disease risk claims neither. If this view is caused by a narrow interpretation of the Regulation, it does not reflect scientific logic and it would be legitimate for EFSA to highlight this. Furthermore, in the case of reduction of the incidence of infection, it would be appropriate that EFSA lists the risk factors it would deem acceptable. |
| ERNA (European Responsible Nutrition Alliance) | 3.3 Claims on oral and gastrointestinal microbiota          | Line 200: The requirement for a meaningful reduction of 1 log value in the presence of pathogenic bacteria is questionable. Experts believe this is neither necessary nor feasible. Also this requirement will need to be discussed in detail with experts in the field in the December technical meeting. |
| ERNA (European Responsible Nutrition Alliance) | 3.3 Claims on oral and gastrointestinal microbiota          | Line 199: Could the NDA panel define what is meant by ‘sustained over time’? What is the period that will be acceptable?                                                                                   |
| ERNA (European Responsible Nutrition Alliance) | 3.3 Claims on oral and gastrointestinal microbiota          | Line 196: It would be good for the EFSA panel to clarify why the pathogenic or toxigenic microorganisms need to be identified and characterised? In case of bacterial infection, the resulting outcomes include diarrhea, pain, fever, etc. It is the reduction of the incidence of these outcomes that matter and should be demonstrated, not what was the causing agent and is it reduced when using the product. In many cases, for outdoor patients, the identification of the causal agent will simply not be possible because of practical considerations. |
| ORGANISATION                                           | CHAPTER TEXT                                      | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                 |
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| ERNA (European Responsible Nutrition Alliance)         | 3.3 Claims on oral and gastrointestinal microbiota | Line 186: The NDA panel states that the evidence available to the panel does not establish that increasing the number of specific microorganisms or any groups of microorganisms, including lactobacilli and/or bifidobacteria, is in itself a beneficial physiological effect but does not provide generally accepted scientific evidence to underpin this statement. It does also appear not to have considered the supportive data relating to described effects of bifidobacteria and lactobacilli from experimental research. Consensus on this view will need to be discussed in detail during the technical meeting with experts in the field. |
| ERNA (European Responsible Nutrition Alliance)         | 3.4 Claims on digestion/absorption of nutrients  | Line 255: No justification is given for this restrictive view. It would be very helpful for the debate to provide a list of those nutrients where the NDA panel considers that absorption is a limiting factor for the maintenance of adequate status of the nutrient.                                                                                                                   |
| ERNA (European Responsible Nutrition Alliance)         | 3.4 Claims on digestion/absorption of nutrients  | Line 251: Could the NDA panel explain what degree of improvement in iron absorption would be acceptable and against what baseline such improvement should be assessed?                                                                                                                                   |
| ERNA (European Responsible Nutrition Alliance)         | 3.4 Claims on digestion/absorption of nutrients  | Line 237: No justification is given on why improved digestion and absorption of nutrients might be considered as a beneficial effect.                                                                                                                                                                                                 |
| ERNA (European Responsible Nutrition Alliance)         | 4.1 Claims on the function of the immune system  | Line 291: The expectations are not clear: is such supportive evidence only acceptable in combination with clinical outcomes? Are they optional or required together with clinical outcomes to have the claim approved?                                                                                   |
| ERNA (European Responsible Nutrition Alliance)         | 4.1 Claims on the function of the immune system  | Line 290: Terminology: ‘cytotoxic T cell’, not ‘cytolytic’.                                                                                                                                                                                                                                                                                   |
| ERNA (European Responsible Nutrition Alliance)         | 4.1 Claims on the function of the immune system  | Line 285: Stimulation of protective antibody titres is a powerful and acknowledge parameter that definitely should be accepted to substantiate immune system-related health claims.                                                                                                                      |
| ORGANISATION                                           | CHAPTER TEXT                                                                 | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| ERNA (European Responsible Nutrition Alliance)        | 4.1 Claims on the function of the immune system                             | Line 277: This is not always possible. Not every allergic response is accompanied by a specific IgE and not every person with specific IgE suffers from the specific allergy. We feel a fundamental discussion is needed on the expectations of the NDA panel in relation to immune-related claims.                                                                                                                                                                                                                                                                 |
| ERNA (European Responsible Nutrition Alliance)        | 4.1 Claims on the function of the immune system                             | Line 277: What is meant by ‘appropriate measures’?                                                                                                                                                                                                                                                                                                                                                                                                                           |
| ERNA (European Responsible Nutrition Alliance)        | 4.1 Claims on the function of the immune system                             | Line 273: In respect to section 3.3, should we understand that claims on the maintenance of normal defense against pathogens and claims on immune function would imply different levels of requirements?                                                                                                                                                                                                                                                                 |
| ERNA (European Responsible Nutrition Alliance)        | 4.1 Claims on the function of the immune system                             | Line 273: It would be good if EFSA could elaborate on what it would consider acceptable changes in immunological parameters, especially in the light of its statements in lines 287-292.                                                                                                                                                                                                                                                                 |
| ERNA (European Responsible Nutrition Alliance)        | 4.1 Claims on the function of the immune system                             | Line 271: Although a reduction in infection incidence may indeed not necessarily represent an effect on the immune system, we would appreciate if the NDA panel could specify what changes in immunological parameters would need to be presented to be acceptable. In the end, if a reduction of the incidence of infection is demonstrated, would the NDA panel refuse the claim is no such changes in immunological parameters are presented? If yes, can the panel explain why knowledge of the biological mechanism would be required? Is the effect in itself not what matters? |
| ERNA (European Responsible Nutrition Alliance)        | 4.1 Claims on the function of the immune system                             | Line 270: It should be specified here whether the duration or the severity of disease/symptoms could be also regarded as core evidence. Furthermore in the opinion on Lactobacillus casei strain Shirota (EFSA-Q-2010-00137), EFSA states that the symptoms used to define the occurrence of upper respiratory tract infection (URTI), i.e. running nose, sore throat, fever and cough, are non-specific, and that the presence of one or more of these symptoms is not an appropriate measure of the occurrence of URTI. Could EFSA provide clarification on the measures it would consider appropriate in this respect? |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| ERNA (European Responsible Nutrition Alliance) | 4.1 Claims on the function of the immune system | Line 268: It is not clear if the coordinating conjunctions “and” should be understood as “and” or “and/or”? In other words, does it mean that all of the 3 following outcome measures need to be provided for a claim on immune function: evidence on the reduction of numbers of pathogens + incidence + immunological parameters? |
| ERNA (European Responsible Nutrition Alliance) | 4.1 Claims on the function of the immune system | Line 266: Why would a claim relating to the natural defenses need to be better defined when a normal functioning of the immune system as such is considered to be beneficial? The extent to which the substance is useful for the maintenance of the natural defenses would be apparent from the data submitted. If more specification is required, it should be specified what further information would need to be supplied and what would not be considered sufficient. Clarification is also needed on what kind of evidence would then be acceptable and what not. |
| ERNA (European Responsible Nutrition Alliance) | 4.1 Claims on the function of the immune system | Line 263: This section refers only to the maintenance of the normal immune function. It would be necessary to clarify whether claims on the improvement of the immune function could be acceptable with the same level of substantiation and if not, what further elements would need to be provided. |
| ERNA (European Responsible Nutrition Alliance) | 4.1 Claims on the function of the immune system | Lines 260-265: Is the only role of the immune system to provide defense against infections caused by pathogenic microorganisms? It should be clarified if the only specification that is needed is an indication if the effect relates to defense against pathogens or response to allergens. |
| ERNA (European Responsible Nutrition Alliance) | 4.2 Claims on reduction of inflammation | Line 304: The reliance on a case-by-case assessment is vague and needs to be clarified by examples of what would be acceptable and what not. |
| ERNA (European Responsible Nutrition Alliance) | 4.2 Claims on reduction of inflammation | Line 297: If these markers are not sufficient as markers for a change in inflammatory response, can EFSA clarify what biomarkers it would consider acceptable and what not? |
| ERNA (European Responsible Nutrition Alliance) | 4.2 Claims on reduction of inflammation | Line 296: We welcome the recognition that inflammation is a physiological response and deduces that effects of foods and food components on a physiological inflammatory response can be considered a health benefit. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| ERNA (European Responsible Nutrition Alliance) | 4.3 Claims on reducing a risk factor for infections or allergy | Line 310: Does this mean that also a biomarker for immune function is needed? If yes, it would be helpful if EFSA could clarify which biomarkers would be acceptable. |
| ERNA (European Responsible Nutrition Alliance) | 4.3 Claims on reducing a risk factor for infections or allergy | Line 308: It is clear that the demonstration of a direct effect on the reduction of infection episodes is far more valuable for consumer health that the demonstration of the reduction of a risk factor for infection. EFSA should not adhere to such a restrictive interpretation of the Regulation, if this would mean that significant benefits are withheld from the consumer. It should at least point this out in its pinion in order for the European Commission to be able to make an informed decision. |
| European Botanical Forum | General comments | Line 159: It would be good to hear how the NDA panels consults experts from various disciplines as such is not documented. |
| European Botanical Forum | General comments | Line 158: It would be interesting to know how the NDA panel arrives as the conclusion of what is generally accepted in the relevant research fields. If a health claim is not in line with the findings of the studies provided, we would expect EFSA to provide a proposal for a suggested rewording of the claimed effect in line with the evidence available, rather than keeping the effect as stated and disqualifying the studies as inappropriate. |
| European Botanical Forum | General comments | Line 155: Even if not exhaustive, it would be very helpful as guidance to provide a listing of those target populations that would be acceptable and those that would not as representative of the normal population. |
| European Botanical Forum | General comments | Lines 148-150: Reproducibility can only be addressed where the evidence allows such assessment. It should not be an automatic prerequisite for each claimed effect. |
| ORGANISATION            | CHAPTER TEXT    | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| European Botanical Forum| General comments| Line 147: The NDA panel states that there is no pre-established formula as to how many or what type of studies are needed to substantiate a claim. We observe however that what has been submitted to date has not resulted to any gut or immune function claims getting a positive opinion (except for some vitamins and minerals). There seem therefore to be a general understanding of the formula that is not sufficient to accept a claimed effect. This element is key for clarity to companies wanting to submit claims applications with a reasonable chance of having the claim approved. A guidance that is not able to provide more clarity of these elements is of little value. It would therefore already be a start to list the elements that with reasonable certainty would be acceptable and to identify these elements that would certainly not be so. A certain pragmatism relating to the possibilities and limitation of nutritional research as opposed to pharmaceutical research would also be welcomed. |
| European Botanical Forum| General comments| Line 144: There is a reference missing in the text.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| European Botanical Forum| General comments| Line 136: In line with the above, the right terminology would be ‘whether the evidence relates to’, not ‘whether the studies have been carried out with’.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| European Botanical Forum| General comments| Line 133: In line with the above, the right terminology would be ‘evidence’, not ‘studies’.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| European Botanical Forum| General comments| Line 132: The right terminology should be ‘human data’, not ‘human studies’. A focus only on studies is too limited and ignores the requirement to assess the totality of the available evidence. We strongly believe observational evidence and traditional use should be given a prominent for claims relating to botanicals as many claims are based on long standing use, which needs to be recognized. We would also like to observe that for article 13.1 applications, the Regulation does not require that human studies are central for the substantiation of health claims. The terminology used in the Regulation is ‘generally accepted scientific evidence’ which is broader than just studies. |
| European Botanical Forum| General comments| Line 123: No fundamental debate has taken place on the relevance of osteoarthritic patients for claims relating to joint health. As this claim does not relate to gut and immune health, this example is therefore best removed from this text and introduced for discussion at a relevant future thematic technical meeting.                                                                                                                                                                                                                                                                                                                                                         |
| European Botanical Forum| General comments| Line 119: The Regulation does not limit health claims to the healthy normal population. Any group, including diseased people must be eligible as a target population for a health claim.                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| European Botanical Forum| General comments| Line 117: More guidance is needed on the extent to which the reduction of a risk factor is beneficial in the context of a reduction of disease risk claim.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| ORGANISATION                  | CHAPTER TEXT     | COMMENT TEXT                                                                                                                                                                                                 |
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| European Botanical Forum     | General comments| Line 109: We feel that the focus on only the risk factor and not on the reduction of the risk of a disease is a narrow interpretation of the Regulation. It may lead to valuable health benefits not being accepted because of a point of principle. When a reduction in infection risk is demonstrated but not accepted because the risk factor is not clear or the underlying biological mechanism is not understood, this would not be serving public health and consumer benefit. Given the lack of scientific knowledge in this field, this is likely to happen. If the interpretation of the Regulation would not allow this, it would be useful if EFSA could point this out towards the European Commission. |
| European Botanical Forum     | General comments| Line 103: The document focuses in great detail on whether an effect is beneficial or not, but does not address the question why a certain effect is judged beneficial or why not. We feel that a judgment of the extend to which a certain health effect of a food is beneficial or not, can only be taken after the assessment of all the evidence and that on the basis of this judgment the proposed wording of the claims should be adapted as appropriate. We would suggest that in their opinions, EFSA would provide more nuanced information on the extend to which the effect is beneficial and substantiated to allow the European Commission to take an informed decision. |
| European Botanical Forum     | General comments| Line 97: There are no examples presented in the text. It would be very useful to illustrate the text with examples, elaborating on why in specific cases the evidence presented was not accepted by the NDA panel as (sufficient) proof of the claimed effect. |
| European Botanical Forum     | General comments| Line 96: Such a list of beneficial effects and studies/outcome measures that are acceptable, even if non-exhaustive would be extremely useful to provide guidance and certainty to companies. |
| European Botanical Forum     | General comments| Comment 3:                                                                                                                                                                                                   |
|                              |                 | We note that it would be very helpful to include more examples, identify more precisely the outcomes that are judged acceptable and the degree of change needed to be considered biologically significant. Examples of protocols and study designs for the substantiation of health claims related to gut and immune function would also be very useful. In addition, it would be extremely useful to include in the document lists including beneficial effects and studies/outcome measures that are acceptable. |
| European Botanical Forum     | General comments| Comment 2:                                                                                                                                                                                                   |
|                              |                 | We note that diarrhea is not covered by the guidance. We think it would be appropriate also to consider diarrhea and loose stools as a determinant of gut function in this guidance. |
| ORGANISATION         | CHAPTER TEXT                  | COMMENT TEXT                                                                                                                                 |
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| European Botanical Forum | General comments             | Comment 1: EBF welcomes the opportunity given to comment on this draft paper, be it at a rather late stage in the process. In general, the paper highlights a number of useful elements but is not sufficiently detailed in many aspects to be of practical use for companies wanting to introduce claims for approval. We would welcome clear guidance on the requirements expected by EFSA on many concrete elements in the document and hope that we will also have a chance of discussing the appropriateness of these requirements during the meeting on 2 December. We also feel that for this guidance to be maximally applied, EFSA should not proceed with its assessments but stop the clock to enable companies to modify and adapt their submissions as appropriate. |
| European Botanical Forum | 3.1 Claims on bowel function | Line 167: Would all of these outcomes need to be demonstrated or is one of them sufficient for the claim to be acceptable? In addition, it would be very helpful if the NDA panel could also provide clarification on how these outcome measures are defined (transit time, frequency of bowel movements, stool bulk), and indicate what is the minimum degree of change that they would accept as biologically significant. |
| European Botanical Forum | 3.1 Claims on bowel function | Line 165: We would like clarification on why the NDA panel is of the opinion that changes in bowel function within the normal range might be and not are considered a beneficial physiological effect. |
| European Botanical Forum | 3.1 Claims on bowel function | Line 165: We would like further clarification on why the NDA panel is of the opinion that only changes in bowel function within the normal range are considered as beneficial and not changes that bring bowel functions back within normality. This should not be considered automatically as a medicinal effect. It is well recognized that specific foods are specifically intended for the dietary management of diseases, disorders or medical conditions. Furthermore, both medicinal and foods can play a role in the management of physiological conditions. If the NDA panel sticks to its view, it would be definitely necessary to establish what is judged to be normal and what would be abnormal and what would be considered as a significant and biologically relevant change to be acceptable. |
| European Botanical Forum | 3.1 Claims on bowel function | Line 163: We would suggest also to include loose stools and diarrhea as important determinants of bowel function in the guidance paper. |
| European Botanical Forum | 3.2 Claims on gastrointestinal discomfort | Line 180: We welcome that patients with IBS are considered as an appropriate study group for claims intended for the general population. If the reasons for that is the lack of an organic cause and a higher frequency and greater severity of symptoms, this obviously also applies to other groups, especially in the field of botanicals. |
| ORGANISATION               | CHAPTER TEXT                                      | COMMENT TEXT                                                                                                                                                                                                 |
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| European Botanical Forum  | 3.2 Claims on gastrointestinal discomfort         | Line 175: We would ask to clarify what is understood by validated questionnaires and provide clarification and examples, indicating what are the minimum requirements for acceptance and what is the level of improvement of symptoms / statistically significant difference that would be acceptable. |
| European Botanical Forum  | 3.2 Claims on gastrointestinal discomfort         | Line 175: It would also be very helpful that the NDA panel explains what degree of change would be considered as acceptable and how many of the different outcome measures investigated would need to improve before a claim in relation to gastrointestinal comfort can be accepted. |
| European Botanical Forum  | 3.2 Claims on gastrointestinal discomfort         | Line 175: It would be very helpful to define what are the acceptable outcome measures for gastrointestinal comfort. The list seems rather limited.                                                                 |
| European Botanical Forum  | 3.3 Claims on oral and gastrointestinal microbiota | Line 228: Could the NDA panel confirm that an increase in the number of beneficial microorganisms (Bifidobacteria/Lactobacilli) in addition to clinical outcomes would also be acceptable as evidence related to maintaining normal defence against pathogens? If not, could the NDA panel explain why not? |
| European Botanical Forum  | 3.3 Claims on oral and gastrointestinal microbiota | Line 228: We would welcome confirmation that clinical outcomes (frequency, number and duration of episodes of infection, severity of symptoms, … ) are acceptable as indirect measures of the function of the immune system. |
| European Botanical Forum  | 3.3 Claims on oral and gastrointestinal microbiota | Line 228: Does this mean that both requirements (reduction of numbers of pathogenic microorganisms and clinical outcomes) together are required?                                                                 |
| European Botanical Forum  | 3.3 Claims on oral and gastrointestinal microbiota | Line 225: More guidance is needed on how such characterization is expected to be performed and which study protocols can be used to provide such information.                                                        |
| European Botanical Forum  | 3.3 Claims on oral and gastrointestinal microbiota | Line 218: There seems to be a part of the sentence missing between the brackets.                                                                                                                               |
| ORGANISATION          | CHAPTER TEXT                                                                 | COMMENT TEXT                                                                                                                                                                                                 |
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| European Botanical Forum | 3.3 Claims on oral and gastrointestinal microbiota                             | Line 203: We would question this narrow interpretation of the Regulation which inverses cause and effect. The meaningful element for the consumer is undoubtedly the reduction in the incidence of infections, irrespective of the underlying mechanism. Knowledge of the mechanism is nice to have, but should not necessarily constitute an essential requirement for a claim to get a positive opinion. |
| European Botanical Forum | 3.3 Claims on oral and gastrointestinal microbiota                             | Line 200: We would appreciate if the appropriateness of a reduction of 1 log could be discussed with experts in the field.                                                                                     |
| European Botanical Forum | 3.3 Claims on oral and gastrointestinal microbiota                             | Line 196: It would be good for the EFSA panel to clarify why and how the pathogenic or toxicogenic microorganisms need to be identified and characterised? We would also ask the panel if it has reflected if in practice collection and characterization of pathogenic micro-organisms is feasible and necessary. |
| European Botanical Forum | 3.3 Claims on oral and gastrointestinal microbiota                             | Line 186: We would appreciate to hear the scientific rational underlying the view of the NDA panel that increasing the number of specific microorganisms or any groups of microorganisms, including lactobacilli and/or bifidobacteria, in itself is a beneficial physiological effect. |
| European Botanical Forum | 3.4 Claims on digestion/absorption of nutrients                               | Line 251: Could the NDA panel explain what degree of improvement in iron absorption would be acceptable and against what baseline such improvement should be assessed? |
| European Botanical Forum | 3.4 Claims on digestion/absorption of nutrients                               | Line 237: Could the NDA panel elaborate in more detail why it is of the opinion that improved digestion and absorption of nutrients might be but not is considered as a beneficial effect. |
| European Botanical Forum | 4.1 Claims on the function of the immune system                               | Line 291: Could the NDA panel clarify if such supportive evidence is only acceptable in combination with clinical outcomes?                                                                               |
| ORGANISATION               | CHAPTER TEXT                                      | COMMENT TEXT                                                                 |
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| European Botanical Forum  | 4.1 Claims on the function of the immune system  | Line 277: What is meant by ‘appropriate measures’?                           |
|                           |                                                  |                                                                              |
| European Botanical Forum  | 4.1 Claims on the function of the immune system  | Line 273: It would be good if EFSA could elaborate on what it would consider acceptable changes in immunological parameters. |
|                           |                                                  |                                                                              |
| European Botanical Forum  | 4.1 Claims on the function of the immune system  | Line 271: It would be very helpful to specify what changes in immunological parameters would need to be presented to be acceptable. If a reduction of the incidence of infection is demonstrated, would the NDA panel refuse the claim when no concomitant changes in immunological parameters are presented? |
|                           |                                                  |                                                                              |
| European Botanical Forum  | 4.1 Claims on the function of the immune system  | Line 270: In the opinion on Lactobacillus casei strain Shirota (EFSA-Q-2010-00137), EFSA states that the symptoms used to define the occurrence of upper respiratory tract infection (URTI), i.e. running nose, sore throat, fever and cough, are non-specific, and that the presence of one or more of these symptoms is not an appropriate measure of the occurrence of URTI. Could the NDA panel provide clarification on the measures it would consider appropriate in this respect? |
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|                           |                                                  |                                                                              |
| European Botanical Forum  | 4.1 Claims on the function of the immune system  | Line 268: Does this mean that all of the 3 following outcome measures need to be provided for a claim on immune function: evidence on the reduction of numbers of pathogens + incidence + immunological parameters? |
|                           |                                                  |                                                                              |
| European Botanical Forum  | 4.1 Claims on the function of the immune system  | Line 266: Why would a claim relating to the natural defenses need to be better defined when a normal functioning of the immune system as such is considered to be beneficial? The extent to which the substance is useful for the maintenance of the natural defenses would be apparent from the data submitted. If more specification is required, it should be specified what further information would need to be supplied and what would not be considered sufficient. Clarification is also needed on what kind of evidence would then be acceptable and what not. |
|                           |                                                  |                                                                              |
| ORGANISATION              | CHAPTER TEXT                                      | COMMENT TEXT                                                                 |
|--------------------------|--------------------------------------------------|------------------------------------------------------------------------------|
| European Botanical Forum | 4.1 Claims on the function of the immune system   | Line 263: This section refers only to the maintenance of the normal immune function. It would be necessary to clarify whether claims on the improvement of the immune function could be acceptable with the same level of substantiation and if not, what further elements would need to be provided. |
| European Botanical Forum | 4.2 Claims on reduction of inflammation           | Line 297: Can EFSA clarify what biomarkers it would consider acceptable and what not? |
| European Botanical Forum | 4.2 Claims on reduction of inflammation           | Line 296: We welcome the recognition that inflammation is a physiological response and deducts that effects of foods and food components on a physiological inflammatory response can be considered a health benefit. |
| European Botanical Forum | 4.3 Claims on reducing a risk factor for infections or allergy | Line 310: Could the NDA panel clarify which biomarkers would be acceptable? |
| European Botanical Forum | 4.3 Claims on reducing a risk factor for infections or allergy | Line 308: It is clear that the demonstration of a direct effect on the reduction of infection episodes is far more valuable for consumer health that the demonstration of the reduction of a risk factor for infection. |
| ORGANISATION                 | CHAPTER TEXT          | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-----------------------------|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| French Academy of Pharmacy  | General comments      | L. 103 How can we differentiate a beneficial physiological effect from a pharmaceutical one since in both cases the reference is homeostasis?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                             |                       | L. 114 What is an independent predictor risk factor?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|                             |                       | L. 116 The relationship of the risk factor to the development of the disease is biologically plausible (or demonstrated?)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|                             |                       | L. 119 - 125 Since the effect must be demonstrated in healthy population, and since the definition of food supplements must demonstrate a beneficial physiological effect, (not pharmaceutical) Is it necessary to use as a reference which is asked for drugs and sometimes more (a same herbal food supplement has a pharmaceutical status, but can’t have a food supplement status)? In those conditions, at which level can we consider that the beneficial effect is relevant? |
|                             |                       | L. 149 Is the reproducibility indispensable if the clinical study is relevant?                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

French Academy of Pharmacy

General comments

L. 103 How can we differentiate a beneficial physiological effect from a pharmaceutical one since in both cases the reference is homeostasis?

L. 114 What is an independent predictor risk factor?

L. 116 The relationship of the risk factor to the development of the disease is biologically plausible (or demonstrated?)

L. 119 - 125 Since the effect must be demonstrated in healthy population, and since the definition of food supplements must demonstrate a beneficial physiological effect, (not pharmaceutical) Is it necessary to use as a reference which is asked for drugs and sometimes more (a same herbal food supplement has a pharmaceutical status, but can’t have a food supplement status)? In those conditions, at which level can we consider that the beneficial effect is relevant?

L. 149 Is the reproducibility indispensable if the clinical study is relevant?
| ORGANISATION            | CHAPTER TEXT                                      | COMMENT TEXT                                                                                                                                 |
|------------------------|---------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| French Academy of Pharmacy | 3.3 Claims on oral and gastrointestinal microbiota | L. 226 and 231 Can you precise what is a normal defence in the GI tract and what kind of measures would be relevant.                       |
| FrieslandCampina       | General comments                                  | General comments                                                                                                                                 |

In general it is indicated that the Guidance is still very vague. The most important general issues are:
• Both function and risk-reduction claims are used pell-mell in this guidance document. Could the panel clarify the difference between the two type of claims in relation to Gut health and immune function?
• The ILSI published in the European Journal of nutrition (2004) [Suppl 2] 43: II/118–II/173 a topic on PASSCLAIM; Gut Health and immunity. The document describes a variety of tests which indicate how Gut Health and Immunity could be tested. Unfortunately this document is not incorporated in the guidance.
• The Document not really gives a description on how possible claim dossiers on Gut Health and immunity will be assessed. How can the panel guarantee that dossiers will be assessed in similar ways taking into account that there will be changing assessment committees?
• In the future will there be possibilities to ask questions in relation to study design, need for further substantiation etc?
• It would be vary valuable if the guidance had a scheme, or a decision tree.

2.1 Beneficial physiological effect
- Ln 108-118: Talks about risk factors, it would be beneficial if a list of approved risk factors are included in the document. E.g. Gut permeability is a very important risk factor for developing (chronic low-grade) inflammation, Ln 232 indicates that this is not sufficient. The PASSCLAIM publication could be of help in this matter.
- Ln 109: only talks about risk factors, why not specify clinical outcomes?
- Ln 114: Talks about a predictor of disease, what is the difference with biomarkers, and can these be further specified?
- Ln 119-125: Talks about target groups, and that that would be the general healthy population. However the possible “Claims on gastrointestinal discomfort” (Ln 177-182) is confusing as IBS is in principle a disease as diagnosed by the Rome II diagnostic criteria in 2000. It is generally accepted that there is no definition for “healthy” indicating that it is relatively impossible to measure physiological beneficial effects in this group. E.g., are obese people healthy? In clinical trials does this mean that, to measure any results, healthy people first have to be induced with an illness? There needs to be a broader possible test group then only people suffering from IBS which can easily be extrapolated to the healthy population in general.

2.2. Studies/outcome measure appropriate for substantiation of claims
- Ln 136-141: Describes that studies have to be done with similar product, in cases of ingredients, does this mean that
Outcome of a public consultation on a draft guidance on the scientific requirements for gut and immune function claims

| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
|--------------|--------------|--------------|
| FrieslandCampina | 3.1 Claims on bowel function | it will be sufficient to show an effect with an ingredient and that the claim then can be used in different types of food matrices?  
• Ln 149-150: Consistence of studies, indicates that more studies need to be done, could it be indicated when studies are sufficient, do we need to perform a meta-analysis?  
• Ln 153: The extrapolation of study results to the target population (e.g., the general population) from studies in groups other than the target population is very vague and needs further specification. Which characteristics makes at study group acceptable, e.g., different age groups, people with a specific disease? |
| FrieslandCampina | 3.2 Claims on gastrointestinal discomfort | • Ln 165: Because normal bowel habits vary considerable from person to person, it might be very helpful when it should be clear what should be understood by “normal ranges”. It would be very helpful when this could be further specified what is normal according the Panel.  
• Ln 181-2: People with other functional gastrointestinal disorders than IBS (which is a disease) should also be considered as appropriate study groups to support claims on the general population. Other wise it is almost impossible to show any effects. |
| ORGANISATION       | CHAPTER TEXT                                      | COMMENT TEXT                                                                                                                                                                                                 |
|--------------------|-------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| FrieslandCampina  | 3.3 Claims on oral and gastrointestinal microbiota | 3.3 Claims on gastrointestinal microbiota                                                                                                                                                              |
|                    | • Ln 189-91: If the Panel considers reduction of specific pathogenic bacteria a beneficial physiological effect, then in the same line of argumentation the increase of beneficial lactobacilli or bifidobacteria can also be considered a beneficial physiological effect (Ln 188). What should be considered as the overriding beneficial effect to allow a claim when the pathogenic bacteria does not change in number whereas the beneficial bacteria increase? |
|                    | • Ln 200: describes a 1 log reduction, it has been shown that when people from nature have a higher content of a specific bacteria, the increases or reduction varies per person. Is it shown by clinical studies that a reduction of 1 log is beneficial for health? Secondly it should be stressed that it is highly impossible to measure a log 1 reduction in a healthy population. |
|                    | • Ln 203-5 are clearly about art 14 claims; are lines 205-8 (claimed effect related to pathogens) referring to functional (art. 13) claims, e.g. immune defenses? Throughout the guidance, a clearer distinction could be made between DRR claims (e.g. Ln 203-5) and functional claims (e.g. Ln 226-35). |
|                    | • Ln 226-30: An increase of potentially beneficial microbes should also be considered as supportive for claims, especially when increases in such amounts that beneficial microbes are considered part of the mechanism of action |
|                    | • Ln 232-235: Indications are mentioned that a variety of outcomes may be considered as supportive. When more the one of these outcomes are shown, would it then be acceptable? Some examples: o For instance the changes in microbiota, accompanied by a lowering of inflammation markers in the blood such as TNF alpha. o For instance the combination of increase of Bifidobacteria and reductions of certain illnesses. o For instance the increase of bifidobacteria, while pathogens stay the same but IL 6 reduction in elderly |
|                    | Overall in this section: if only the reduction of pathogens needs to be shown for claims on improvement of the gastrointestinal microbiota, and the study needs to be done in healthy people. What type of ethical study design will be suitable? |

Supporting Publications 2011:136
| ORGANISATION       | CHAPTER TEXT                        | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
depleted resulting in decreased SCFA production. Together with the absorption of the SCFAs, this results in a gradual decrease of the butyrate levels towards the distal colon. These regional differences of butyrate concentrations are taught to have implications towards the occurrence of diseases, such as colon cancer and UC, with the distal colon demonstrated to be more frequently and severely affected. Moreover, the studies of Vanhoutvin et al. (2) and Hamer et al. (3) showed beneficial effects in the rectum and sigmoid colon in healthy volunteers following rectal administration of butyrate at physiologically relevant doses.

In view of the essential role of butyrate in the colon function, it is undeniable that well tolerated nutritional interventions providing increases of colonic butyrate within the physiological range are beneficial to health. In human intervention trials the assessment of luminal butyrate levels is practically restricted to the measurement of fecal butyrate levels. Although the analysis of the butyrate levels in the feces may not allow concluding on the butyrate production throughout the entire colon, it is indicative of the butyrate levels in the distal colon, which particularly benefits from increased presence of luminal butyrate.

For a more detailed argumentation please contact Olivier.lescroart@fugeia.be.

Hamer et al 2008 Aliment Pharmacol Ther 27, 104-119
Vanhoutvin et al 2009 Neurogastroenterol Motil 21, 952-e76
Hamer et al 2009, Clinical Nutrition 28, 88-93

| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
|--------------|--------------|--------------|
| HFMA         | General comments | Overall the EFSA draft guidance is very informative & sensible. The types of beneficial effects and the appropriate outcome measures are all logical & understandable. General issues and comments are: In sections 3 and 4 more information is required on the degree of evidence necessary in terms of the duration & numbers of persons studied. It would also be helpful to have advice on suitable controls in studies to minimise bias and overcome the issue of blinding. Advice on the number of outcome measures per claim on which EFSA requires data is also needed. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
|--------------|--------------|--------------|
| HFMA         | 3.1 Claims on bowel function | More advice is needed on what are the acceptable study groups – for example will data in constipated subjects be viewed as pertinent data to substantiate a claim? It would be helpful to give guidance on how many of the appropriate outcome measures EFSA would like to see data for – i.e. is it acceptable to have good data on just one of these measures, or is EFSA looking for data on all of these measures, or something in between. More information would be helpful about how EFSA views subjective data in this area – can this be used to substantiate a claim, or would this only be considered as supporting data? Are subject-reported data on stool frequency considered as objective or subjective evidence, and is this a sufficiently strong end point to substantiate the claim? |
| HFMA         | 3.2 Claims on gastrointestinal discomfort | In section 3.2 we note that the appropriate outcome measures are based on subjective data. It would be helpful to have more information to understand the scientific basis of cases for which EFSA will consider subjective data as pertinent to substantiate a claim, and cases where it is not acceptable. |
| HFMA         | 3.4 Claims on digestion/absorption of nutrients | In section 3.4, more advice would be helpful in relation to situations where absorption is a limiting factor for nutrient status. It would be helpful to have information about the acceptability of using particular population sub-groups, and particularly in relation to medical conditions e.g. situations of poor B12 absorption in older people. |
| HFMA         | 4. Immune system | The sections in part 4 are particularly complicated and would benefit from a summary table for purposes of clarity. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
|--------------|--------------|--------------|
| IDACE        | General comments | IDACE welcomes the EFSA initiative to organize a meeting with scientific stakeholders to give more guidance to applicants on scientific requirements for health claims related to gut and immune function. However, IDACE would like to underline that with this Guidance the Panel may not have taken fully into account scientific elements specific to infants and young children, including those associated with the immature physiology specific to infants and young children in the first three years of life. Infants are born with physiologic parameters, like digestive processes, intestinal barrier function and immune function not yet fully developed. As a consequence, the impact on gut health and immunity from foods and food constituents may differ from that of older children and adults; therefore, outcome measures for assessing the impact of nutritional interventions should be adapted accordingly. IDACE scientists believe, and seek confirmation from EFSA, that the promotion of normal development and maturation of these functions is considered a beneficial physiological effect and that the development of these functions in breastfed infants can be taken as a reference. |

IDACE would underline that its members produce very specific categories of foods falling under Directive 2009/39 on Foods for particular nutritional use for specific target groups:

- very specific targeted population with specific nutritional needs due to their physiological condition
- and people with specific disease (Foods for Special Medical Purpose)

As a consequence, IDACE requests that EFSA take into account these very specific target groups when providing guidance on scientific requirements for health claims and while assessing health claims for products for these target groups. Furthermore, IDACE stresses the importance of considering outcome measures special to these target groups, particularly those that can be used in clinical trials conducted with infants and young children. IDACE understands that the Panel is aware of special considerations related to clinical research conducted with infants and young children and wishes to remind the Panel that clinical research in this special population group can only be done under strict conditions not applicable to older populations. No healthy volunteers centers are available (as the case for adults) and assessment by ethical committees is generally stricter. Repeating trials to reproduce results may be considered unethical, especially when results of completed, well-conducted trials are considered to be substantial by the scientific community.

IDACE believes that consideration should be given to innovation. The development of health claims for new foods or food constituents proceeds along a sequential path based upon clinical trial design and conduct, in some cases utilizing novel biomarkers. It would be appropriate for EFSA to give consideration and support to innovative claim development when it is well supported by science, but is "new" in terms of biomarkers or health outcomes, and not only based on classical deficiency or currently accepted disease risk reduction scenarios.
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3.3 Claims on oral and gastrointestinal microbiota

Lines 186-188: Claims on gastro-intestinal microbiota. Pediatric scientists have always accepted that the “golden standard”, health and development outcomes of the breastfed infant, should be considered the reference when assessing outcomes of formula-fed infants. Pediatric studies, therefore, focus more on increasing the number of lactobacilli and/or bifidobacteria, to be consistent with those of the breastfed infant, rather than on decreasing the number of pathogens. It has been known for a long time that bifidobacteria are dominant in the intestinal microbiota of breastfed babies. Moreover, the differences are not only quantitative but also qualitative; breast-fed infants’ microbiota are dominated by specific bifidobacteria species distribution such as Bifidobacterium breve, B. infantis, B. bifidum and B. longum, that have health effects later in life (Salminen & Satokari, 2009). IDACE therefore proposes, and seeks clarification, on whether the EFSA agrees that for infants and young children a gut microbiota composition closer to a microbiota of a breast-fed infant is seen as a beneficial effect by the Panel.

Line 200. The Panel mentioned that a microbiologically relevant reduction of pathogens should be demonstrated by a decrease of at least one log. IDACE would like to stress that in a population of infants and young children the occurrence of proposed pathogenic or toxicogenic bacteria is low, which makes it clinically irrelevant to use the cut-off of one 1 log for this specific target population.

IDACE proposes, and seeks confirmation, that with infants and young children it is meaningful to consider significant (statistically and biological relevant) reductions in numbers of pathogens (being possibly less than 1 log reduction) or a reduction in prevalence, as well as a bifidobacteria dominant composition.

Line 225. Microbiological risk in the first years of life is endowed with peculiar features when compared to the same risk in adulthood. Specific pathogens can be harmful for infants and groups of infants at greater risk than for older individuals (e.g. E. Sakazakii). We wish to get clarification from the Panel regarding which groups of micro-organisms it especially considers as pathogenic or toxicogenic for infants and young children. We would be glad to work with the Panel to generate lists considered important by pediatric scientists.

The Panel sees both reduction of numbers of pathogens or their toxins AS WELL AS clinical outcomes demonstrated in human intervention studies as appropriate outcome measures for claims related to maintaining normal defence against pathogens in the GI tract. IDACE seeks confirmation that a claim related to maintaining normal defence against pathogens can be substantiated by ONLY clinical outcomes in human intervention studies OR ONLY reduction of pathogens or their toxins. In addition, in case the pathogen itself is not detectable, is a beneficial effect on the clinical outcomes sufficient to substantiate a claim related to maintaining normal defence against pathogens?
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Line 237-253. IDACE is pleased that the Panel acknowledges that improved digestion or absorption of nutrients might be considered as beneficial physiological effects. Infants and young children are at particular risk for micronutrient deficiency, for example, iron and zinc. IDACE asks for clarification on specific outcome measures and cut-off points to be considered for infants and young children.
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
|--------------|--------------|--------------|
| IDACE        | 3.4 Claims on digestion/absorption of nutrients | Line 237-253. IDACE is pleased that the Panel acknowledges that improved digestion or absorption of nutrients might be considered as beneficial physiological effects. Infants and young children are at particular risk for micronutrient deficiency, for example, iron and zinc. IDACE asks for clarification on specific outcome measures and cut-off points to be considered for infants and young children. |
| IDACE        | 4.3 Claims on reducing a risk factor for infections or allergy | Line 308-321 Claims on reducing risk factors for infections or allergy. The Panel explained that the decision on whether or not the alteration of a risk factor is considered to be beneficial in the context of a reduction of disease risk claim depends on the extent to which it is established that the risk factor is an independent predictor of disease risk. IDACE seeks additional clarification from the Panel on the type of substantiation required to prove that a risk factor is an independent predictor of disease risk, especially with reference to the infant and young child. What would then constitute evidence for a disease risk reduction? The Guidance could spell out clearly that a decrease on the outcome measure of the risk factor needs to be shown. This is not stated clearly but can only be inferred from the current draft. Alternatively, the Guidance could note that for specific population groups, for example infants and young children, evidence of risk reduction could be evaluated based on the current, substantiated science associated with that specific group. IDACE therefore seeks confirmation that in order to substantiate a claim on reducing a risk factor, it is not required to show an effect on clinical outcome as long as the risk factor is confirmed to be an independent predictor of disease risk and the relationship of the risk factor to the development of the disease is biologically plausible. For example, the Panel noted the presence of pathogens as validated risk factors for claims related to infections is required. Could the Panel clarify whether both a reduction of infection, in addition to a reduction in numbers of pathogens, are required or whether only one of the 2 outcomes is sufficient? And, can this be considered on a case by case basis depending on the target population under consideration? IDACE also requests clarification from the Panel on criteria to establish differences between diseases and symptoms in certain cases, for example for constipation and diarrhea. Finally, IDACE wishes to express its sincere thanks to the EFSA for facilitating a means, through the comment period on the Guidance and the scheduled meeting, to reach consensus on reasonable guidance for substantiating health claims, particularly in special populations such as infants and young children. |
IDACE

4.3 Claims on reducing a risk factor for infections or allergy

Line 308-321 Claims on reducing risk factors for infections or allergy. The Panel explained that the decision on whether or not the alteration of a risk factor is considered to be beneficial in the context of a reduction of disease risk claim depends on the extent to which it is established that the risk factor is an independent predictor of disease risk. IDACE seeks additional clarification from the Panel on the type of substantiation required to prove that a risk factor is an independent predictor of disease risk, especially with reference to the infant and young child.

What would then constitute evidence for a disease risk reduction? The Guidance could spell out clearly that a decrease on the outcome measure of the risk factor needs to be shown. This is not stated clearly but can only be inferred from the current draft. Alternatively, the Guidance could note that for specific population groups, for example infants and young children, evidence of risk reduction could be evaluated based on the current, substantiated science associated with that specific group. IDACE therefore seeks confirmation that in order to substantiate a claim on reducing a risk factor, it is not required to show an effect on clinical outcome as long as the risk factor is confirmed to be an independent predictor of disease risk and the relationship of the risk factor to the development of the disease is biologically plausible.

For example, the Panel noted the presence of pathogens as validated risk factors for claims related to infections is required. Could the Panel clarify whether both a reduction of infection, in addition to a reduction in numbers of pathogens, are required or whether only one of the 2 outcomes is sufficient? And, can this be considered on a case by case basis depending on the target population under consideration?

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ILSI Europe aisbl

General comments

We appreciate EFSA’s intention to issue a guidance document for specific health claim requirements to increase the understanding between applicant and EFSA, as well as the planned workshops.

The document has a good structure, but it should be improved in terms of the distinction between the requirements in Part 3 in contrast to Part 4. For example in part 4.1 the description in line 268 to 273 relates to part 3.3 as reference. It would be much clearer also to state the examples given in part 3.3 again in the light of the focus of part 4.1.

Many examples in the draft Guidance are based on what will not be appropriate or sufficient; could the Panel provide more positive examples in terms of what will be appropriate or sufficient?

The draft Guidance does not refer to PASSCLAIM guidance related to immunity and gut health (Cummings et al.)
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
|--------------|--------------|--------------|
| 2004 Eur. J. Nutr. (S2):II/118-II/173); could the Panel explain why this seminal paper was not cited? | Ln 103-6 and Ln 117-8: Key elements of a claim are a food constituent and an effect. What the draft guidance now implies is that a given effect can be considered to be beneficial if caused by food constituent x, but not if caused by food constituent y. How can the health relevance of an effect depend on what causes the effect? Can the Panel give any insight, or an example of an effect being beneficial in one ‘context’ but not in another one? Or, if these sections are not meant to be interpreted as above, can the Panel then clarify these parts? | Ln 107: “Maintenance of a function”. Could the Panel kindly clarify what is meant by “function”? Does the Panel really give any room for “improvement of a function”, for example the immune function, or is the interpretation on the effect of dietary components on immune function reduced to naming the minimal nutritional requirements needed for basal immune functions? |
| Ln 108-10: We assume that the last part of this sentence in brackets means to express that to make a disease risk reduction claim one cannot just demonstrate disease risk reduction; one must (additionally or possibly solely) demonstrate disease risk factor reduction. | Ln 114-116: Please clarify whether both conditions should be met (114-115 and 116), or whether meeting one condition is sufficient. | Ln 120: Could the Panel possibly clarify what is meant by these “specific subgroups” and how they are defined?|
| Ln 142-50: Could the Panel possibly make this section more specific, e.g. in terms of how to appropriately conduct as to minimise bias. Are there certain specific “non-negotiable” criteria? | Ln 147-50: Does consistency necessarily have to be demonstrated across several studies, or can it also be shown in one large study, comprising a variety of subjects in a variety of settings such as one may have across several smaller studies? Furthermore, would the Panel agree that a meta-analysis of the pertinent studies or, even better, an analysis of the pooled data of such studies, is more pertinent than the individual studies? | Ln 153-6: Could the Panel give any insight in how they evaluate whether such extrapolation is biologically justifiable? From the IBS example in lines 177-82 we deduct that if the differences between people with or without a certain condition are “gradual” rather than ‘systematic’, data from people with such condition can be extrapolated to people without such condition; would the Panel agree? |
| As to the ranking of benefits (is, may be or might be beneficial for health), what are the criteria for this kind of ranking? How will the “might be beneficial” claims be evaluated; can they reach a positive opinion from EFSA or will they be rejected because they are not sufficiently relevant for health? | | |
| ORGANISATION       | CHAPTER TEXT     | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|--------------------|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ILSI Europe aisbl  | 3.1 Claims on bowel function | Ln 161: “Claims on bowel function” implies that more than one (type of) claim on bowel function may be possible. Effects on transit time, on frequency of bowel movements and on stool bulk are related and will often coincide. If one demonstrates one of these effects only, can one such effect be considered to be sufficiently substantiated?
Ln 165-6: Bowel habits vary considerably from one person to person, within a range one can refer to as “normal”. We need to define related “normal ranges”. Are changes in bowel function within the normal range beneficial for health? If so, what would be the smallest relevant effect? If not known, how can we progress in this respect? Does EFSA consider a change from normal to normal (i.e. within the normal range) beneficial? From the following we conclude that EFSA may see subtle changes in maintenance or improvement within the normal range as beneficial: In the context of article 13.1 claims on plant constituents, EFSA has evaluated the following effects as beneficial for human health: 1) maintenance of normal bowel function, 2) bowel motor function within normal range, 3) improvement of bowel motor function, 4) improvement of bowel motor function within the normal range, and 5) improvement of intestinal transit.
Ln 167-8: Appropriate measures of bowel function include stool consistency, as it is the parameter of constipation that correlates best with transit time. Constipation is defined by the American National Institute of Diabetes and Digestive and Kidney Diseases as having fewer than three bowel movements per week; possibly to be adapted to the European situation. We recommend that the Panel adopts a definition of constipation, and measures that validly reflect this. Consistency of the stools is related to the water content, which is around 70-80%. Constipated subjects generally pass harder stools with water content of less than 70%. In general, as daily stool weight increases, stools become softer and less well formed. Particularly, it is the hardness and dryness of stools that is thought to cause discomfort on defecation (Cummings et al. 2004 Eur. J. Nutr. (S2)43: II/118). Consistency of the stools (e.g. increased softness) could be considered as an outcome measure. Consistency is usually recorded in a diary after visual inspection (Bristol Stool Form Scale) or measured by physical analysis of water content. We would like to suggest to consider subjects with functional constipation as appropriate study group. Functional constipation has been defined according to the Rome III Diagnostic Criteria on the basis of occurrence of straining, lumpy or hard stools, number of defecations per week, etc. Segmental contraction and propulsive activities are affected by endocrine, metabolic and environmental factors. Frequency of defecation is high in infancy and becomes less frequent during ageing. Environmental influences affecting colonic motility are stress, eating patterns/dietary intakes and physical activity. Due to the many influential factors, high inter- and intra-individual variation exists in the levels of colonic motility (Wyman et al. 1978 Gut 19: 146). Episodes of low motility and in some cases of (temporary) incontinence can occur also in healthy people. Functional constipated subjects could be considered as appropriate study group to support claims on bowel function intended for the general population. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| ILSI Europe aisbl | 3.2 Claims on gastrointestinal discomfort | Ln 169: Ease and completeness of defecation are important factors in gastrointestinal comfort and need to be added to the beneficial physiological effects in the area of gastrointestinal (dis)comfort. Ln 175-6: Symptom severity questionnaires are targeted towards patients, e.g. dyspepsia and irritable bowel disease. The discriminate validity of the Functional Digestive Disorders Quality of Life questionnaire (FDDQL) has been shown by the more severe the functional digestive disorder appears to be, the more impaired the quality of life is. Also, validity has been supported by the correlation found between FDDQL and SF-36 questionnaire scales for more general measures of well-being (Chassany et al. 1999 Gut 44: 527). For other questionnaires, e.g. Gastrointestinal Symptom Rating Scale modified for IBS patients (GSRS-IBS), validity has been tested against several disease specific health-related quality of life questionnaires showing good correlation (incl. FDDQL) (Wiklund et al. 2003 Scand. J. Gastroenterol. 38, 947). Can the Panel specify against what subjective questionnaires must be validated? EFSA questioned in one opinion on LGG (EFSA-Q-2008-444) the relevance of a (statistically significant) increase of score of bowel symptoms domain by 0.25 points on a 0-7 scale. Can ‘rules of the thumb’ be developed on, in order to be meaningful for health, how many % one must minimally change on the total span of a scale? We believe urgency, feeling of incomplete evacuation, straining, belching, heartburn, nausea, post-meal fullness, vomiting and mucus or blood in stools also reflect gut (dis)comfort and therefore effects on any of these phenomena are relevant for health; would the Panel agree? Ln 179-81: Does the Panel say that if the differences between people with or without a certain condition are gradual rather than ‘systematic’, data from people with such condition can be extrapolated to people without such condition? Ln 181-2: People with other functional gastrointestinal disorders such as functional dyspepsia, functional constipation, functional diarrhea should also be considered as appropriate study groups to support claims on the general population, having milder versions of the same symptoms. |
| ILSI Europe aisbl | 3.3 Claims on oral and gastrointestinal microbiota | If the Panel considers reduction of specific pathogenic bacteria a beneficial physiological effect, then in the same line of argumentation the increase of beneficial lactobacilli or bifidobacteria can also be considered a beneficial physiological effect. Breast milk is generally seen as the gold standard for infant nutrition, and it has bifidogenic effects. Amongst the many functions bifidobacteria and lactobacilli have, is the creation of a non-permissive environment for pathogenic bacteria in the large bowel. This can be induced by metabolic shifts (production of anti-microbial substances) and/or occupying ecological niches of virulent microorganisms restricting their abundance in the colonic microbiota (Servin 2004 FEMS Microbiol. Rev. 28: 405). Ln 190-1: Can the Panel elaborate on the need to identify for example the pathogen that causes travellers’ diarrhoea, given that what matters in the end, is that an individual gets such diarrhoea less often, for a shorter period and with less severity. Ln 192-5: Has the Panel here in mind a functional claim on immunity being art. 13, or a disease risk reduction claim, infection being the disease of which the risk is to be decreased, art. 14? |
| Organisation | Chapter Text | Comment Text |
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| Ln 200:      | What is the basis for considering a one log reduction, being a 10 fold reduction, as not meaningful? Would this not also depend on the starting level: a decrease from 109 to 108 might not be the same as a decrease from 105 to 104. Furthermore, can we also assume that a change > 1 log is meaningful? |
| Ln 199-200:  | Can EFSA also provide the same type of clarity on the statement "sustained over time": for how long? |
| Ln 203-5     | Are lines 205-8 (claimed effect related to pathogens) referring to functional (art. 13) claims, e.g. immune defences? |
|              | Throughout the guidance, a clearer distinction could be made between DRR claims (e.g. ln 203-5) and functional claims (e.g. ln 226-35). For DRR claims, the data needed primarily demonstrate reduction of a risk factor; does it mean that the effect on the disease outcome (disease risk) is secondary, e.g. only supportive, and even not necessary? Would, for functional claims, a reduced number of pathogens be sufficient, or is an effect on a clinical outcome needed as well? In other words, should the "as well as" (ln 228) be understood as and or and/or? Meaning, if positive results are available on incidence, duration and/or severity of infection (e.g. diarrhea), would that be enough to make a functional claim such as "defences against pathogens in the GI tract", without having to show a reduced number of pathogens, because implicit from the effect on the infection? Apart from that clinical outcomes are in the end what counts, it may often be almost impossible to demonstrate reduction of pathogens, e.g. in children where sampling might be difficult or non-ethical. |
| Ln 209-25:   | The vast majority of the organisms listed by the NDA are food-borne pathogens that normally do not reside in the gastrointestinal tract of the general healthy population. Would individuals who are carriers for these organisms still be considered as representative for the general population? |
| Ln 232-3:    | "effects on intestinal permeability (...) are in themselves insufficient for the substantiation of the claim". In order for a pathogen to invade and translocate to extra-intestinal tissues, it has to pass the intestinal barrier, the integrity of which is essential for human health. Thus, strengthening the epithelial barrier function could be considered a beneficial physiological effect to substantiate a functional claim related to the improvement of normal defence against pathogens in the gastrointestinal tract. The Cr-EDTA test as an example is considered a valid marker to assess intestinal barrier function. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| ILSI Europe aisbl | 3.4 Claims on digestion/absorption of nutrients | Ln 240-53: The examples on lactose and iron suggest that for an increased bioavailability to be beneficial for health, one must demonstrate that health will be improved by increasing bioavailability of the food constituent concerned; lines 255-6 confirm this. We suggest to put latter upfront in this Section.  
Ln 246: We suggest inserting between “clinical symptoms” and “or”: ‘such as nausea, cramping, bloating, diarrhoea and flatulence’  
Ln 251-3: How much improvement in mineral absorption would be considered meaningful? The body of evidence for certain minerals in specific population is quite comprehensive and could be leveraged herein - specific guidance could be given for key “risk” nutrients for population segments. For example, guidance on meaningful improvement in nonheme iron absorption in children and young women, endpoints being hemoglobin and serum ferritin.  
Ln 255-6: Can only the increased bioavailability of nutrients be a beneficial effect, and not of e.g. antioxidants or other food constituents that are not ‘classical’ macro- or micronutrients?  
Ln 255-6: This restrictive limitation appears not in line with the previous positive opinions by the Panel. For example, using the same logic, should the cholesterol lowering effect be only limited to those subjects in which the elevated cholesterol is the main factor dictating the true risk of CVD? Or should the claims on vitamins and minerals, using similar logic, be limited only to the cases where the availability of these nutrients to immune cells etc. is the limiting factor in the maintenance of normal functions? |
| ILSI Europe aisbl | 4. Immune system | In comparison to Chapter 3.1.-3.3, in Chapter 4.1-4.3 examples for biomarkers are rare and not well defined. It would be very good to have a table with markers on immune parameters as a kind of summary with an assessment of the validity or suitability of these markers in relation to certain immune functions, as an update of the work done in PASSCLAIM (Cummings et al. 2004 Eur. J. Nutrition (S2) 43: II/118), Albers et al. 2005 British J. Nutrition 94, 452 and Calder et al. 2009 British J Nutrition 101, S1.  
Part 4 in general only relates to infections by bacteria. The most common infections in humans, such as common cold, are the result of a viral infection. Can this be integrated into the guidance document, especially in terms of markers to be used? |
| ILSI Europe aisbl | 4.1 Claims on the function of the immune system | L260: The immune system also helps to defend against tumour cells.  
L263: Maintenance of normal immune function should be extended to recovery of normal immune function or immune homeostasis, e.g. in cases of deficiencies, infections or challenges.  
L269: We believe ‘and’ is to be read as ‘and/or’, and we propose to specify this.  
L271-3: Is the Panel referring here to a functional claim on immune defences? Is the best proof of better immune defences not in a decreased number of infections (or fewer and/or less severe episodes)?  
L268-73: We are aware that EFSA’s remit is the EU Health Claim Regulation, which prescribes that a claim on disease risk reduction must be substantiated by disease risk factor reduction. At the same time, getting ill less often or |
for shorter time or with less severity (whether accompanied with reduced risk factors, or not) is a crucial element. We therefore fail to understand why, even when making “functional” claims on some kind of ‘protection’ or ‘defences’, human intervention studies that show a reduction in disease incidence, duration or severity are not considered as core, but as supportive evidence only.

L273: When referring to the immune system, a concomitant change in immunological parameter is needed. Does it mean that for a claim on immune system / defence against pathogens, evidence has to be provided for effects on: infections + reduction of pathogens + immune parameter? And for a claim on the immune system related to response to allergens: incidence of allergic manifestations + immune parameter?

L275-7: Could the Panel give examples of such appropriate measures? Are they the same, or different from the ones in lines 289-92?

L279-86: As indeed vaccines are usually produced with adjuvants that are already very effective in stimulating protective antibody titres, it is very difficult to demonstrate any further stimulating effect by food constituents. Can claims be substantiated by studies with “non efficient” vaccines (e.g. ETEC vaccine)? Must the claim specify the specific pathogen (e.g. defence against E. coli ETEC), or could the effect be generalised (e.g. defence against pathogens)? Is it relevant for health if a food constituent increases antibody titres within the “protected” range? Could that be seen as improving normal function of the immune system?

L283: Does “as well as” express “and”, or “and/or”?

L287-92: Can the Panel give insight in the criteria that have resulted in this list? We observe that it differs from PASSCLAIM conclusions; can the Panel explain? In particular, two parameters have been reported, in several publications, to be associated with risks of infections: low NK cell activity, and a decline or deficiency in sIgA. A consistent effect on such parameters could be considered as evidence of reinforcement of immune defences and/or improved normal function of the immune system, and is therefore relevant for a related function claim. The only example mentioned for stimulation of protective antibody titres is derived from medicine. It would be more helpful to have an additional example in relationship to nutrition.

The use of the term “incidence” as an outcome measure is not clear. Incidence is a measure of the risk of developing a new condition (disease) within a specified period of time. This refers, however, to the development of disease itself. An example for a clinical measure for allergy could be the SCORing Atopic Dermatitis scale (SCORAD), a clinical tool for assessing the severity of atopic dermatitis.

Many vaccines are multivalent and individuals may respond to some of the included antigenic variants and not others. An increase in the number of antigenic variants to which the individual responds should also be considered beneficial.
| ORGANISATION     | CHAPTER TEXT                          | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                 |
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| ILSI Europe aisbl| 4.2 Claims on reduction of inflammation | Ln 294-304: The science may be more advanced than implied in this draft guidance; it seems that more specifics could be provided. For example, the American Heart Association considers hsCRP as an independent risk factor for cardiovascular disease and stroke. Would the Panel consider interventions that to reduce hsCRP?  
Ln 294-304: For which diseases or in which contexts would reduced inflammation be beneficial?  
Ln 301-4: How can decreased inflammation be a good thing if caused by food constituent x, but not if caused by food constituent y? Can the Panel provide examples? Or, if this section is not meant to be interpreted as above, can the Panel then clarify this part?  
Lines 297-298 mention that "changes in markers of inflammation such as various interleukins do not indicate a beneficial physiological effect per se”. In contrast, lines 299-300 state "Chronic inflammation is associated with a number of diseases, and under certain circumstances reducing levels of markers of inflammation might indicate a beneficial physiological effect.” Could these apparently conflicting statements be explained? |
| ILSI Europe aisbl| 4.3 Claims on reducing a risk factor for infections or allergy | Ln 308-11 (see also lines 203-8, 226-35): One cannot substitute the other; can the Panel clarify if that means that only the risk factor reduction will do, or must one show as well incidence or duration of … diseases?  
Ln 312-5: Additionally, reduced or absence gut defence factors (antimicrobials, IgA …) are risk factors, and increases in these factors are beneficial physiological effects.  
Ln 315: Which (types of) samples are suitable? Can the Panel provide examples? What are the “appropriate outcome measures”?
Ln 316-7: How can decreased risk factor be a good thing if caused by food constituent x, but not if caused by food constituent y? Can the Panel provide examples? Or, if this section is not meant to be interpreted as above, can the Panel then clarify this part?  
Ln 320-1: Consider adding a section 4.4. on claims on reducing severity and duration of infections or allergic events.  
In line 314 of part 4.3 there is reference to section 4.3 - but it is the same section. Should this be section 3.3? If yes, please refer to our remarks in the General comments, as we would like to see a clearer distinction between the two parts. |
| Institut Rosell    | General comments                     | lines 153 and 156: extrapolation of studies on other groups than the target group (healthy population): would it be possible to give some examples in the guidance?                                                                                                                                                          |
Institut Rosell

General comments

lines 142 to 150 What about number of subjects involved in the clinical trial? In some of the opinions, the Panel considers that “50 subjects” is a small sample size, could the Panel precise the criteria for a sample population being adequate? Regarding power calculation in general: Our understanding is that the a priori power calculation is done in order to ensure that the lack of significant difference between groups means that there is no significant difference between treatments. What is the Panel view on the following question: if we have a significant difference but the N calculated was not reached, and considering that we have enough patients in each arm (more than 30) allowing the application of a good statistical test, would the results of such a study be accepted by the Panel? According our exchanges with statisticians of a French department of evaluation of drug and biological product, methodology and biostatistics, it seems they agree on the following: The power calculation are virtual data and is not so relevant as it is actually. If we have a significant difference and if statistical tests are performed according the respect of application condition (determined by the sample size) these results are acceptable. Also, as we understand there is no pre-established formula as to how many or what type of studies are needed to substantiate a claim, we would appreciate the applicant have the possibility to have dialogue with EFSA in a more formal manner before a dossier is submitted and even before a clinical study would be put in place. We would ask for an official pre-submission meeting.

Institut Rosell

General comments

Lines 136-141: Food constituent vs Food Product

What type of evidence will be requested for a probiotic having had a claim approved as a food supplement to have the claim approved in a different food matrix? For instance, in the case of a food supplement having two different galenic forms (capsules and sachets as examples). Would the studies performed on one galenic form be accepted for the other galenic forms? What kind of evidence would be required to have the claim approved in both forms? Could it be sufficient to demonstrate that the concentration of the active substance is the same in both forms?

Institut Rosell

General comments

Lines 119 to 125: regarding the population groups or target groups. We would appreciate more precisions or examples in this guidance relating to that point. For instance, does the Panel have examples to propose? What about Diarrhea? Our view is diarrhea could be understood as being a situation of a healthy person whose functionality has been altered temporarily (bad functionality of the intestinal system that is only transient in some types of diarrhea like AAD or traveler’s diarrhea).

Institut Rosell

3.2 Claims on gastrointestinal discomfort

Lines 177 to 182: IBS patients are considered an appropriate study group to support claims on GI discomfort intended for general population. What about other populations, like people suffering from diarrhoea? We would appreciate if the Panel could give its opinion on that specific example of extrapolation.
### Institut Rosell

#### 3.3 Claims on oral and gastrointestinal microbiota

**Text:** lines 203 to 208: for Disease risk reduction claims, the studies that show only a reduction in incidence or duration of infections would not constitute evidence for reduction of the risk factor (e.g., numbers of pathogens); however, clinical outcomes could be supportive of the claims related to pathogens.

**Comment:** Does it mean that both (clinical outcomes and outcome measures of pathogens in suitable samples) are necessary to substantiate a claim on reduction in incidence or duration of infections? In that case, we see no difference between DRR claims and claims related to maintaining the normal defence against pathogens in the GI tract, for which the Panel requires also both (clinical outcomes and outcome measures in suitable samples, as per stated in lines 226 to 228 of this draft guidance. Could the Panel clarify this point?

#### 4.1 Claims on the function of the immune system

**Text:** lines 268 to 273: the Panel says the following “for claims involving the immune system, appropriate evidence of a concomitant change in immunological parameters needs to be provided” by referring to section 3.3.: claims on gastrointestinal microbiota. If we understand correctly, this is a clear reference to the link between gastrointestinal microbiota and immune system? Could the panel develop more this part? Does the panel considers that reducing the presence of pathogens in the GI tract is an appropriate outcome measure and considered as an immunological parameter?

### Joint comments: EFFCA / IPA / IFAC

**General comments:**

EFFCA (European Food and Feed Cultures Association), IPA (International Probiotics Association and IFAC (International Food Additives Council) welcome the publication by EFSA’s NDA Panel of the draft Guidance on the scientific requirements for health claims related to gut and immune function. This communication effort of EFSA is definitively an important step forward. By providing insight on the approach and reasoning used by EFSA in the case by case evaluation of applications it provides more certainty for the applicants.

Although the legal framework in place does not foresee any possibility of improvement of applications already filed (mainly due to anonymous character of applications for existing claims) we highly appreciate the ongoing discussion between EFSA, Commission, industry and consumers.

It remains unclear though how in practice this valuable information could benefit to the dossiers filed for existing (art. 13.1.) claims, both already rejected by EFSA and those which are still under review.

Also, the fact that this information is provided when the evaluation is already been underway (and not before the submission) of the dossiers risks to create uncomfortable situation for some market players and cause market distortion.

The possibility to have an open discussion with EFSA and the Commission during the case by case evaluation of claims is of core importance, especially for such products as Probiotics. In fact it is necessary to allow greater flexibility in evaluating these types of claims since studies in healthy population are often unpublished, scarce due to...
### General comments

Kraft welcomes the intention of EFSA to provide further guidance on specific type claims regarding 2 key issues related to substantiation of health claims:

- beneficial physiological effect
- and studies/outcome measures that are considered appropriate for the substantiation of health claims.

First, we would like to comment on the general content of the guidance:

Regarding the beneficial physiological effect, could EFSA provide the criteria applied to evaluate the extend (is/may/might/is not) to which a claimed effect is considered beneficial physiological effect?

What is the final outcome of the assessment ‘might be a beneficial physiological effect’ for a health claim on healthy people?

For studies/outcome measures that are considered appropriate for the substantiation of health claim, the document provides guidance on which markers are considered appropriate by the EFSA but:

- neither on method used to measure these outcomes,
- Example: for claim on bowel function, appropriate outcome measures of the claimed effect in human studies considered by the EFSA include transit time. In this document, the EFSA provide no guidance on appropriate method: radioisotope, coloration, questionnaires etc.
- nor on study designs (number of subjects considered as appropriate, etc).

It will be useful for applicant if the EFSA could provide also guidance on these two issues

General comment regarding the scientific requirements to substantiate health claims:

- the originality of the science and amount of work involved, and therefore could be at risk to be too quickly judged as not representative or not conclusive.
- Without particularly requesting a special treatment for Probiotics, we would appreciate if the EFSA and the Commission try to ensure a higher degree of flexibility of scientific and regulatory judgement. These are badly needed in order to ensure the development of science and innovation and provide sufficient private investment in research and development in the European Union.

More specifically, regarding intervention studies, will it be possible for EFSA to provide more information on requirements regarding to intervention studies, e.g. scientific design and desired outcome? A publication of a reference table with appropriate studies on human intervention design per claim category could be welcomed.

We look very much forward the possibility to have an open and constructive discussion on 2 December in Amsterdam.

EFFCA / IPA / IFAC
| ORGANISATION       | CHAPTER TEXT                          | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                 |
|-------------------|---------------------------------------|                                                                                                                                                                                                                                                                                                                                                                                                       |
|                   | In a global manner, in this document we don’t perceive any proportionality between the level of requirements for the demonstration of the effect and the strength of the claim (art 13 claim: functional claim vs art 14: reduction of a disease risk factor claim). How the EFSA takes into account the strength of the claim in its scientific evaluation? We would expect a document that will leave room for innovative marker and health relationship. How the new science will be taken into consideration in this document? Is it planned to update this document regularly? |                                                                                                                                                                                                                                                                                                                                                                                                       |
|                   | Target population:                    |                                                                                                                                                                                                                                                                                                                                                                                                       |
|                   | Line 119-125: Could the EFSA provide a clear definition of which subjects are considered as part of the “general (healthy) population” and please, give some examples?                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                       |
|                   | Line 119-125: Could the EFSA clarify in which conditions the applicant must specify the study group in the claim wording?                                                                                                                                                                                                                                                                                                                                   |
|                   | Line 153-156: Could the EFSA provide some criteria to help the applicant to define in which case extrapolation from a specific study group to the general population is biologically justifiable?                                                                                                                                                                                                                             |
|                   | Outcome measures:                     |                                                                                                                                                                                                                                                                                                                                                                                                       |
|                   | Line 128-130: Does it mean that the scientific wording approved by EFSA could include a reference to overall good health or health-related well being, if accompanied by a mention on an objective outcome? For example: The food/constituent X contributes to your digestive well-being by improving lactose digestion. If not what is the level of precision required in the scientific wording? Are validated subjective questionnaires considered as appropriate for substantiation of claim or should they be always accompanied by objective outcome measures? How the EFSA considers validated self-reporting questionnaires? |
|                   | Reproducibility of the effect:        |                                                                                                                                                                                                                                                                                                                                                                                                       |
|                   | Line 147-150: We would like to highlight that this is the first time that reproducibility of the effect is discussed in EFSA guidance. Even if the number of studies of demonstration is not precised, does the reproductibility requirement means that it is necessary to perform at least two clinical studies? |
| Kraft Foods Europe | 3.1 Claims on bowel function          | Line 165-166: As mentioned by the EFSA (line 170-173 of paragraph 3.2), alteration of bowel habit is one of the factors that can be associated with abdominal pain or discomfort. So it’s difficult to understand why EFSA evaluate claims on intestinal discomfort “is a beneficial physiological effect” and claim on bowel function as only “might be a beneficial effect”. Could the EFSA explain the logic for the attribution of “is” or “might”?                                 |
| ORGANISATION         | CHAPTER TEXT                           | COMMENT TEXT                                                                                                                                                                                                 |
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| Kraft Foods Europe   | 3.2 Claims on gastrointestinal discomfort | Line 170-173:  
This sentence mentioned drug intake as one of the factor commonly associated with abdominal pain or discomfort. Will the reduction in side effects linked to drug intake be considered as a new beneficial effect of a food or constituent?  
In this case, is the target population the general population? |
| Kraft Foods Europe   | 3.3 Claims on oral and gastrointestinal microbiota | Line 186-188:  
The panel considers that the evidence available does not establish that increasing the number of specific microorganisms or any groups of microorganisms, including lactobacilli and/or bifidobacteria or modulating their activity (increased the SCFA like butyrate or propionate, decreased colon pH etc.) is in itself a beneficial physiological effect. This conclusion is not in line with the one of ILSI (Roberfroid et al., 2010) or the position of the University of Reading on bifidobacteria and human health (letter of July 2009).  
Line 200:  
We would like to highlight that a decrease of 1 log is not relevant for all pathogens. For some pathogen a disappearance is necessary to get a beneficial effect, for others a substantial decrease is sufficient. So we do not think that the threshold of 1 log to reach a significant effect on decreased pathogen is relevant.  
Line 226: we were surprised to find the claims related to the maintenance of normal defence against pathogens in this paragraph. As the EFSA considers different sites of actions (urinary tract, upper respiratory tract), we suggest to include this part (from line 226 to line 235) in the immune system part 4. So, the differences between the substantiation of claims for maintaining a normal immune function and the ones related to the maintenance of normal defence could be more easily shown. |
| Kraft Foods Europe   | 3.4 Claims on digestion/absorption of nutrients | Does it mean that EFSA considers only claims on lactose digestion and iron absorption as appropriate? Is it possible to extrapolate these two examples to other macro- or micronutrients?  
Line 249-253:  
Our understanding is that this paragraph refers to bioavailability of iron, no general intestinal absorption of nutrients. So we suggest using the term iron bioavailability instead of iron absorption.  
We suggest distinguishing in two separate items claims on digestion/absorption of nutrient from claims on bioavailability of micronutrients. |
| ORGANISATION                        | CHAPTER TEXT                          | COMMENT TEXT                                                                                                                                                                                                 |
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| Kraft Foods Europe                 | 4.1 Claims on the function of the immune system | Lines 263-292 and lines 305-320, could the EFSA clarify the primary outcomes requested for the substantiation of claims for maintaining the immune system and for reducing a risk factor for infection? |
| Kraft Foods Europe                 | 4.2 Claims on reduction of inflammation | Line 301-304:                                                                                                                                                                                                                           |
|                                    |                                       | Could EFSA provide more details on this? What is the context in which a claim is considered as beneficial? Which markers are appropriate? Is an effect on disease development required in the demonstration? |
| Kraft Foods Europe                 | 4.3 Claims on reducing a risk factor for infections or allergy | It is not clear how these art. 14 claims differs from art. 13 on function of the immune system as scientific exigencies are quiet similar? Could you precise the criteria for scientific exigencies in these two different cases? |
| LABIP "Lactic Acid Bacteria Industrial Platform" | General comments | LABIP reaction to EFSA draft guidance on gut and immune function claims                                                                                                                                                                      |
|                                    |                                       | LABIP welcomes the initiative from the EFSA NDA panel to provide additional guidance on the scientific requirements for heath claims, related to gut and immune function. This is an important step forward and LABIP sees this as a start of a scientific dialogue with industry. |
|                                    |                                       | The guidance is not, however a representative list of acceptable benefits to health or of studies and outcome measures/endpoints that would support substantiation of a claim. This means that there still are many uncertainties when initiating a research program or filing a dossier. Therefore there is a real need for a scientific dialogue, for instance by allowing applicants to present their dossier and/or strategy for a dossier to the panel. |
|                                    |                                       | LABIP is surprised to see that e.g. the ILSI initiative leading to the PASSCLAIM paper by Cummings et al. (2004) on Gut health and immunity was not mentioned even once in the guidance document. |
|                                    |                                       | From the opinions of EFSA now published it becomes clear that only RCT’s are considered to deliver relevant evidence to substantiate a health beneficial effect. This is typical for drug development, but may not necessarily be applicable to nutritional interventions. The current EFSA approach does not leave space for the subtle effects that nutrition has on health. Nutrition is not a medical treatment aimed at solving a health issue. Nutrition is not expected to lead to acute or immediate responses, as drugs do. |
|                                    |                                       | In the guidance many examples are included on what is considered not appropriate. It would be most helpful and highly welcomed if examples of what are sufficient or suitable - e.g. acceptable endpoints/markers to substantiate health benefits would be included. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Mead Johnson Nutrition | General comments | Mead Johnson Nutrition response on the public consultation request from EFSA on the draft scientific guidance for health claims on gut health and immune function. Mead Johnson Nutrition welcomes the effort of EFSA to provide guidance on the scientific requirements for health claims on gut health and immune function and appreciates the possibility for external experts in the field to comment on and discuss the draft guideline. Find below general questions and comments from Mead Johnson and comments line by line. The draft guidance was reviewed and commented upon by the R&D Departments of Mead Johnson Nutrition: Dr Jon Vanderhoof, MD, pediatric gastroenterologistDr. Timothy Cooper, MD, neonatologistDr. Peter van Dael, PhD, nutrition scientistDr. Deshanie Rai, PhD, nutrition scientistDr. Deborah Diersen-Schade, PhD, nutrition scientistDr. Hugh Lippman, PhD, nutrition scientistDr. Carey Walker, PhD, microbiologistDr. Udo Herz, PhD, immunologist, expert in allergyDr. Ric van Tol, PhD, immunologist, expert in gastro-intestinal healthAnnemieke Tops, MSc, regulatory/nutrition scientistDr. Udo Herz and Dr. Ric van Tol will participate in the December 2nd meeting. |

There is a clear need for a precise description of what EFSA means by health in general. Is it the more classical view - i.e. “absence of disease” - or a more sophisticated one – i.e. “resilience to adverse conditions”? With the current lack of markers for “general health” it would be impossible to prove better health in healthy people. In contrast, based on the resilience concept it might be possible to show that, for instance, consumption of a probiotic leads to faster recovery from an intestinal infection, which in our view would corresponds to a benefit for the consumer. Industry needs clarification on which population should be considered for clinical studies: would populations with common pathologies be considered part of the general population? Also would the different physiology of newborns be taken into account, and so will it be possible for industry to mention the benefits associated with the stimulation of normal development of babies?

Other urgent needs include:

1. Further clarification of what "whole body of evidence" means. This includes to know which type of clinical studies will be taken into account e.g. the number of requested clinical studies in relation to the extent of each of them, the value of secondary outcomes when statistically significant, the value of results on the biological plausibility of the effect (even if not sufficient per se are bringing substantial “body of evidence”).
2. Clarification on which magnitude of effect will be considered as relevant, taking into account that we are dealing with food and general healthy population and therefore cannot expect effect at the level of a drug on diseased people.
3. Establishment of a list of recognized or accepted risk factors and when not available, clarification of what will be required to show the predictability of a risk factor.

LABIP are looking forward to an open and constructive workshop in Amsterdam.
| ORGANISATION          | CHAPTER TEXT        | COMMENT TEXT                                                                 |
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| Mead Johnson Nutrition | General comments    | 1. Primary, secondary, tolerance parameters, follow up studies from primary intervention studies Numbers of study participants per study group are calculated (power calculation) for any randomized, double-blind, placebo-controlled study based on the primary outcome parameter. However, if study outcomes on secondary parameters are clearly significant and biologically relevant, it should be possible to consider the study as pertinent for the substantiation of a health claim on the secondary outcome.  
   • Does the NDA panel agree on this interpretation?  
   • What is the opinion of the NDA panel on long-term (years) follow up studies with respect to different parameters that will be measured in the follow up studies?  
   E.g. if an intervention study is done during the first year of life and long-term follow-ups at 3 to 10 yrs of life. In these follow up studies other parameters (appropriate for specific outcomes at specific ages) than in the first intervention study will be measured.  
   • Does the NDA panel regard these “other parameters” that are different from the study outcome in the primary intervention study also valid for the substantiation of a health claim?  
2. Specificity of infant physiology & development and specificity of studies in infants & young children  
   The overall guidance is very general and seems to be focused on substantiation of claims for the “general population”. The guidance does not take into account specific requirements for studies performed in infants e.g. the impossibility to randomize breastfed infants and formula fed infants and the understandable reluctance of ethical committees to approve the use of invasive techniques (e.g. blood samples) in healthy babies. Also getting other samples encounters practical challenges in babies such as e.g. urine samples in baby girls and stool samples.  
   Apart from this the physiological condition of babies is different with regards to maturity of the gut and the immune system.  
   • Does the NDA panel agree that specificity of studies performed in infants and young children needs to be taken into account when defining appropriate parameters?  
   • If yes, could the NDA panel be more specific for infants and young children in the definition of appropriate outcome measures for the different claim areas as specified in part 3 and 4?  
3. Disease risk factor reduction claims-how to communicate to consumers  
   Although communication to consumers is not the topic of this guidance, health claims can only be made if they are understandable for the consumer. Consumers would generally not know risk factors of diseases. Especially for risk factors with regards to immunity or allergy, it will be very difficult to make an understandable claim on a risk factor only, without mentioning the clinical endpoint associated with this risk factor.  
   • What is the position of the NDA panel on consumer understandable wording versus science specific wording?  
   • Is the NDA panel planning to propose alternative wording instead of only reject proposed wording by the applicant?  
4. Disease risk factor/at risk population/remission episode  
   There should be a more clear-cut line between managing states of disease (associated with acute and chronic
| ORGANISATION               | CHAPTER TEXT                  | COMMENT TEXT                                                                                                                                 |
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| Mead Johnson Nutrition    | 3. Gastro-intestinal tract    | 5. Find below questions and comments indicated per line of the document                                                                      |
|                           |                               | Line 114: “The risk factor is an independent predictor of disease risk”. It is obvious that a risk factor needs to be a predictor of a disease. However, is there any risk factor that is truly independent for prediction of a disease? This cannot be said even of cholesterol in relation to heart disease.  
  • Therefore Mead Johnson proposes to delete the word “independent” from this sentence.  |
|                           |                               | Line 120-122: EFSA considers the target population for which claims are intended to be the healthy population or specific subgroups of this population such as pregnant women or elderly.  
  • Does the NDA panel also consider “populations at risk” to be a subgroup of the healthy population?  
  • How large should a subpopulation be in order to extrapolate the claim to the general population?  |
|                           |                               | Line 132-135: The term “pertinent”. Although the EFSA states to look at the totality of the evidence, until now not much weight is given to other studies than clinical studies in the target population. The role of in vitro and in vivo studies should be more clearly defined, as should studies that are done in different matrices with surrogate markers.  
  • Studies that are regarded supportive should be clearly mentioned in EFSA opinions.  |
|                           |                               | Line 160 With regards to gastro-intestinal health there is no focus on different levels of development of subpopulations. Infants are not yet fully developed and the gut is immature.  
  • Mead Johnson proposes to provide a list of outcome parameters relevant for infant gut health. These outcome parameters are currently not included in the draft guidance on the scientific requirements for health claims related to gut and immune function.  |
| ORGANISATION              | CHAPTER TEXT         | COMMENT TEXT                                                                                                                                 |
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| Mead Johnson Nutrition   | 3.1 Claims on bowel  | Line 162: Could the NDA panel provide a definition of bowel function?                                                                          |
|                          | function             | Line 164-168: Hard stools are mentioned in association to constipation and diverticular disease, However stool consistency is not mentioned |
|                          |                      | in the appropriate outcome measures. This parameter should be added in line 168.                                                           |
|                          |                      | • Does the NDA panel agree that an outcome measure on bowel function could serve as substantiation for a “general wellbeing claim” such as |
|                          |                      | gastro-intestinal comfort?                                                                                                                   |
|                          |                      | Line 175-176:                                                                                                                              |
|                          |                      | • Could a questionnaire for parents be used as substantiation for gastro-intestinal comfort/discomfort in infants and young children?       |
|                          |                      | • How could such a questionnaire be validated?                                                                                              |
|                          |                      | Line 177-182 Mead Johnson is of the opinion that IBS is a severe, chronic disease which requires close supervision and particular medication. |
|                          |                      | Moreover the mechanism on onset and perpetuation of this disease is still not well understood. Relating IBS to gastrointestinal comfort in the |
|                          |                      | general population is in this case not appropriate.                                                                                          |
|                          |                      | • Therefore IBS is an inappropriate example used in the context of gastrointestinal discomfort.                                                |
| ORGANISATION                  | CHAPTER TEXT                      | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
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| Mead Johnson Nutrition       | 3.2 Claims on gastrointestinal discomfort | Line 183-188: For infants breastfeeding is the gold standard. Consequently bifido predominant microbiota of breastfed infants is regarded as a positive outcome. • An increase in specific species of bifido bacteria resulting from nutritional intervention should be regarded as well as a beneficial outcome. Molecular approaches in combination with in vitro and animal models are yielding good results but are discounted as not applicable to the human host. Most questions of physiology cannot be answered via human studies given ethical and scientific constraints so there must be some accommodation. • Mead Johnson welcomes an in-depth discussion with the experts on this specific topic. Line 190-200: The document lists a series of pathogens that if encountered in a clinical trial would severely compromise the health and wellbeing of the host and no addition of probiotic, prebiotic or functional nutrient is likely to affect the outcome. If significant populations of most of these pathogens are present in a clinical trial, first and foremost we are not dealing with a healthy population and second, the participants are likely to become ill. With some of these pathogens, the infective dose is small enough that a reduction in a log would not interfere with their capacity to cause disease in infants. Few labs have the expertise to deal with such microbes and their occurrence in the general population is likely to be low enough that detection is unlikely. It seems more reasonable to work with experts to define the constituents of a “healthy” microbiota and propose that any nutritional intervention that shifts the microbiota toward that pattern be considered an appropriate outcome. For similar reasons the reduction of detectable microbial toxins as acceptable surrogates is not appropriate. In addition, the presence of pathogens is likely not the only risk factor in the development of infectious disease. This is where the specific patterns of cytokines, immune cell populations, etc. could reflect a fully functioning immune system. Appropriate targets (patterns) need to be defined. In conclusion: any numerical reference in terms of reduction of pathogens and potential reduced risk of infection/disease cannot be substantiated from a scientific point of view. • Mead Johnson does not agree with the 1 log reduction of pathogens as outcome parameter for immune function and does not see "a microbiologically relevant reduction of pathogens", as an appropriate outcome measure for human clinical trials, particularly with infants.
Outcome of a public consultation on a draft guidance on the
scientific requirements for gut and immune function claims

| ORGANISATION               | CHAPTER TEXT | COMMENT TEXT |
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| Mead Johnson Nutrition     | 4. Immune system | Line 201-235 The difference between a function claim and a disease risk factor reduction claim: |
|                            |              | • Does the NDA panel consider that for a function claim such as “supports respiratory health”, the clinical endpoint of incidence of respiratory infection is sufficient without proving a reduction in pathogens? |
|                            |              | • In the draft guidance it seems that the endpoints of a disease such as e.g. reduced incidence of certain infections is regarded less pivotal for substantiation of a health claim than the risk factor that may be associated with this disease. A clinical endpoint should be regarded as more important than reduction of one of the risk factors for this disease. |
|                            |              | • Does the NDA panel agree that for “maintenance of health” claims such as “maintains gastrointestinal health” or “maintains respiratory health”, clinical endpoints such as reduction of incidence of diarrhea, reduction of incidence of bronchiolitis etc. would be the appropriate outcome measure? |
|                            |              | • In other words if in a trial a significant reduction of disease incidence is proven without showing a concomitant significant reduction in a risk factor, would the trial outcome be regarded as appropriate for substantiating a “maintenance of….. health” claim? |
|                            |              | Line 266: Natural defenses: it is clear from the guidance that natural defense needs to be more specified. It is our understanding that the substantiation for a claim like “natural defense to support respiratory health” or “natural defense to support gastrointestinal health” can be made based on clinical endpoints such as significant decrease in incidence of diarrhea or a significant decrease in the incidence of respiratory infection. |
|                            |              | • Does the NDA panel concur with above explanation? |
| ORGANISATION          | CHAPTER TEXT                                                                 | COMMENT TEXT                                                                                                                                                                                                 |
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| Mead Johnson Nutrition | 4.1 Claims on the function of the immune system                             | Line 276: Non IgE versus IgE mediated allergy                                                                                                                                                                  |
|                      |                                                                              | Up to 50% of all allergic manifestation, especially the gut intestinal related symptoms in infants are not associated with detectable IgE antibody titers directed against food allergens. Therefore the term non-IgE mediated was introduced. However it has to be taken into consideration that neither validated measurements nor surrogate markers for non-IgE mediated allergy are established. |
|                      |                                                                              | • Therefore laboratory measurements should be only taken into account where they are established.                                                                                                               |
|                      |                                                                              | Line 277-286: Mead Johnson agrees with the paragraph on vaccination.                                                                                                                                           |
|                      |                                                                              | Line 287-292: It seems that the ILSI Passclaim paper on biomarkers for gut health and immunity has not been taken into account.                                                                                   |
|                      |                                                                              | • Does the NDA panel agree that a change in markers like e.g. eicosanoids and neutrophils could also be regarded as supportive evidence for substantiation of an immunity claim? |
| Mead Johnson Nutrition | 4.3 Claims on reducing a risk factor for infections or allergy              | Line 305-311: Mead Johnson believes that the reduction of allergic manifestations should be sufficient to substantiate a health claim on reduction of (food) allergy. In the Directive for infant and follow on formula a health claim is approved on reduction of risk of (cow’s milk) allergy. This claim is established for the general healthy infant population. Many consensus papers have been developed with established clinical endpoints on allergy prevention in which food plays a crucial role. |
|                      |                                                                              | • Does the NDA panel agree with this approach?                                                                                                                                                                |
Without going further into detail on all other individual biomarkers, there is one aspect in line with biomarkers we would like to address. One of the main aspects that is lacking in this guidance is the general scientific accepted view that the composition of the intestinal microbiota in general is quite important for the health status of people. Much literature has shown that stability and diversity of the microbiota is beneficial for a healthy life. It is also well described that the relatively stable microbiota is negatively influenced by different factors like antibiotic use, stress, travelling and use of medicines. Restoring these effects is proven to be beneficial. In the guidance, nothing is mentioned concerning this subject. The only adopted biomarker in this field is, according to the guidance, the inhibition of specific pathogens. Adopting this biomarker instead of the support of a healthy, rich and stable microbiota does again confirm the disease-oriented approach EFSA has in executing the health claim regulation.

To think further on the aspect of the complete microbiota, preventing people from developing further side effects for example due to disturbances in their microbiota would aim for nutritional products restoring this balance, and thus targeting specific groups of the population (i.e. people taking antibiotics, travelling people, stressed people) that are basically healthy but suffer from side effects of their lifestyle. In line with that, also people suffering from chronic inflammatory diseases like IBD and IBS and people ‘suffering’ from metabolic syndrome would be considered as relatively healthy people but are just specific target groups. All these people are subgroups of the complete population, and their health will benefit by taking nutritional products with health claims. In the guidance the NDA Panel considers that the population group for which health claims are intended is the general (healthy) population. Furthermore it is mentioned that applications that specify target groups other than the general population are the subject of ongoing discussion. By this statement one would exclude thus the subgroups as outlined before (IBS/IBD/metabolic syndrome ‘patients).

Based on all above mentioned critical notes we come to the conclusion that this guidance is very late however we appreciate this guidance as a positive reaction on all comments the stakeholders gave on the regulation and how EFSA handled it. Nevertheless, this guidance should not be a way whereby EFSA tries to get etrospectively approval from the industry on the comments they have made the last four years and the underlying basis for their rejections. All this is a missed chance for a firm assessment process, based on open scientific reasoning. However, this could be overcome when EFSA adopted a procedure wherein the applicant and EFSA can communicate about the claim and the presented data, where scientific arguments can be exchanged and where additional data can be presented. EFSA should in that sense learn from the ways notified bodies judge about medical devices. Such a transparent procedure will prevent the impasse an applicant is faced with and will give EFSA the opportunity to enter in a learning process.

As stated above, currently EFSA uses the pharmaceutical paradigm in evaluating the presented evidence. NPN does not agree with this on ethical, conceptual and scientific grounds. We would from that perspective highly recommend EFSA, and especially the NDA panel, to consult more scientists in the field of nutrition and microbiology so a peer reviewed opinion by scientists in the field of microbiology and therefore general accepted scientific opinion is established.
| ORGANISATION               | CHAPTER TEXT       | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| Natuur- & gezondheidsProducten Nederland (NPN) | General comments | Of course NPN appreciates the fact that EFSA is finally listening to the concerns from the market, but again a lot of remarks can be made on the guidelines issued. In this letter we will just keep our comments at a more general level, although we also support the more detailed feedback as provided by Dr. Ger Rijkers and the EHPM. The major comment from a scientific point of view is that nutrition (including food supplements, functional foods, etc.) has a complete different working mechanism in the body than pharmaceutical products do. From a pharmaceutical approach, products are developed to target a specific receptor and by that might interfere with a certain mechanism of action. Nutrition is focussed on health and maintenance of the healthy situation by a much more gradual and multifactorial approach. Health claims for nutritional products should therefore not be judged in a medicinal way. To point ‘biomarkers’ for nutritional effects is for that reason quite difficult and maybe impossible (i.e. what would be the biomarker for homeostasis?). In our view this is one of the main reasons that its opinions are received by the scientific community with so much comment. The guidance as proposed now is in our opinion therefore too narrow in possibilities. Another major comment on the guidance is that it confuses the applicants and thus still gives no clearness on the evidence that is required to support a health claim. The following quote is an example of the non-information presented in this guidance and clearly illustrates the impasse an applicant is faced with: For disease risk reduction claims studies that show only a reduction in incidence or duration of infection(s) would not constitute evidence for a reduction of the risk factor (e.g. numbers of pathogens). However, clinical outcomes (e.g. number of episodes of infection, severity of symptoms, or duration of infection such as indicated by diarrhoea diagnosed as infectionrelated using specific criteria), demonstrated in human intervention studies could be supportive of the claimed effect related to pathogens. This quote suggests that a specific product reducing the incidence of infection does not fulfil EFSA’s demand because there is no proof of a reduction of a risk factor while the same product showing reduction in the numbers of episodes of infection could be supportive of the claimed effect related to the product. We do not think there is any expert capable of discriminating between “reducing the incidence of infection” and “reducing the numbers of episodes of infection”. Moreover, in the absence of a clear procedure (where communication is an important part of) the applicant can only guess what EFSA means with this quote and whether the phrase “could be supportive” has any other meaning than its doublespeak character suggests: “will be rejected nevertheless”. More discrepancy in the guidance is in the fact that the guidance states that a health claim only could be approved when proven effects have been shown on influencing a certain biomarker that is biologically plausible for a certain health effect (clinical results seem to be not even necessary).Nevertheless, when critically reading this guidance, the only ‘biomarkers’ considered to be proven are on bowel function (but even that is only focussing on constipation and what about diarrhoea?) and on inhibition of specific pathogens. Furthermore the guidance stays very reticent and careful in mentioning that certain effects could be beneficial. It seems that EFSA makes hereby use of a catch- 22-principle, all the way supporting rejection of the majority if not all claims. |
| ORGANISATION | CHAPTER TEXT       | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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| Natuur- & gezondheidsProducten Nederland (NPN) | General comments | NPN would hereby like to react on the recently published draft guidance for health claims to gut and immune function, as published in September 2010 in the EFSA Journal. Principally we support the fact that health- and disease-risk-reduction claims on nutritional products should only be communicated to the consumers when there is evidence for the beneficial effects by those products. In line with this, members of NPN, for example Winclove Bio Industries (as SME) invested a lot in performing research on its bacterial strains and final probiotic formulations and subsequently on writing EFSA dossiers. During the assessment, EFSA was unclear about the requirements, has changed them during the procedure and was not willing to communicate with us about the evidence a product should have to get its health claim approved. As stressed also in our letter to Mr. Mathioudakis of April this year (which was even accompanied by a support letter of our Ministry of Health, Welfare and Sports) the way the health claim regulation is currently executed results mainly in loss of confidence of the industry and slow their willingness to invest in innovative products with higher health properties. Besides negatively influencing the industry also other stakeholders and the final consumers, for whom the regulation was initially set up, are harmed by the way the regulation is now executed. The estimation of today is that over 90% of all health claims will be rejected. Even more alarming is the situation with respect to health claim applications for probiotics and prebiotics, since not a single claim has been approved so far. For the main part health claims on probiotics were purely rejected on the fact that the strains were not characterised sufficiently. Nevertheless, during the whole procedure it is never made clear which were the requirements for ‘sufficiently characterising’ nor was there (until quite a few products were rejected) the possibility to provide EFSA with the additional requested information. To get already ahead of feedback on the EFSA’s draft guidance, not even in that proposed guidance document assistance is given on how to characterize the active ingredients. After much comments from stakeholders on the way the EFSA judges, EFSA’s rejections based on beforehand unclear requirements and EFSA’s unwillingness to communicate, last month a draft guidance on the scientific requirements for health claims related to gut and immune function was published. The first time a concrete action on many requests from companies is now made, 4 years after launching the claim regulations. From this perspective the timing of publishing the guidance is late. |
| Nestlé       | General comments | * The draft Guidance explains in many cases what will not be appropriate or sufficient, or what to avoid; could the Panel provide more positive examples in terms of what will be appropriate or sufficient?  
* The draft Guidance does not refer to PASSCLAIM guidance on immunity and gut health. Are the conclusions of this work are no longer valid? If so, can the Panel explain why?  
Throughout the guidance, a clearer distinction could be made between disease risk reduction claims for art. 14 (e.g. ln 203-5) and functional claims for art. 13 (e.g. ln 226-35).  
Ln 101: We understand that “beneficial physiological effects” is meant to express functional benefits as well as disease risk (factor) reduction. The title of 2.1 could specify this by extending to “Beneficial physiological effects and reduction of disease risk”, referring to article 13 and 14 claims, respectively.  
Ln 103-6: Every health claim contains a food (constituent) and an effect. The draft guidance now implies that a given effect can be considered beneficial if caused by food (constituent) x but not if caused by food (constituent) y. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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|              | However, cancer is a bad thing, no matter what causes it; anything that lowers LDL-cholesterol we now generally consider to be a good thing. How and when does the health relevance of a given effect depend on what causes the effect? Can the Panel give any insight, or an example of an effect being beneficial in one ‘context’ but not in another? Or, if the section is not meant as interpreted above, can the Panel then clarify how it is meant? Ln 109-10: We assume that the last part of this sentence in brackets means to express that to make a disease risk reduction claim one cannot just demonstrate disease risk reduction (itself); one must - additionally or possibly solely-demonstrate disease risk factor reduction. Ln 117-8: How can reducing a given risk factor by food constituent x be a good thing but reduction of the same risk factor by food constituent y not? Can the Panel provide examples of reduction of a given risk factor being relevant for health in one situation but not in another? Or, if the section is not meant to be interpreted as above, can the Panel then clarify how it is meant? Ln 123-5: We applaud the fact that making claims for groups other than the general population are under debate with the Commission and member states, and we would like to ask that all stakeholders including food companies are involved in this discussion as early and as much as possible. Ln 145-6: Could the Panel make this section more concrete, e.g. in terms of “how” to “appropriately conduct as to minimise bias”? Are there certain specific "non-negotiable" criteria in this respect? Ln 147-50: Does consistency necessarily have to be demonstrated across several studies? Or can it also be studied in one large study, comprising a variety of subjects in a variety of settings, comparable to the variety one may have across several smaller studies? In that case “study” could be replaced by "study/studies". Furthermore, would the Panel agree that a meta-analysis of the pertinent studies or, even better, an analysis of the pooled data of such studies, is more pertinent than the individual studies? If not, why not, given that a claim needs to be valid for its overall target population (and not necessarily in each segment of the target group)? Ln 153-6: Could the Panel give any insight in “how” they evaluate whether such extrapolation is biologically justifiable? The IBS example (ln 179-82) implies that if the differences between people with or without a certain condition are “gradual” rather than ‘systematic’, data from people with such condition can be extrapolated to people without such condition; would the Panel agree? |
### OUTCOME OF A PUBLIC CONSULTATION ON A DRAFT GUIDANCE ON THE SCIENTIFIC REQUIREMENTS FOR GUT AND IMMUNE FUNCTION CLAIMS

| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Nestlé       | 3.1 Claims on bowel function | • Ln 161: “Claims on bowel function” implies that more than one (type of) claim on bowel function may be possible. Effects on transit time, on frequency of bowel movements and on stool bulk are related and will often coincide. Still, if one demonstrates one of these effects only, can one such effect be considered to be sufficiently substantiated?  
• Ln 165-6: Bowel habits vary considerably from person to person, within a ‘normal’ range. Apart from that we have not defined “normal ranges” for all parameters: are changes in bowel function within the normal range beneficial for health? If so, what would be the smallest relevant effect? If not known, how can we progress in this respect? Does this depend on where one is, within the normal range? From the following we deduct that EFSA may see subtle changes in maintenance or improvement within the normal range as beneficial: In the context of article 13.1 claims on plant constituents, EFSA has evaluated as beneficial for human health: 1) maintenance of normal bowel function, 2) bowel motor function within normal range, 3) improvement of bowel motor function, 4) improvement of bowel motor function within the normal range, and 5) improvement of intestinal transit.  
• Ln 167-8: Appropriate measures of bowel function include stool consistency (Bristol scale), the parameter of constipation that correlates best with transit time. Constipation is defined by the American National Institute of Diabetes and Digestive and Kidney Diseases as having fewer than three bowel movements per week. We recommend adopting a definition of constipation, indicating which measures validly reflect this. |
| Nestlé       | 3.2 Claims on gastrointestinal discomfort | • Ln 169: Ease, urgency, feeling of incomplete evacuation, straining, belching, heartburn, nausea, post-meal fullness, vomiting and mucus or blood in stools also reflect gut (dis)comfort. Therefore, effects on any of these phenomena are relevant for health.  
• Ln 175-6: Subjective questionnaires must be validated “against what”? EFSA questioned in an opinion on LGG (EFSA-Q-2008-444) the relevance of a (statistically significant) increase of score of bowel symptoms by 0.25 point on a 0-7 scale. Can rules of the thumb be developed on, in order to be meaningful for health, how many % one must minimally change on the total span of a certain scale?  
• Ln 179-81: Can data from people with a condition be extrapolated to people without such condition if the differences between people with or without a such condition are gradual rather than ‘systematic’?  
• Ln 181-2: Following lines 179-81, people with other gastrointestinal disorders such as dyspepsia, constipation and diarrhea, having milder versions of the same symptoms, should also be considered as appropriate study groups to support claims for the general population. |
Outcome of a public consultation on a draft guidance on the scientific requirements for gut and immune function claims

| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Nestlé       | 3.3 Claims on oral and gastrointestinal microbiota | • Ln 186-8: Pediatric studies focus on bifidus rather than on pathogens because human milk, being bifidogenic, is seen as the gold standard for infant nutrition. Does this not make it – sufficiently - plausible that bifidogenic effects are relevant for health?  
  • Ln 189-91: If reduction of specific pathogenic bacteria is beneficial, similar argumentation implies that an increase in beneficial bifidobacteria or lactobacilli is also beneficial.  
  • Ln 190-1: What matters in the end for consumers, and also scientifically and medically, is that one get e.g. diarrhea less often, shorter and less severely: why the need to identify the pathogen that cause travelers’ diarrhea? And how could one, when travelling: 1) have access to a medical unit to get an analysis of one’s microbiota? 2) compare results between countries, e.g. the country of destination and the home country? 3) show a sustainable effect, over which period of time?  
  • Ln 192-5: Would this be a functional claim (art. 13 if not in children) on immunity, or a disease (infection) risk reduction claim (art. 14)?  
  • Ln 200: What is the basis for considering a one log reduction, being a 10 fold reduction, as not meaningful? Does this not depend on the starting level: e.g. a decrease from 10-9 to 10-8 might not be the same as from 10-5 to 10-4. Can we assume that a change > 1 log is meaningful?  
  • Ln 200: ‘sustained over time’: for how long?  
  • Ln 201-2: This refers to art. 13 and 14 claims, respectively; correct?  
  • Ln 202: Between “disease and reduction”, “risk” needs to be inserted.  
  • Ln 203-5 are clearly about art. 14 claims; are Ln 205-8 (claimed effect related to pathogens) about functional claims (art. 13 if not in children), e.g. “immune defenses”?  
  • Throughout, a clearer distinction could be made between DRR claims for art. 14 (e.g. Ln 203-5) and functional claims for art. 13 (e.g. Ln 226-35). For DRR claims, the data need to primarily demonstrate reduction of a risk factor; does it mean that the effect on the disease outcome (disease risk) is secondary, e.g. only supportive, and not crucial? Would, for functional claims, a reduced number of pathogens be sufficient, or is an effect on a disease outcome needed as well? In other words, should the "as well as" (Ln 228) be understood as “and” or “and/or”? Meaning that if positive results are available on incidence, duration and/or severity of infection (e.g. diarrhea), would that be enough to make a functional claim such as "defenses against pathogens in the GI tract", without having to show a reduced number of pathogens? Having fewer, shorter or less severe episodes of diarrhea entails improved defenses; how can it not?  
  • Ln 225: What exactly is needed to sufficiently characterise pathogens in a way that their pathogenicity is confirmed?  
  • Ln 226-30: For claims on defense against pathogens in the gastrointestinal tract, outcomes could be a reduction of pathogens or their toxins, as well as improved disease outcomes. Can an increase of potentially beneficial microbes also be supportive for such claims, especially when such increases are part of the mechanism of action? If not, why not? |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
|--------------|--------------|--------------|
| Nestlé       | 3.4 Claims on digestion/absorption of nutrients | • Ln 228: Does the “as well as” express it is sufficient to demonstrate either pathogen reduction only or better clinical outcomes only, or must one demonstrate both? Apart from that disease outcomes are in the end what counts (if not, why not?), it may often be almost impossible to demonstrate reduction of pathogens, e.g. in children where sampling might be difficult or non-ethical.  
• Ln 232-4: An enhanced intestinal barrier function decreases the risk of penetration by a pathogen or allergen; can a claim be based on such improved barrier function in combination with relevant clinical outcomes?  
• Ln 240-53: The examples on lactose and iron suggest that for an increased bioavailability to be beneficial for health, one must argue the case that health will be improved by increasing bioavailability of the food constituent concerned; lines 255-6 confirm this. We suggest putting this upfront in this Section.  
• Ln 246: We suggest to insert between “clinical symptoms” and “or”: “such as nausea, cramping, bloating, diarrhea and flatulence”  
• Ln 251-3: How much must mineral absorption improve in order to be meaningful? The evidence for certain minerals in specific population is comprehensive and could be leveraged herein - specific guidance could be given for key ‘risk’ nutrients for population segments. For example, it will be helpful to have guidance on smallest health-relevant improvement in non-haem iron absorption in children and young women, endpoints being hemoglobin and serum ferritin.  
• Ln 255-6: Can only the increased bioavailability of “nutrients” be a beneficial effect, and not of e.g. antioxidants or food constituents other than ‘classical’ macro- or micronutrients? |
| Nestlé       | 4.1 Claims on the function of the immune system | Ln 287-92: Which criteria have resulted in this list? It differs from PASSCLAIM; can the Panel explain why? In particular, two parameters have been repeatedly reported to be associated with risks of infections: 1) low NK activity, so called low NK syndrome, and 2) sIgA, being inversely associated with risk of infections. Consistent effects on such parameters could be considered as evidence of reinforcement of immune defenses; they are therefore more than just supportive by giving insight in mechanism of effect; they may also add – potentially crucial – evidence for efficacy. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Nestlé | 4.1 Claims on the function of the immune system | • Ln 263: In cases of deficiencies, specific conditions (e.g. infections) or challenges (e.g. by UV): extend “maintenance of normal immune function” to recovery of normal immune function; • Ln 268-71: Should a claim on “defenses against pathogens” be based on infections as well as reduction of pathogens? Can a claim on “response to allergens” be based solely on reduced incidence of allergic manifestations? If not, no what else? Which outcomes should be primary and which ones secondary? Or all as co-primary? • Ln 268-73: The EU Health Claim Regulation prescribes that a claim on disease risk reduction is – intriguingly - not to be substantiated by disease risk reduction, but by disease risk factor reduction. At the same time, getting ill (or e.g. being affected by allergy) less often and/or for shorter time and/or with less severity (be it accompanied with reduced risk factors, be it not) is – eventually – a crucial element of everyone looks for. So why, even when making ‘functional’ claims on ‘protection’ or ‘defenses’, reduction in disease incidence, duration and/or severity is not considered as core, but as supportive evidence only? • Ln 269: Is the “and” to be read as “and/or”? • Ln 270: Infections and allergies involve very different causes, risk factors, manifestations and immune factors; infections and allergies each deserve a separate section. • Ln 270-1: For allergy-related claims: like for infections, not only incidence of allergic manifestations is a relevant outcome, but also their severity and the relapse time in between. • Ln 271-3: Does this refer to a functional claim on immune defenses? Is the best proof of better immune defenses not in a decreased number of infections (or fewer and/or less severe episodes)? This is the whole “raison d’être” of the immune system. • Ln 273: When referring to the immune system, a concomitant change in an immune parameter is needed. Does one need to have, for a claim on immune system or defense against pathogens, evidence for effects on: infections + reduction of pathogens + immune parameter? And for a claim on the response to allergens: incidence of allergic manifestations (or intensity of allergic symptoms) + immune parameter? Which ones should be primary and which ones secondary? Or all as co-primary? • Ln 273: Please specify to what exactly in section 3.3 “see section 3.3” refers to. Or does it refer to another section? • Ln 275-7: Could the Panel give examples of such appropriate measures? Are they the same as the ones in Ln 289-92? • Ln 279-86: As indeed vaccines are usually produced with an adjuvant that already very effectively stimulates protective antibody titers, food constituents cannot provide an additional effect in such situation. Can claims be substantiated by studies with ‘non-efficient’ vaccines (e.g. ETEC vaccine)? Must the claim specify the pathogen (e.g. defense against E. coli ETEC), or can the effect could be generalised (e.g. defense against pathogens)? Are increases in antibody titers within the ‘protected’ range, not necessarily increasing in protection rate, relevant for health? Could that be seen as improving normal function of the immune system? • Ln 283: Does “as well as express “and”, “or” or “and/or”? In other words, does one need both, or is demonstrating one of them sufficient? • Ln 285-6: Which criteria does the Panel apply in deciding whether a certain antibody is “protective”? |
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| Nestlé       | 4.2 Claims on reduction of inflammation | • Ln 294-304: The science may be more advanced than implied here, and more specifics could be provided. The American Heart Association considers hsCRP as an independent risk factor for cardiovascular disease and stroke; would the Panel value interventions that reduce hsCRP?  
• Ln 294-304: For which diseases or in which contexts would reducing inflammation be beneficial?  
• Ln 301-4: How can decreased inflammation be a good thing if caused by food constituent x, but not if caused by food constituent y? Can the Panel provide examples? Or, if this section is not meant to be interpreted as above, can the Panel then clarify this? |
| Nestlé       | 4.3 Claims on reducing a risk factor for infections or allergy | • Ln 305: Infections and allergies involve very different causes, risk factors, manifestations and immune factors; infections and allergies each deserve a separate section.  
• Lines 306-7: An enhanced intestinal barrier function decreases the risk of penetration by a pathogen or allergen; can a claim be based on improved barrier function in combination with relevant clinical outcomes?  
• Ln 308-11 (see also 203-8, 226-35): “could not substitute the other”: can the Panel clarify if that means that only the risk factor reduction will do, or must one show as well incidence, duration or severity of diseases?  
• Ln 312-5: Additionally, logically, “reduced or absence gut defense factors (antimicrobials, IgA …)” are risk factors, and increases in these factors are beneficial physiological effects.  
• Ln 315: Which (types of) samples are suitable? Can the Panel provide examples?  
• Ln 316-7: How can decreasing a risk factor be a good thing if caused by food constituent x, but not if caused by food constituent y? Can the Panel provide examples? Or, if this section is not meant to be interpreted as above, can the Panel then clarify this part? |
EFSA draft guidance presents a limited list of beneficial effects. The document states that these examples are drawn from finished or ongoing evaluations. The comments received on the guidance during this public consultation will be discussed at EFSA’s meeting of December. This simply means that claims that are not listed in the guidance will not be discussed during the meeting.

We suggest EFSA to consider the claim “support the intestinal health” so that it can be discussed during the workshop. The reason is that this claim is currently used by many food operators in Europe, and has been submitted to EFSA in different dossiers:

Dossiers with completed evaluation
- ID 1602 on glucosamine. EFSA Journal 2009; 7(9):1235
- ID 3391 on Hibiscus sabdariffa. EFSA Journal 2009; 7(9):1293

Dossiers with ongoing evaluation
- Wheat bran and wheat bran enriched food (EFSA-Q-2008-1626, EFSA-Q-2008-3798, EFSA-Q-2008-3799)

This claim has also been used as illustrating example in presentations given by EFSA. See the link: www.efsa.europa.eu/fr/events/documents/stakeholder091201p2.pdf

EFSA draft guidance focuses on microbiota composition, and nothing is said concerning microflora activity. Indeed scientists recognize that outcomes related to microflora activity may be good indication of intestinal health:

Butyric acid, produced by bacterial fermentation, is considered to be of key importance for gut health. Epidemiologic studies have shown an association between diet and the incidence of colorectal cancer, and that butyrate is a potential anticarcinogenic compound (Roy et al, 2009). This anticancer property is widely demonstrated in the scientific literature through different well-designed animal model studies (McIntyre et al, 1993; Bauer_Marinovic et al, 2006; D’argenio et al 1996; Kameue et al, 2004; Medina et al, 1996; Reddy, 1998; Takahashi et al, 1999; Wong et al, 2005).

Short chain fatty acids (SCFA), as a whole, acidify the luminal pH which suppresses the growth of pathogens (Blaut, 2002). They also influence intestinal motility (Dass et al, 2007).

P-Cresol and phenol, the major phenolic compounds from proteolytic fermentation, act as co-carcinogens. Their levels have been reported to correlates with colon cancer (Bone et al, 1976).

Therefore we propose EFSA to consider butyric acid, SCFA, p-cresol and phenol as markers of intestinal health.

References
Bauer-Marinovic et al (2006). Carcinogenesis; 27: 1849–1859.
Blaut (2002). Eur J Nutr 1 (Suppl. 1):111-116.
Bone et al (1976). Am J Clin Nutr. 29: 1448-1454.
| ORGANISATION          | CHAPTER TEXT                  | COMMENT TEXT                                                                                                                                 |
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| Puratos Group        | 3.3 Claims on oral and       | Disagreement with EFSA approach on the evaluation of microbiota status. EFSA states that only reducing the numbers of 190 specific pathogenic microorganisms is a beneficial physiological effect. We disagree with this position because a reduction of pathogen can occur when the final result is that these microorganisms remain dominant in the microbiota. This is not a sign of a healthy intestinal microflora. Scientists of PASSCLAIM had concluded that a healthy, or balanced, intestinal flora is one that is numerically dominates by bacteria such bifidobacteria and lactobacilli (Cummings et al, 2004). Therefore our position is that maintaining pathogens at subdominant level, through the increase of beneficial bacteria such as bifidobacteria and lactobacilli, is a better indication of a healthy intestinal microflora than merely reducing the numbers of pathogens as proposed by EFSA. EFSA proposal of using pathogens reduction as marker of microflora status raises the question to know how to measure specific pathogens on a healthy population. Reference Cummings JH, Antoine JM, Azpiroz F, Bourdet-Sicard R, Brandtzaeg P, Calder PC, Gibson GR, Guarner F, Isolauri E, Pannemans D, Shortt C, Tuutjelaars S, Watzl B (2004). Eur J Nutr [Suppl2]43 :II/118-II/173. |
| Rudolf Wild GmbH & Co. KG | General comments             | Overall we appreciate the attempt from EFSA to issue a guidance document for specific health claim requirements to increase the understanding between applicant and EFSA. The document has a good structure, but it should be improved in terms of the distinction between the requirements in Part 3 in contrast to Part 4. For example in part 4.1 the description in line 268 to 273 relates to part 3.3 as reference. It would be much clearer also to state the examples given in part 3.3 again in the light of the focus of part 4.1 |
| ORGANISATION                  | CHAPTER TEXT                  | COMMENT TEXT                                                                                                                                                                                                 |
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| Rudolf Wild GmbH & Co. KG    | 4. Immune system              | In comparison to Chapter 3.1-3.3 in Chapter 4.1-4.3 examples for biomarkers are rare and not well defined. It would be very good to have a table with markers on immune parameters as a kind of summary with an assessment of the validity or suitability of these markers in relation to certain immune functions. This was tried in PASSCLAIM (J. H. Cummings et al. (2004) PASSCLAIM - Gut Health and Immunity. European Journal of Nutrition Suppl. 2; 43: II/118-II/173) but would be very helpful to be updated. Part 4 in general also only relates to infections by bacteria. The most common infections in humans, such as common cold, are the result of a viral infection. Can this be integrated into the guidance document, especially in terms of markers to be used? |
| Rudolf Wild GmbH & Co. KG    | 4.1 Claims on the function of the immune system | The only mentioned example for stimulation of protective antibody titres is derived from medicine / pharma - namely "vaccination". It would be more helpful to have an additional example in relationship to nutrition.                                                                 |
| Rudolf Wild GmbH & Co. KG    | 4.2 Claims on reduction of inflammation | In the lines 297-298 it is mentioned, that "changes in markers of inflammation such as various interleukins do not indicate a beneficial physiological effect per se" and in the lines 299-300 the opposite is stated "Chronic inflammation is associated with a number of diseases, and under certain circumstances reducing levels of markers of inflammation might indicate a beneficial physiological effect." - Could this obviously opposing statemente be explained? |
| Rudolf Wild GmbH & Co. KG    | 4.3 Claims on reducing a risk factor for infections or allergy | In line 314 of part 4.3 there is reference to section 4.3 - but it is the same section. Should this be section 3.3? If yes, please refer to our remarks in the General comments as we would like to see a clearer distinction between the two parts |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Sensus       | General comments | A definition or description what EFSA means by health in general is lacking. Is it the more classical view “absence of disease” or a more sophisticated one “resilience to adverse conditions”? Such a definition is important for the discussion on health claims; are we forced to show improved health in healthy people by the consumption of an ingredient or can we show that healthy people can get better easier or have less disease symptoms once they have fallen ill? With the current lack of markers for general health it will be impossible to prove better health in healthy people, but with the resilience concept it might be possible to show that for instance consumption of a probiotic leads to faster recovery from an infection by rotavirus. In other words does the panel consider healthy people that are challenged (e.g. by travelling to high risk countries) a suitable model system to show a health benefit? EFSA’s approach does not do justice to the subtle effects that nutrition has on health. Nutrition is not a medical treatment aimed at a certain unwanted phenomenon, be it a common cold or pneumonia. Nutrition does not show a dose-response relationship for effects, as drugs have. Nutrition science is not the same as medical science. Many nutrition studies were not set up to answer medical type questions, or to support health claims. From the opinions of EFSA now published it becomes clear that only RCT’s are considered to deliver evidence for an effect. This may be true for drugs, but is not the case of nutrition. Drugs are mostly taken for a limited period of time, whereas nutrition is taken every day and for a whole life span. For medical research it is easy to compare a drug free group with a drug taking group; this is impossible for nutrition research, a nutrition free state does not exist. With EFSA’s approach it will be impossible to show that a certain type of diet might be beneficial for heart health, that certain product categories such as fatty fish or fruit and vegetables, certain ingredients, such as dietary fibres can have certain health benefits. This is often also in conflict with dietary guidance and advice as given be national authorities or advisory bodies. It will also confuse consumers: whose advice should I follow, EFSA has a negative opinion on dietary fibres and heart health, but the fibre guidance by our health council is based inter alia on the association between fibre consumption and heart health. Especially the latter is a nice example for the problems encountered: certain specific fibres may have a specific benefit (oat beta glucans for heart health) and it has been possible to show this specific effect by RCT’s. But dietary fibres in general are necessary for a proper defecation pattern. How it will be possible to do a randomised controlled trial with “all” fibres to show this effect is unclear to me, and again the beneficial effect on bowel habit of fibres is the basis for dietary guidance. In the guidance document many examples are included on what is considered not appropriate. It would be more helpful to include examples on what is sufficient or suitable. I am also surprised to learn that the PASSCLAIM paper by Cummings et al. (2004) on Gut health and immunity (Eur. J. Nutr. 43 (suppl. 2): 118-173) was not mentioned even once in the guidance document. This reflects the consensus view of the scientific view of many experts in the field and offers therefore a generally accepted scientific opinion about gut health and immunity. Why was this not included? |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Sensus       | 3.1 Claims on bowel function | Could the panel indicate what the normal range comprises? Is it possible using slightly constipated volunteers (people that have a low defecation frequency, but do not seek medical treatment) as a suitable model system to investigate the effects on bowel function? |
| Sensus       | 3.2 Claims on gastrointestinal discomfort | Can IBS sufferers also be used as a model in bowel function research since discomfort may also be related to a disturbed defecation pattern? |
| Sensus       | 3.3 Claims on oral and gastrointestinal microbiota | The NDA panel accepts the paradigm less pathogens in the gut lead to less disease or a lowered risk of disease. It is not clear why this not also applies to healthy bacteria, i.e. more healthy bacteria lead to better health. In the first case the causal link is through toxin production etc. by the pathogens, whilst in the latter case this link is through more healthy products (fermentation products like acetate or butyrate) and/or less production of toxic products such as ammonia. Looking at it this way, the bifidogenic effect can be considered a beneficial effect. It is well documented that bifidobacteria and lactobacilli do not produce toxins and have a saccharolytic metabolism. Here we refer also to Cummings et al. (2004) Gut health and immunity. Eur. J. Nutr. 43 (suppl. 2): 118-173. In this paper that expresses the consensus view of many experts as developed during the PASSCLAIM project, we can read: “A healthy, or balanced, flora is, therefore, one that is predominantly saccharolytic and comprises significant numbers of bifidobacteria and lactobacilli (see below). The exact numbers are difficult to give at present because a proportion of the gut flora have yet to be identified”. Apparently there is scientific agreement on what a healthy flora constitutes, even without exactly knowing which species are present and in what numbers. The tables below provide further evidence that the increase in bifidobacteria per se is beneficial and for the many effects associated with this increased level of bifidobacteria. These tables are compiled on the basis of available literature data, and it is therefore surprising that the Panel is of the opinion that the available evidence is not sufficient to show the beneficial consequences. Admittedly, this literature was not provided in the process of submission for Article 13.1 claims, because at the time of submission the requirements were not known. Health benefits of bifidobacteria and lactobacilli: No known pathogens among these species Saccharolytic rather than proteolytic metabolism Fermentation products have potential benefits: butyrate is a preferred fuel for colon cells Proteolytic products are hazardous Ammonia, S-compounds Production of vitamins Inhibition of growth and adhesion of pathogens Lower bifidocounts in some colon disorders and diseases; improvement by raising this count, e.g. in IBS sufferers |
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| Sensus       | 4.1 Claims on the function of the immune system | Higher bifidobacterial counts in breast fed infants associated with less infections Higher bifidobacteria in faecal flora in non-eczema infants vs. eczema infants Physiological effects associated with increased faecal bifidobacteria Effect: Physiological benefit Improved calcium (and magnesium) absorption: bone health (BMD) in adolescents and postmenopausal women Improved levels of serum lipids (cholesterol, triglycerides): Heart health Improved resistance against infections: less severity of travellers’ diarrhoea, esch diarrhoea, vomiting, fever in children; lower incidence of GI and URT infections in infants Enhanced feeling of satiety, lower energy intake: eight loss or aid for weight maintenance Improved defecation frequency, improved faecal consistency, faecal bulking effect: improved bowel habit The bacteria mentioned are food-borne pathogens that usually do not occur in the GI tract or only in very low numbers. C. difficile is always present, but only pathogenic under certain conditions of overgrowth (and also viruses can cause disease of the GI tract). In the light of this the 1 log reduction mentioned in the Guidance is not clear. It merely reflects a 10-fold decrease, but a change from log 7 to log 6 is much less than from log 9 to log 8. Could the Panel indicate why this reduction was included and also what is meant by sustained over time? Should we conclude from lines 203-208 that it is not sufficient to show less incidence or duration of an infection for a disease reduction claim because the clinical endpoints do not show a reduction of a risk factor? Or is such evidence only suitable for an enhanced function claim? This seems puzzling and confusing, it poses a considerable burden on such trials as it is not always known and often hard to find what the causative agent is. The paper by Albers et al. (Markers to measure immunomodulation in human nutrition intervention studies. Br. J. Nutr. 94: 452-481, 2005) offers a good overview of immune markers and their relevance. This excellent paper was not mentioned in this paragraph despite the fact that it shows that for systemic immune function markers the in vivo response to vaccination (measured as vaccine specific antibodies) or the delayed type hypersensitivity (DTH) response (measured by the local response to antigen application) obtained a marker score “high”. For the immune functions of GALT this was the case for salivary and stool IgA and for the response to attenuated pathogens. Using combinations of markers reflecting different aspects of immune function in combination with clinically relevant endpoints such as incidence or severity of infections is currently the best approach (see also Cummings et al., 2004; Aggett et al., PASSCLAIM-consensus on criteria. Eur. J. Nutr. (suppl. 1): 5-30). As mentioned above we fail to see why the endpoint of less disease severity, getting better sooner or the like cannot be used for making claims without data on a risk factor. As mentioned a lower infection rate does not necessarily reflect an increased activity of the immune system; enhanced colonization resistance may also be the cause for this effect. (The mechanism is then due to competition for biding sites for pathogens or for growth factors). We think that this enhanced defence phenomenon should be included in the section on gastrointestinal microbiota; it can also be measured in faecal samples. Suppose it is proven adequately that a food ingredient lowers the risk for travellers’ diarrhoea, can we then make a |
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| SPPAIL       | General comments | The SPPAIL, which is representing the French producers of food microbial cultures and probiotics, welcome the opportunity to comment the draft guidance on scientific requirement for health claims related to gut and immune function, prepared by the EFSA’s NDA panel. The implementation of the Health claims regulation has proved that there is a real need for the operators to have a clear view of the experts’ expectations. We believe it could be achieved through the guidance, provided that clear and acute requirements are mentioned in the guidance. First of all we would like to thank EFSA for this document which is a clear sign that EFSA is open to discussion. To go one step further, we would like to know whether it is possible to request for dialogue between EFSA and the applicant, before submission of the dossier? That would allow the applicant to produce a dossier of higher quality and that should be beneficial to EFSA, as less time would be needed for review of the dossier. Does EFSA have some guidance on how stability and bioavailability should be recorded? For the “article 13.1 Health claims”, the assessment requirements should be based on the proportionality principle, as mentioned in the recital 26 of the Health claims regulation: “Health claims other than those referring to the reduction of disease risk and to children's development and health, based on generally accepted scientific evidence, should undergo a different type of assessment and authorisation.” Part 2.1 Lines 119-125: How to extrapolate results from a target group to the general population? And what are the markers to take into account? How to show an improvement of health in healthy subjects, knowing that the target population shouldn’t have any disease? To show maintenance of health in healthy subjects could be possible if very large cohorts were used over long periods of time. As an alternative, could EFSA accept studies with subjects with high risk of acquiring the anomaly e.g. osteoarthritis, diarrhoea, urinary tract infections….? Part 2.2 Lines 151-152: The question is: can results from, for example infection studies in children (known for having higher incidence of infection), be used as evidence for a claim beneficial for a general population? Lines 131-159: Are animal and in vitro studies relevant to support a claim? Will EFSA take into account these studies or not? Line 154: What is the EFSA definition of a general population? |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| SPPAIL       | General comments | The SPPAIL is representing the French producers of food microbial cultures and probiotics, welcome the opportunity to comment the draft guidance on scientific requirement for health claims related to gut and immune function, prepared by the EFSA’s NDA panel. Since the publication of the first batch of opinions in October 2009, industry has expressed its need to have a clear view of the experts’ expectations, which could be achieved through a dialogue between EFSA and stakeholders. This is the reason why we do welcome the dialogue that EFSA has pursued since June 2010, and will pursue with the forthcoming meetings on specific health relationships. The current consultation is a clear sign that EFSA is open to discussion with stakeholders. We would like to submit some additional comments. |
| SPPAIL       | 3.1 Claims on bowel function | Line 165: “Changes in bowel function within normal range”; what does it mean? For which criteria and which value? Line 165-168 Should a beneficial effect be demonstrated in short term studies for example 4 weeks treatment or will it be necessary to show a long term sustained effect? |
| SPPAIL       | 3.1 Claims on bowel function | Line 168: In order to guide industrial applicants, what are the “generally accepted methods” that EFSA considered as acceptable? Is there an existing list of reference methods? |
| SPPAIL       | 3.2 Claims on gastrointestinal discomfort | Lines 175-176 Measurement with validated tools: If tools validated in an IBS population are modified as necessary for use in general population will these be considered sufficiently validated? |
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| SPPAIr       | 3.2 Claims on gastrointestinal discomfort | Lines 177-182: If a probiotic reduces gastrointestinal discomfort in a study group of IBS patients, can we use this probiotic as a preventive measure on symptoms of trouble for the general population? |
| SPPAI r      | 3.3 Claims on oral and gastrointestinal microbiota | Lines 198-199 How should a sustained reduction overtime be demonstrated (time frame for sustained reduction or number of repeated measurement)? |
|              |              | Line 200 Is the decrease “by at least 1 log value” supported by any scientific data? What is the scientific meaning and background of this 1 log value? This value should be microorganisms specific. Furthermore, a reduction may be irrelevant if initial levels are high; the subject may still be colonized with sufficient pathogens to become/remain ill. On the other hand, when levels are already very low, further reductions may not have any relevance either. What really counts is reducing levels of potential pathogens to levels below where they can cause disease? |
| SPPAIr       | 3.3 Claims on oral and gastrointestinal microbiota | Lines 183-235 According to EFSA: "the abnormal presence of pathogenic... microorganisms in the intestine may lead... to gastrointestinal infection. Reducing the numbers of specific pathogenic microorganisms... is a beneficial physiological effect." Such pathogens are Salmonella, Campylobacter, Listeria, E. coli, Yersinia.... - Probiotics used to fight against intestinal infections act as drugs. Where is the distinction between a probiotic decreasing the pathogen population in a man (ill since infected) and a drug? How is it possible to lead studies in healthy humans to demonstrate a beneficial effect against infections? For this topic, it is more feasible to carry out studies on animal models, with a level of well-defined contamination. Will these studies be examined and taken into account by EFSA? - Human studies on potentially pathogenic microorganisms, such as Clostridium or Candida should be subject to the same criticisms as those on the lactic flora or bifidobacteria (variability from one individual to another, subject to environmental factors ....). Why potential pathogens, which are part of the microbiota, are less dependent on the intestinal environment, like food constituents, than what is underlined for Bifidobacteria and Lactobacilli? So, why consider meaningful a decrease of 1 Log of a potentially pathogenic flora, for reducing a risk factor for infection, and reject the increase of 1 Log of protective microflora such as Bifidobacteria or Lactobacillus? |
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| SPPAIL       | 4.1 Claims on the function of the immune system | Line 263 Does it mean that only « maintain » claim will be accepted for immunity? Or can a claim for improvement of immune function be accepted? Lines 287-292 Which criteria were taken into account to define these markers as supportive evidence? What is the procedure to have a criterion considered/approved as a marker? |
| SPPAIL       | 4.2 Claims on reduction of inflammation | Lines 301-304 The case-by-case approach is not sufficiently safe for the applicant. Would it be possible to have more information on the criteria taken into account? Our understanding is that only one beneficial effect has to be demonstrated. But how many parameters? |
| SPPAIL       | 4.2 Claims on reduction of inflammation | Lines 294-304 Interleukins are cellular mediators and their change can be used to substantiate a health claim on the function of the immune system (cf lines 285-292). In this paragraph, it is said that “changes in markers of inflammation such as various interleukins do not indicate a beneficial physiological effect per se.” but “whether or not it could be considered beneficial depend on the context and will be examined on a case-by-case basis”. Could the panel be more precise on the context in which a modification of interleukins in a beneficial way could be considered as a beneficial effect? |
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| Südzucker AG | General comments | SÜDZUCKER/BENEO understands (but does not necessarily agree) that EFSA as an authoritative body must take a conservative role in order to ensure consumer protection - in the context of health claims the misleading of the consumer. However, the scientific views expressed in the draft Guidance - should be consistent with Opinions given in other contexts and manifest in Regulations (e.g. definition of probable benefit, fermentation as fibre effect). - should appreciate scientific judgements of other academic panels that have been subject to peer review (e.g. PASSCLAIM, prebiotic concept). - must be cautious when measurable markers reflect current state-of-the-art and thus a possible standard in nutrition science, but cannot provide a pharmacological-driven targeted evidence (healthy flora vs. pathogens). - need to be backed up by scientific references that led the NDA panel to its conclusions why it considers specific effect that have large support by nutritional scientific experts in the field or other panels not as probable beneficial physiological effects. - need to balance probable benefit vs. risk to lose a chance - need to take advances of nutritional science into account that have a younger history than 30 years. This guidance document supports marker that are clinically (pharmcologically) acknowledged and used. Nutrition and pharmacology are, however, separate disciplines with different approaches (including standards). This document ignores nutritional concepts such as prebiotic or fermentation that are accepted by a large body of nutritional experts in the field. If this current view of the NDA panel is taken for granted, nutritional research from academia and industry will be reduced to targeting defined clinical (= drug) outcomes; investments in nutritional research that is based on markers others than accepted by clinicians would phase-out. When effects themselves are assessed, it requires a broad scientific debate with all expert in the field. The way this Guidance document can be commented with 3800 characters/item is not the way to show a willingness for an unbiased scientific approach. We further request that equivalent standards need to be applied (“validated”) for all nutrients. In other words, currently for several vitamin/mineral claims in the area of immune defence, positive opinions suggest to the consumers that the respective effects have been established following the same criteria which others failed; this is misleading as at least several - if not many/all - were not assessed systematically and specifically for immune defence by any panel yet. If vitamins/minerals will not pass such a validation "run" with exactly the same criteria used for other nutrients, we query whether the current approach is appropriate for nutrients. Finally, the conservative mandate of the panel needs to be particularly stressed to put views on effects into perspective that are regarded as beneficial by a large community of nutritional scientists outside the EFSA even though an ultimate consensus may not have been reached. It is the evaluation criteria that have been changed rather than the science. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| SVUS Pharma a.s. | 4.1 Claims on the function of the immune system | Part 4. line 257 - To embrace such a complex and difficult subject as immune system with its multilateral functions the evaluators have to bear in mind that our knowledge of the body's immune system is still evolving and there are many unanswered questions, and some of the things that seem true today will be proven false tomorrow... - the immune system is maintaining health by really sophisticated "network" comprising many different players who interact with each other to such extent not yet fully understood and therefore insider would expect that for such health category some "grading of evidence" should be naturally possible since the limited knowledge can not be conclusive even with the latest "highest possible standard" (line 46) of scientific assessment - Therefore the grading of health claims could be the solution and might be arranged in similar way as the US FDA deals with so called "Qualified Health Claims" (i.e. "Supportive but not conclusive research shows that consumption of XY... may reduce the risk") The yes or no system is not functional in immunity world where modality words are more appropriate and sometimes maintaining a normal immune system means more "harmonization" of immune system than one-way boosting or mitigating hypersensitivity reactions. Part 4.1, line 258 - there seems to be inconsistence in Part 4.1 Claims on the function of the immune system where a) between lines 279 and 286 are described the principles of vaccination that is completely out of reach of food HC and strictly limited to medicines and b) between lines 287 and 292 where the markers of the function of the immune system that can be only used in substantiation of immunity HC, reads that "They may be considered supportive evidence..." and not weighed, when explained the mechanism of action and elevated/decreased activity past food /food components in long term ingestion, they should be more in rank of convincing evidence There should be possible some some shift in thinking in sense how to accept positive development of a.m. markers as convincing evidence when the "incidence of infection may not necessarily represent an effect on the immune system ..." (line 271 + 272). |
| SYNPA | General comments | SYNPA, which is representing the French producers of food additives, food enzymes, novel ingredients and functional ingredients, welcome the opportunity to comment the draft guidance on scientific requirement for health claims related to gut and immune function, prepared by the EFSA’s NDA panel. The implementation of the Health claims regulation has proved that there is a real need for the operators to have a clear view of the experts' expectations. We believe it could be achieved through the guidance. For the “article 13.1 Health claims”, the assessment requirements should be based on the proportionality principle, as mentioned in the recital 26 of the Health claims regulation: “Health claims other than those referring to the reduction of disease risk and to children's development and health, based on generally accepted scientific evidence, should undergo a different type of assessment and authorisation.” |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| SYNPA | 3.1 Claims on bowel function | Line 165: “Changes in bowel function within normal range”: what does it mean? For which criteria and which value? The IBS–C and IBS-D can be analyzed in this axis of bowel function (with modifying stools) Is the pH considered in that part for claims on “bowel function”?

Would it be possible to have a dialogue between EFSA and the applicant, before the submission of a dossier? That would allow the applicant to produce a dossier of higher quality and it would be beneficial to EFSA, as less time would be needed to review the dossier.

What is the classification of a key part of an healthy gastro-intestinal tract; the intestinal barrier? (part N°5 ?) And what is the request for prebiotic claims? Meaning what is the adequate and request balance of micro-organisms (and which one? Ratio?) to be considered as an healthy person?

We also have comments on the parts 2.1 and 2.2.

Lines 119-225:

How to extrapolate results from a target group to the general population? What markers are taken into account? How to show an improvement of health in healthy subjects, knowing that the target population shouldn’t have any disease? To show maintenance of health in healthy subjects could be possible if very large cohorts were used over long periods of time.

A non exhaustive list of symptoms and/or risk factors should be established.

In a recently published opinion (http://www.efsa.europa.eu/fr/scdocs/doc/1809.pdf) we note that “the Panel assumes that the claimed effects refer to aspects related to increasing numbers of bacteria that are considered to be beneficial” and also “The Panel considers that the evidence provided does not establish that increasing numbers of gastro-intestinal microorganisms is a beneficial physiological effect.” Thus the conclusion is: “a cause and effect relationship has not been established between the consumption of the food(s)/food constituent(s) which are the subject of the health claims and a beneficial physiological effect related to increasing numbers of gastro-intestinal microorganisms.”

We would like to know if we have to make the largest clinical trial to prove a beneficial physiological effect related to the increasing numbers of gastro-intestinal microorganisms? Would it possible to organize at European level a collective clinical trial with and for all interested stakeholders in that field, just due to the fact that this scientific challenge looks like more an academic research than a private industrial one.

Part 2.2

Line 157: It would be helpful and useful to have a non–exhaustive list of biological markers requested and/or recognized by EFSA for each physiological field. Would it be feasible within the next months? How many subjects are needed in a study to be considered as a pertinent study? Can a claim be based on one study? Or should there be at least two studies, one that shows an effect, and a 2nd study to confirm the effect?
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| SYNPA        | 3.2 Claims on gastrointestinal discomfort | Lines 177-182:
EFSA is considering the IBS, but which one? IBS –C (constipation) or IBS-D ‘diarrhea) or IBS-Mix ? Stools are not modified in these subjects; then could we consider IBS claim as a bowel function or gastrointestinal discomfort? Can we consider that person with IBS-C or IBS-D are included in that healthy population, either possible to have a claim in article 13. ?
Lines 181-182:
The IBS is a inflammatory bowel syndrom considered as a physiological status (not physiopathological one): we would like a confirmation of our understanding. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| SYNPA        | 3.3 Claims on oral and gastrointestinal microbiota | Line 200: Is the decrease “by at least 1 log value” supported by scientific data? This value should be microorganisms specific. Furthermore, a reduction may be irrelevant if initial levels are high; the subject may still be colonized with sufficient pathogens to become/remain ill. On the other hand, when levels are already very low, further reductions may not have any relevance either. What really counts is reducing levels of potential pathogens to levels below where they can cause disease. Lines 185-186: “It is not possible to define the exact numbers of the different bacterial groups” according EFSA. It would be more precise to talk about “predominant populations living in the colon where a true symbiosis with the host exists” leading to a “normobiosis” (meaning a healthy and well being microbiota). We kindly ask EFSA to take into account the work of the ILSI Prebiotic Task Force. Mr. Gibson and Mr Roberfroid are part of the task force: they have worked since a long time on this field and also defined it at first. Reference: “Prebiotic effects: metabolic and health benefits” just published on the British Journal of Nutrition. «The different compartments of the gastrointestinal tract are inhabited by populations of microorganisms. By far, the most important predominant populations are in the colon where a true symbiosis with the host exists that is key for well-being and health.» [Roberfroid M ] Furthermore, to measure the “exact numbers of bacteria” which technique to analyze is recommended by EFSA; for quantitative value, is it recommended to use qPCR for example (on DNA or RNA)? It’ll be fruitful to have a list of healthy and pathogenic bacteria according to their taxonomy (from the phylum to the sub-species which make not misunderstanding of studies or data results whatever would be the technique used in microbiology)… And what about the DGGE methods? Can we analyze the balance between the main phylum or group of bacteria (cf. taxonomy) in the correct way for EFSA? Line 189: Furthermore, what about the use of antibiotics? Consequence of a treatment or a currently use leading to a modification of the microbiota and favoring some pathogen bacteria … but which one? Does EFSA prefer to picture through phylum and balance, and/or species levels? In each case, it’s necessary to take into account the possible competition between bacteria. Lines 196-200: Is the method used relevant for the numeration of bacteria? Knowing that for example, some bacteria are not cultivable on plates … then is the qPCR made with DNA or RNA are the EFSA recognized method? Line 224: Clostridium perfringens contains pathogenic bacteria but also non-pathogenic! Then is it possible to precise which sub-species are considered by EFSA as pathogenic? |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| SYNPA | 3.3 Claims on oral and gastrointestinal microbiota | Line 200: Is the decrease “by at least 1 log value” supported by scientific data? This value should be microorganisms specific. Furthermore, a reduction may be irrelevant if initial levels are high; the subject may still be colonized with sufficient pathogens to become/remain ill. On the other hand, when levels are already very low, further reductions may not have any relevance either. What really counts is reducing levels of potential pathogens to levels below where they can cause disease. Lines 185-186: “It is not possible to define the exact numbers of the different bacterial groups” according EFSA. It would be more precise to talk about “predominant populations living in the colon where a true symbiosis with the host exists” leading to a “normobiosis” (meaning a healthy and well being microbiota). We kindly ask EFSA to take into account the work of the ILSI Prebiotic Task Force. Mr. Gibson and Mr Roberfroid are part of the task force. They have worked since a long time on this field and also defined it at first. Reference: “Prebiotic effects: metabolic and health benefits” just published on the British Journal of Nutrition. «The different compartments of the gastrointestinal tract are inhabited by populations of microorganisms. By far, the most important predominant populations are in the colon where a true symbiosis with the host exists that is key for well-being and health.» [Roberfroid M] Furthermore, to measure the “exact numbers of bacteria” which technique to analyze is recommended by EFSA; for quantitative value, is it recommended to use qPCR for example (on DNA or RNA)? It would be fruitful to have a list of healthy and pathogenic bacteria according to their taxonomy (from the phylum to the sub-species which make not misunderstanding of studies or data results whatever would be the technique used in microbiology)…. And what about the DGGE methods? Can we analyze the balance between the main phylum or group of bacteria (cf. taxonomy) in the correct way for EFSA? |
| SYNPA | 4.1 Claims on the function of the immune system | Line 266: Can we consider that a beneficial immune function is an immune reaction balanced between tolerance and allergy? Meaning that a level and reaction of Th1, Th2 and Th0 are request for each person. Otherwise, a dysbalance between Th1/th2 could lead either to an allergy or an inflammation status …. Lines 285-286: How to be sure that the increase of protective antibody titres will have a beneficial physiological effect? Which increase is considered as meaningful? Is there any upper limit (risk of auto-immune reaction?) Lines 287-292 Which criteria were taken into account to define these markers as supportive evidence? What is the procedure to have a criterion considered/approved as a marker? |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| SYNPA        | 4.2 Claims on reduction of inflammation | Lines 297-298: Some interleukins are well known to be involved in inflammation process through the gastro-intestinal immune system. Is it possible to have a non exhaustive list of interleukins considered by EFSA as pro-inflammatory interleukins? |
| SYNPA        | 4.3 Claims on reducing a risk factor for infections or allergy | Line 318: Why are the 2 main types of allergy (the immediate (type I) and the delayed one (type IV)) not defined? |
| Tate & Lyle Plc | General comments | We thank you for the opportunity to comment on this document. We think the document represents a good start and sincerely welcome the initiative. We feel it could benefit from further detail in terms of risk factors and biomarkers/outcome measures and have raised some specific questions to this effect. Additionally line 114 a propos risk factors, could EFSA clarify in its guidance whether it would consider bowel habit and transit time as risk factors for disease (constipation/motility)? We also feel some clarity is needed to the title of section 2.1. Beneficial physiological effect. This should be extended to clarify that EFSA is referring to beneficial physiological effects in the context of specific health claims relating to functional benefits and reduction of disease risk factors. We would suggest "Beneficial physiological effects in function and disease risk reduction claims". We would also seek further guidance on section 3.3 in the context of gastrointestinal microbiota. Currently there appears to be conflicting scientific views from academic experts in the field of "prebiotics" as to what constitutes a "beneficial physiological effect" in the context of gastro-intestinal microbiota "prebiotic" health claims. We hope this can be discussed in detail by all experts at the forthcoming EFSA Technical meeting on the 2nd December so that the scientific specifics involved can be ironed out and clarity brought to these claims for the benefit of current and future development. |
| Tate & Lyle Plc | 3.1 Claims on bowel function | What is considered the normal range of bowel function? Is stool consistency not a validated outcome measure? Bowel function relates to gut comfort and we would consider that changes in transit time, frequency of bowel movement, stool bulk, stool consistency are also valid for claims on gastrointestinal discomfort? |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Tate & Lyle Plc | 3.2 Claims on gastrointestinal discomfort | Since IBS patients are considered an appropriate population to measure discomfort and claim this for the general population, what is the panel’s view on IBD patients (in remission) as representative to measure effects of the immune system to support immunity claims for the general population? |
| Tate & Lyle Plc | 3.3 Claims on oral and gastrointestinal microbiota | There is a substantial body of published data concerning the stimulation of bifidogenic bacteria and health benefits (A very recent publication in the British Nutrition Journal reviewing the evidence "Prebiotic effects: metabolic and health benefits"; Vol 104, Supp 2, Aug 2010 might be useful to the panel, if not yet seen). |
| Tate & Lyle Plc | 3.4 Claims on digestion/absorption of nutrients | What about mineral absorption, calcium in particular and also protein digestion and absorption among others? |
| Tate & Lyle Plc | 4.1 Claims on the function of the immune system | line 273: would changes in IL10, IL1 and/or TNF alpha be considered valid changes in immune parameters? |
The draft guidance on gut and immune function claims assert that a reduction in pathogenic microorganisms or their toxins in stool would represent an appropriate outcome upon which to base a health claim. A pathogen such as *Listeria monocytogenes* (the genus *Listeria* is included on the list of approved pathogens, line 211) is not normally present in the stool of healthy individuals. A 2005 study identified *Listeria monocytogenes* in only one stool sample of 827 tested (0.12%) (1). This would make it impossible to gather a meaningful cohort of carriers for a human intervention. In addition, carriage can be sporadic rather than long-term (2). Obviously *Listeria monocytogenes* cannot be safely administered in human studies because of the risk of initiating disease. This is especially important in the case of listeriosis which has a very high mortality rate of ~20%. This essentially rules out any prospect of ever demonstrating a reduction in the levels of *Listeria monocytogenes* in the stool of humans. However, a food or treatment which reduces the risk of listeriosis could prove very significant in terms of reducing the morbidity and mortality associated with *Listeria monocytogenes*. This is an unmet need given that recent evidence shows that the incidence of listeriosis is on the increase in the EU (3).

I ask that the EFSA NDA Panel should accept that animal studies or the use of surrogate bacteria in humans should be considered as sufficient evidence on which to base a claim, for those specific organisms where no alternative is ever likely to be possible. For example, demonstrating a significant reduction of bacterial numbers in stool in animal models of listeriosis (supported by actual reductions in disease outcomes such as lethality), or demonstrating a reduction of deliberately introduced *Listeria innocua* in humans (if ethical permission could be achieved for such an approach). The use of the genus *Listeria* in the approved list rather than the species *Listeria monocytogenes* seems to favour an interpretation that evidence compiled using *Listeria innocua* would meet the criteria set out in the draft guidance, but it would be helpful if this could be clarified.

This is a very important question, since there are risk groups among healthy consumers (e.g. pregnant women, elderly consumers) who could benefit from consuming food designed to reduce risk associated with *Listeria monocytogenes*, but will never be able to receive such foods if human trials with *Listeria monocytogenes* are mandatory. Food is the most obvious vehicle to address this risk, since the rarity of listeriosis does not lend itself to vaccination or prophylactic chemotherapeutic strategies. Food which could reduce the risk of developing this often fatal disease would represent a low risk, high benefit strategy. The same issues may also apply to other pathogens, but this comment is specifically addressed at *Listeria monocytogenes* and listeriosis.

1. Saunders et al., 2005. *J. Food Protection*. 68: 178-181.
2. Grif et al., 2003. *Eur. J. Clin. Microbiol. Infect. Dis.* 22:16-20.
3. http://ec.europa.eu/health/ph_information/dissemination/echi/docs/listeriosis_en.pdf
| ORGANISATION   | CHAPTER TEXT   | COMMENT TEXT                                                                                                                                 |
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| UMC Utrecht  | General comments | **Lines 157**                                                                                                                                 |
|               |                | whether the studies used (an) appropriate outcome measure(s) of the claimed effect. This only is an appropriate formulation for FUTURE studies. For existing studies, the outcome measures are the one which justify the scientific conclusion. When the proposed health claim is at variance with these scientific conclusions, the health claim should be re-worded but not the study disqualified. Lines 157-159  |
|               |                | For this, the NDA Panel considers what is generally accepted in the relevant research fields and consults experts from various disciplines, as appropriate. I support this approach, provided that this is done UPFRONT. In such a way guidelines can be designed and agreed upon. |
| UMC Utrecht  | General comments | **2. General considerations**  
Lines 102-103  
According to the Regulation, the use of health claims shall only be permitted if the food/constituent, for which the claim is made, has been shown to have a beneficial physiological effect.  
As a personal note: when a given effect is NOT considered to be beneficial for health, such as increase in antioxidants, then what claim can be made. It will not be evaluated by EFSA, because by definition it is not a health claim then. So would it be allowed to carry any claim? “Our product is high in anti-oxidants”. Or even ”Contains anti-oxidants which support your immune system”?  
Lines 103-106  
In assessing each claim, the NDA Panel makes a scientific judgment 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. This can lead to a list/database of beneficial physiological effects. Now they are interspersed in the document. An appendix with approved beneficial effects would be helpful.  
Lines 117-118  
The extent to which the reduction of a risk factor is beneficial in the context of a reduction of disease risk claim needs to be considered on a case-by-case basis. No, does not need to be considered on a case-by-case basis. Guidance will require actual examples and even preferably an extensive list.  
Lines 137-138  
This requirement means that there should be sufficient definition of the food/constituent for which the claim is made. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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|              | Only up to the degree that it is clear what is meant and that it can be reproduced. As such the exact nutrient content of e.g. dried tomatoes doesn’t have to be detailed for me. Lines 139-140 |  |
|              | The evaluation also considers how the conditions under which the human studies were performed relate to the conditions of use Most studies will be controlled but the results will have to be extrapolated to the field situation. Lines 142-143 | The evaluation takes into account the hierarchy of evidence as described in the EFSA guidance (ref), Reference is missing Lines 145-146 |
|              | whether the design and quality of the studies allow scientific conclusions to be drawn for the substantiation of the claim. At this point the EFSA considers itself better than their scientific peers: design and quality of PUBLISHED studies already has been evaluated during the peer review process prior to publication in a scientific journal. Line 144 | Intervention studies should be appropriately conducted so as to minimise bias. See comment above on being better than the peers Lines 147-148 |
|              | 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. But this is needed! How can you design your studies if there are no criteria? Lines 148-150 | 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. Extremely vague statement; what is meant here? Does reproducibility mean that 2 independent studies are needed? And if this should be 2 identical studies, then who is going to publish the replication study? Lines 151-152- whether the studies have been carried out in a study group representative of the population group for which the claim is intendedSee remark on IBS (below) Lines 154-156- 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. This is vague and certainly not the guidance which is needed Lines 157 | In this regard, the reproducibility of the effect of the food/constituent as indicated by consistency between studies is an important consideration. Extremely vague statement; what is meant here? Does reproducibility mean that 2 independent studies are needed? And if this should be 2 identical studies, then who is going to publish the replication study? Lines 151-152- whether the studies have been carried out in a study group representative of the population group for which the claim is intendedSee remark on IBS (below) Lines 154-156- 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. This is vague and certainly not the guidance which is needed Lines 157 |
|              | whether the studies used (an) appropriate outcome measure(s) of the claimed effect. This only is an appropriate |  |
| ORGANISATION     | CHAPTER TEXT       | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                 |
|-----------------|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| UMC Utrecht     | General comments   | 1. Introduction  
Lines 12-15  
It is not intended that the document will include an exhaustive list of beneficial effects and studies/outcome measures that are acceptable.  
Why not. And, if an exhaustive list is not possible, a list of the most relevant beneficial effects would be very helpful.  
Lines 45-46  
According to the Regulation, health claims should be only authorised for use in the Community after a scientific assessment of the highest possible standard to be carried out by EFSA. But who determines what is the highest possible standard and HOW realistic is this. If NO ONE can reach that standard then what is the use?  
Lines 92-93  
it represents the views of the NDA Panel based on the experience gained to date with the evaluation of health claims in these areas. But for probiotics all these views were negative .  
Lines 96-97  
It is not intended that the document will include an exhaustive list of beneficial effects and studies/outcome measures that are acceptable. But it could, and maybe even should, have appendixes with such lists.  
Lines 97-98  
Rather it presents examples drawn from evaluations already carried out Again, as indicated above, that is not very helpful when most of those evaluations are negative |
| UMC Utrecht     | 3. Gastro-intestinal tract | Lines 224-225 Candida, Clostridium perfringens (when producing enterotoxin), other clostridia, Escherichia coli (certain serotypes). Unacceptable generalization. There are many beneficial clostridium species. Example is Clostridium butyricum which has received approval by EFSA for use in chickens!Line 225Sufficient characterisation is required in the studies to confirm their pathogenicity. What study design has EFSA in mind that would include these type of characterisation? Lines 232-234  
While effects on intestinal permeability, production of short chain fatty acids, pH, can be assessed in human studies, such outcomes are in themselves insufficient for the substantiation of the claim. Why is intestinal permeability not acceptable? Improvement of mucosal barrier function (and as such that could be the claim) may be even more important for prevention of infection than reducing the number of potential pathogens in the intestine |
| ORGANISATION   | CHAPTER TEXT | COMMENT TEXT                                                                                                                                                                                                 |
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| UMC Utrecht   | 3. Gastro-intestinal tract | Lines 165-166 Changes in bowel function within the normal range might be considered beneficial physiological effects. Unclear statement. Changes within the normal range? Is this meant then: closer to the median? But, “everywhere” within the normal range (at the upper end or at the lower end) is normal.  
Lines 168 These outcomes may be measured by generally accepted methods. No, SHOULD be  
Lines 170-173 Episodes of abdominal pain or discomfort (e.g. distension/bloating, abdominal pain/cramp, borborygmi (rumbling) etc.) in the absence of organic disease or biochemical abnormalities are commonly associated with food or drug intake or alterations of bowel habit and vary between individuals in frequency and severity. Drug intake is equivalent to having a disease (in my view), so this is an unclear statement  
Lines 175-176 Appropriate outcome measures of the claimed effect in human studies include validated subjective global symptom severity questionnaire(s).  
EFSA: Please provide a reference for such questionnaire(s) and an indication on the minimal required degree of improvement to be clinical meaningful.  
Lines 179-180 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. If this is acceptable (and that’s fine with me) then it should also be allowed to apply these criteria for infectious episodes: Episodes of respiratory infections occur both in healthy people and well as in elderly, the difference being the higher frequency and greater severity of the symptoms in the elderly.  
Lines 184-186 The composition of the microbiota in the intestine may be altered by food constituents. Based on current scientific knowledge, it is not possible to define the exact numbers of the different bacterial groups that would constitute a normal microbiota.  
But within the very near future it will!! More important however: if EFSA does not know what constitutes a normal microbiota then how can you be qualified to evaluate these dossiers?  
Lines 186-188 The evidence available to the panel does not establish that increasing the number of specific microorganisms or any groups of microorganisms, including lactobacilli and/or bifidobacteria, is in itself a beneficial physiological effect. This statement makes it VERY difficult for prebiotics to ever get a claim approved.  
Lines 198-200
Therefore, a microbiologically relevant reduction of pathogens, which is sustained over time in the same study group, should be demonstrated. Generally, a decrease by less than 1 log value is not considered meaningful.

This may sound like a reasonable factor for bacteria which occur in high numbers but for pathogens? As the opinion of expert medical microbiologists on this aspect, and, as in the previous comment, whether a 1 log unit reduction is applicable to every pathogen.

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

Totally unclear what is meant here.

The Panel considers that maintaining a normal immune function is a beneficial physiological effect. Given the multiple roles of the immune system, the specific aspect of immune function that is the subject of the claim should be indicated, e.g. related to defence against pathogens or response to allergens. Yes, but how?

In this regard, it is considered that claims related to ‘natural defences’ need to be defined more clearly regarding the specific aspect of immune function that is the subject of the claim. But HOW defined more clearly. “Our product support maintainance of normal innate immune function”? “Our product supports Natural Killer cell function”? And, more important for now: what kind of evidence is needed for a claim on natural defences?

Similarly, allergic symptoms are not always easy to distinguish from non-allergic phenomena, and self reported allergies are usually unreliable and insufficient for diagnosis of allergy. This is another examples where EFSA considers itself more qualified than the scientific peers!

Studies on allergic diseases need to include physician diagnosed allergies, and the immunologic nature of these allergies needs to be corroborated with appropriate measures. When possible. Not every allergic response to peanut is accompanied by peanut specific IgE. Also, not every person with peanut specific IgE has to suffer from peanut allergy.

Stimulation of protective antibody titres could be used to substantiate a health claim on the function of the immune system related to defence against pathogens.
CAN be used in my opinion. And, also take the next step: for pneumococcal and influenza vaccination, international, validated response criteria have been defined which can be used in the design of clinical studies.

lytic activity of natural killer cells and cytolytic T cells, Cytotoxic T cells

They may be considered as supportive evidence, in as much as they are proposed as mechanism of the effect. But are they required? Or only in combination with a clinical outcome? Less viral infections and improved NK cell function, is that sufficient to claim stimulation of the natural defence against viral infections?

Adequate inflammatory responses are of primary importance for the defence against injury of any origin. So, stimulation of a physiological inflammatory response can be considered a health benefit?

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

No, not on a case by case basis. Propose guidelines, otherwise everyone remains in the dark.

While human intervention studies that show only a reduction in the incidence or duration of the infectious or allergic diseases could not substitute for evidence of a reduction in a risk factor for the disease, such studies could be supportive for the claim. ??; does this mean that also a biomarker of the immune system is needed?

| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Unilever     | General comments | Comments were prepared on behalf of Unilever and submitted by Danielle Wolvers |
| Unilever     | General comments | Comments on this document were prepared on behalf of Unilever and submitted by Danielle Wolvers |
| Unilever     | General comments | Comments were prepared on behalf of Unilever and have been submitted by Danielle Wolvers |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
|--------------|--------------|--------------|
| Unilever     | General comments | 137 There is a paragraph on characterization in the accompanying briefing document (a/o mentioning the advice to show "consistency in the final product for those characteristics considered pertinent to the claimed effect"). We propose to specify that characterization can mean demonstrating a specific nutrient or (food) constituent such as a vitamin or mineral. In cases where this is not possible because the activity is delivered by a natural extract comprising many constituents, characterization can also comprise of characterization using specified marker molecules in combination with demonstration of consistent biological efficacy using a bioassay relevant to the proposed mechanism of action. 158: Although in the accompanying briefing document further details are given as to how EFSA decides whether a health claim is substantiated, we would appreciate input from the panel on what they consider "generally accepted" outcome measures. Especially for those areas where clear clinical guidelines exist or where scientific associations or other regulatory bodies have laid out guidelines (e.g. for scoring of diseases) that are acceptable to EFSA, it will be helpful to have a document containing examples of such generally accepted measures. In addition we propose to include in such a document examples of acceptable validated questionnaires for the assessment of symptoms of infections, such as the Jackson and WURSS scores for respiratory infections. |
| Unilever     | 3.1 Claims on bowel function | 165-168 Normal ranges of various bowel functions have been defined, therefore, we would welcome the panel's view of what they consider normal ranges of the various functions are and what the generally accepted measurement methods are, or input from the panel specifying what criteria apply to determine whether methods and ranges are generally accepted. |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Unilever     | 3.2 Claims on gastrointestinal discomfort | 175-176  
We propose to include acceptable validated questionnaires in the guidance document. E.g. for scoring of diarrhea this may include the Vesikari score  
177-182  
We agree with the panel that evidence derived from certain sub-populations may be appropriate to support claims for the general population. It would be useful if the panel could specify which criteria determine whether or not certain effects in specific subpopulations may be extrapolated to the general population. We propose that important criteria include underlying (patho)physiology principles which also apply in the general population (be it with a different magnitude) and that it is biologically plausible that effects would also benefit the general population (even though benefits may not be immediately measurable). In our opinion, examples that apply for extrapolation to the general population would be:  
- people with antibiotic-associated diarrhea are an appropriate study group to support claims on gastrointestinal infections (add to paragraph 3.3)  
- people with traveler’s diarrhea are an appropriate study group to support claims on gastrointestinal infections (add to paragraph 3.3)  
- people with experimentally induced infections, such as intestinal infections and respiratory tract infections, are an appropriate study group to support claims on the respective infections in the general population |
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Unilever     | 3.3 Claims on oral and gastrointestinal microbiota | 199 Can the panel clarify what is meant by "sustained over time"? Would the effect need to last during the period of intervention, beyond the period of intervention, and would there be any relevant time-span? 200 A decrease of at least 1 log could be meaningful for certain pathogens, however, this cannot be regarded as a generally accepted reduction that has a biological relevance for all pathogens. Some pathogens are pathogenic when present in very low numbers, therefore a decrease smaller than 1 log could be clinically relevant. In other cases, a reduction of 1 log would not be meaningful when compared to the number of microorganisms normally present. We would suggest that the term “biologically relevant decrease” or “clinically relevant decrease” may be more appropriate. 203-208 In addition to the reduction in the number of pathogenic microorganisms that are mentioned as acceptable risk factor, we propose that other gastrointestinal markers (such as intestinal permeability, production of short chain fatty acids, pH as mentioned in line 232, but also potentially beneficial microbes) should also be considered risk factors, provided that: 1) a statistically significant effect on both an infection outcome and a gastrointestinal marker has been demonstrated in the same study and a biological plausible hypothesis exists or 2) a reduction/increase of changes of the gastrointestinal marker, possibly in sub populations, is associated with a demonstrated reduced/enhanced resistance to infections. |
| Unilever     | 3.4 Claims on digestion/absorption of nutrients | 237-239 In addition to the improved digestion and absorption of nutrients, it may, in certain cases, be beneficial to reduce the absorption of substances, e.g. energy in overweight subjects, cholesterol, LPS, toxins etc. We thus suggest that such effects might also be considered beneficial physiological effects. In addition, it should be demonstrated that improved absorption of nutrients is linked to a beneficial physiological effect as there is no difference in final effect between a product with double absorption efficiency (due to improved technology) and a product with double amounts per serving. The beneficial effect should be obtained at similar dose or common intake from the diet, or should be possible without going beyond RDA limits. 254 The guidance document states; "Iron absorption can be measured in humans by generally accepted methods". This should be specified further since some methods to investigate iron absorption e.g. single dose isotope studies, are not predictive for long term effects on iron status. E.g. effects from such single dose studies are not good predictors for daily life. |
### Outcome of a public consultation on a draft guidance on the scientific requirements for gut and immune function claims

| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Unilever     | 4.1 Claims on the function of the immune system | **266-7** The bodies "natural defences" or “resistance” is a function that comprises several physiological mechanisms, e.g. immune function and physical barriers like skin and gut barrier, that in turn comprise various functional elements. Effective natural defence/resistance results in protection against challenges (e.g. infections, UV) and maintenance of homeostasis. We propose that claims on "natural defence/resistance (against a specified challenge)" are acceptable without specific reference to an underlying mechanism, if effects on a clinical outcome are demonstrated 268-273. We propose that the outcome of an infection (incidence, pathogenic load, severity, duration) be the gold standard for substantiation of a claim on defence/resistance against pathogens and need not be accompanied by demonstration of an effect on underlying mechanisms provided confounding factors are adequately addressed. As the document is unclear on this, can the panel confirm that it regards reductions in clinical outcome of infection as sufficient evidence for claims related to defence against pathogens? We agree that for claims involving the immune system, appropriate evidence of a concomitant change in immune parameters is needed. Likewise, for claims involving other aspects of resistance such as colonization resistance or barrier function, appropriate evidence of a concomitant change in relevant markers is needed. 268-9. We propose to include acceptable validated self-reported scoring systems/questionnaires for the assessment of symptoms of infections in the document, e.g. the Jackson score (Jackson et al, 1958) or the Wisconsin Upper Respiratory Symptom Survey (Barret et al 2005) for the common cold 272-3. What is meant by "appropriate evidence”? What connection is needed between clinical outcome measurement and immune parameter(s)? As it is impossible to demonstrate a causal relationship between a change in immune parameters and infection outcome in a human study, we propose that a statistically significant change in an immune parameter should be demonstrated concomitantly with a statistically significant change in a clinical outcome, supported by a biologically plausible hypothesis 285-6. The response against vaccination has been proposed as model to study responsiveness of the immune system to infections (Br J Nutr. 2005 Sep;94(3):452). We propose that increased responsiveness to vaccination (increased specific antibody levels or protection rate) is appropriate evidence to substantiate a health claim on immune function. It is unclear what the panel means by "Stimulation of protective antibody titers”. Stimulation of antibody titers within a group or increased number of individuals attaining protective levels are both biologically relevant and we propose that both provide evidence to substantiate a health claim on immune function 287-292. We agree that changes in immune parameters alone do not constitute a health benefit. However, in several situations parameters are changed outside normal ranges, e.g. reduced NK cell activity/numbers/salivary IgA in elderly and...
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Unilever     | 4.2 Claims on reduction of inflammation | 301-305 Although we share the opinion that changes in inflammatory markers alone do not constitute a beneficial effect, there are a number of situations relevant to the normal population where certain inflammatory markers are changed and where these markers are outside normal reference ranges, as would be observed by a significant change from a reference control group or from clinical reference values. In several situations such changes have been suggested as risk factors for development of disease. An example is the association between increased levels of pro-inflammatory cytokines and CRP and future cardiovascular and metabolic disease. We propose that claims on reduction of inflammation may be supported by evidence of changes of inflammatory markers back to normal ranges (normal clinical ranges, control group ranges) 1) in a population that is naturally (e.g. ageing) outside this normal range, 2) in study populations with specific life styles (e.g diet) or life events (e.g. injury) 3) in study populations where the response of inflammatory tone following an experimental challenge-model representative for a life style or life event (such as exposure to a high fat meal) is out of normal range and that such evidence alone is sufficient to substantiate a claim on improved inflammatory tone. |
| Unilever     | 4.3 Claims on reducing a risk factor for infections or allergy | 316-320 As there are no validated risk factors for infections related to immune function or gastrointestinal function, we would welcome a further discussion with the panel and their opinion on how this could be approached. There are several types of data (epidemiological and experimental) that show an association between certain immunological or gastrointestinal parameters and resistance to infections. Examples of these are the reduced NK cell activity and numbers, sIgA levels and the susceptibility of airway infections in elderly, subjects under chronic mental stress and subjects under strenuous exercise. In order to arrive at the qualification of a risk factor we propose the following criteria to establish such markers as acceptable risk factor for infection susceptibility: 1) demonstration of a statistically significant effect on both an infection outcome and a biomarker in the same study 2) demonstration of a statistically significant effect on both an infection outcome and a biomarker in the same study as well as a biologically plausible hypothesis linking the biomarker with the infection outcome 3) demonstration of changes of immune parameters (or other biomarkers) in sub populations associated with demonstrated compromised resistance to infections |
| UNIV Navarra | General comments | POINT 3 |
|--------------|------------------|---------|
|              | Research on the role of Probiotics concerning GI functions should continue since results during decades has produced promising outcomes that if substantiated will provide successful applications | POINT 3 |

4) demonstration of reduced changes of immune parameters (or other biomarkers) in sub populations associated with demonstrated improved resistance to infections

Furthermore we want to raise the point that it is possible that a risk factor may in fact be a composite of various factors, rather resulting in a risk profile than a single risk factor. An example of this would be the immune risk profile defined in elderly. How would such risk profiles be considered by EFSA?

312-315

We appreciate the fact that a reduction in the number of pathogens at the infectious site, (such as the gastrointestinal tract for a number of pathogens that are listed in 3.3) can be used as risk factor in a disease risk reduction claim. As we welcome the list of microorganisms that are considered pathogenic or toxicogenic in the GI section, we would appreciate to see a list of microorganisms that can be considered as pathogens relevant to the general population with respect to infections occurring at other sites in the body, such as the airways, urinary tract and skin. Such microorganisms may include respiratory syncytial virus among others and may be measured in nasal lavage, bronchial fluid, urine, depending on the primary infectious site, to support both claims related to defense against pathogens and reducing a risk factor for infection. In addition, as many infections are transmitted via other routes than the primary infectious site and as the reduction of pathogens at distant bodily secretions and surfaces would reduce the risk of (re)infection, we suggest that the list "suitable samples" may include distant bodily secretions and surfaces including but not limited to:

- Fecal material for non-GI pathogens: e.g presence of airway pathogens here may be an indication for infection or a route of transmission (e.g De Jong, Pediatr Infect Dis J 2008;27: S54) In fact, this is comparable to what is described for C. tetani under 3.3, as GI pathogen, but infectious via wounds

- Hands: Hands are a primary route of contact transmission for many infections. The presence of pathogens on the hands should thus be considered as a risk factor for infections http://www.who.int/gpsc/country_work/en/
| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| University Hospital Motol, Prague, Czech Republic | 4. Immune system | As an immunologist I follow with great interest discussions concerning the role of probiotics on human health. I also read carefully arguments of Danone, as I’m involved in Danone Institute Czech Republic, and EFSA. on that topic I find arguments of both sides very important, however, I still see problems in communication. I would strongly suggest for the upcoming meeting the urgency to create such atmosphere and format of the meeting that would allow to all participants to reach the goals that would be respected by both sides. I see particualrly important to clearly define the nature and extent of scientific studies that would support (or deny, event if this is not very probable) the role of probiotics on human health and immune system. Further, I would see the opportunity to organize this effort throughout whole Europe. This would be very beneficial and would lead to more important clinical studies, stronger than these currently available. Hopefully such effort might also unify so far a little fragmetned research apporach to the topic. |
| University Hospital Vall d’Hebron | General comments | Lines 12-13: The document is clear and coherent. A very important point stated in the Summary is that it does not include an exhaustive list of beneficial effects and studies/outcome measures that are acceptable. In fact, there is a lack or at least a deficit of well established biomarkers to be used as endpoints/variables in studies to investigate efficacy. There are some valid markers for bowel function and for abdominal discomfort. However, gastrointestinal well-being is ill defined and appropriate questionnaires have not been developed (well-being is a fundamental characteristic of WHO definition of health). The situation is even worse when addressing the evaluation of immune functions or healthy characteristics of the intestinal microbiota, where science is continuously expanding our knowledge, and new markers and concepts will be emerging. Thus, the current state of the art stresses the importance that NDA panel opinions should rely on evaluation in depth by external experts with the highest level of expertise in the particular field addressed by the studies of the dossier. It is very difficult that the members of the NDA by themselves would cover all the areas of human biology and health. Preferably more than one external outstanding experts should be used, as it is always the case in scientific evaluations. Lines 153-156: This is an important point that the panel should take into account. It seems that it has not been the case in the past. Patients and disease are many times a clear model to see beneficial effects of interventions difficult to observe in the fully healthy status. Consider the effect of probiotics in pre-mature children. Certain probiotic strains have been shown to improve survival. It is obvious that they are producing beneficial effects at the intestinal mucosal level. However, in healthy normal weight babies (without risk of death) you may not be able to recognize the beneficial effect without doing mucosal biopsies (babies!). There is a clear need of accepting and understanding disease models to learn and validate effects and mechanisms that will be eventually useful for the ‘normal population’. |
| ORGANISATION                        | CHAPTER TEXT                                                                 | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                 |
|-----------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| University of Milan/ Istituto     | 4.1 Claims on the function of the immune system                              | The EFSA initiative to provide guidelines for health claims is timely and appropriate. In this general framework a further effort should be made to better define selected principles and outcomes. Specifically, here is a series of reflections for consideration related to some open issues. 1. Quality of clinical studies  
   a. Better definition of appropriate study population in relation to the general population is warranted.  
   b. Infants and children pose specific challenges related to maturation of the immune system, the intestinal barrier function, etc. Therefore addressing the specificity related to child health would be advisable.  
   c. Aspects related to the quality of clinical trial data need to be better defined. These include the size and design of a single large scale pivotal study; the use of meta-analysis and their relative importance; the importance of surrogate endpoints and the relative weight of secondary end points turning out positive in the presence of a non-met primary endpoint; biological plausibility. Indeed, mechanism of action and biological plausibility are key elements for final judgement and are at present underestimated. 2. Effects on the immune system  
   a. I share the view that changes in markers of immunity including number and function of leukocytes, cytokines etc. are insufficient for a claim of beneficial effects on immunity per se. It should be clarified whether correlates of immunity are indeed valuable readouts for a claim in the presence of positive beneficial clinical response.  
   b. As indicated by the Panel, altered susceptibility to infectious agents is not necessarily representative of changes in immunity. It would be important to better delineate dissociations of the two and the appropriate type of data establishing a link.  
   c. It would be appropriate to better define conditions under which results of separate studies, addressing for instance clinical versus biological outcomes, can be linked in a claim.  
   d. Vaccine studies are widely used and meet an important health need. It would be helpful to better delineate the vaccines for which validated cut off values are indeed considered; the relationships between stimulation of antibody titres in response to vaccination and resistance in the context of natural infection; the relative weight of average increments in titres in a population versus frequency of individuals obtaining protective titres.  
   e. A general issue relates to the specific aspects of immunity affected in the general context of “natural defences”. This is an important question given the complex networking of the immune system. Even for conventional classic adjuvants, the specific claim would be hard to define.  
   f. In relation to defence against pathogens, better definition of criteria for a claim is warranted, including the sufficiency of clinical outcomes of infection, the reduction of pathogen load in disease, the reduction of commensal pathogens versus pathogens in infection, the importance of markers of wellness (e.g. fever, appetite). |
| ORGANISATION                  | CHAPTER TEXT                                      | COMMENT TEXT                                                                                                                                                                                                 |
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| UNIVERSITY OF MONTREAL       | 4.1 Claims on the function of the immune system   | Lines 268-73 The claim that a product improves the immune system should be accepted if supported by several independent lines of evidence. 1. Well controlled intervention studies on healthy individuals of different ages showing increased resistance to common infectious diseases as revealed by shorter duration of disease and reduction of fever. 2. Multiple independent studies on healthy individuals showing: (i) increased production of neutralizing antibodies following routine influenza vaccination (ii) enhancement of NK cell function/ maintenance of their circulating level during stress episodes (iii) enhancement of the stimulated oxidative burst of phagocytes. All these published observations on the multiple facets of the protective mechanisms against infection should be taken together to indicate that the product has favorable effect on the immune response. |
| University of Reading        | 3.3 Claims on oral and gastrointestinal microbiota| Thank you for the opportunity to comment on the draft claims document relating to gut and immunity. Line 188: As a general principle I vehemently disagree with the contention that increased bifidobacteria and lactobacilli is not of benefit to the host. My view is that this ignores the vast body of literature (>7000 published articles) and research on probiotics and prebiotics. This field has good quality science and techniques to back up mechanistic explanations of effect. Many trials are conducted at a high quality with rigorous control. To me, using increased populations and activities of these microbial groups in the gut is as useful a biomarker of improved health as most others. If we do not strive to capitalise upon this with the functional food concept then ultimately it will be to the detriment of European consumer health. Here are more specific comments: 1) Lines 211-225: These pathogens can be harboured without ill effects, so in many people reducing their numbers would be meaningless in terms of health. My view is that asymptomatic carriage is at least partly explained by increased populations of microbes such as the bifidobacteria. and why probiotics and prebiotics should target such components of the microbiota. 2) Line 200: The one log reduction figure does not make sense to me, given that the pathogens exert effects at different doses e.g. shigella (mentioned) can cause dysentery at 10-100 cells so reduction by one log in this regard would mean nothing. 3) Lines 211-216: Showing a one log decrease in the viruses would be hard to prove, as they need living cells to survive. 4) Line 218: H. pylori is not an environmental pathogen. 5) Line 218: C. tetani is by no means just a wound pathogen. 6) Generally, the document comes across as viewing the microbes in isolation (e.g. a laboratory) not the complex ecosystem of the gut. 7) The way to reduce these pathogens, at least the bacteria, is through antibiotics. But, the document relates to food. I cannot foresee how any food will suppress pathogens by more than a log value. 8) By the time these acute pathogens cause symptoms they are on their way out. So, eliciting a reduction then is of no
| ORGANISATION       | CHAPTER TEXT | COMMENT TEXT |
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| University of Ulster | General comments | Comments by: Raymond O’Rourke, Fellow, Faculty of Biomedical Sciences, University of Ulster, Coleraine, Northern Ireland - raymond.orourke@ireland.com Silvia Banares, Food Lawyer, Barcelona, Spain - sbanaresv@uao.es |

1. “beneficial physiological effect”
EFSA has to define more clearly what is a "beneficial physiological effect" and the criteria it applies to judge if a claimed effect is beneficial or not. “Beneficial physiological effect” is an indeterminate concept, not only from a scientific point of view, but also from a legal point of view. This definition is very important, as it is a step that precedes the assessment.

2. “health” or “healthy population”
There is no definition about what health means. The EU has not included the WHO/FAO definition in 1924/2006 Regulation.
Also, there is no definition either for a "healthy population". Both concepts are important as the studies must be done with a target population (healthy people according EFSA guidelines).
Gut & immune claims must consider people with mild clinical hypertension, with IBS, gastrointestinal discomfort, or elderly people—that means, people that are not in a perfect state of physical wellbeing—and therefore could be termed an ‘ill’ group rather than a ‘healthy’ group.

3. Vague legal terms
The draft:
   a) Introduces some new concepts that are not included in 1924/2006 regulation, such as "function claims" (point 2.1)
   b) It also uses some confusing expressions, like "disease risk reduction claims" "disease reduction claims", while according 1924/2006 they should be "reduction of disease risk claims"

4. Number of studies and kind of studies
There is no statement about how many studies with humans are needed to show efficacy, and applicants should know about it before summiting any dossier.
The role of observational studies must be clarified too.

5. Reduction of risk factors.
The concept of "reduction of risk factors" should be clarified. The actual position of EFSA is clear for some cases (i.e. cholesterol and coronary diseases), but it is not so clear for other cases (i.e. probiotics which reduce diarrhoea risk)

| University of Western Ontario | General comments |
|-----------------------------|------------------|
|                             | 102 - Trying to make rules on health Claims when the definition of Health is antiquated makes little sense. |
|                             | 146. What does "adequate" mean? What if it is not easy to control these? |
| ORGANISATION               | CHAPTER TEXT                                      | COMMENT TEXT                                                                                                                                                                                                 |
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| University of Western     | 3.3 Claims on oral and gastrointestinal microbiota | 186. Would increasing the number of E. coli 0157:H7 be referred to as a harmful physiological effect? Yes, because it induces illness. Thus, increasing the number of organisms that are known to confer a beneficial effect should be acceptable. 189. I don’t necessarily agree. If you reduce the number of E. coli 0157:H7 by ten fold the child might still die. 192. The document needs to site specific examples here. Most toxigenic organisms are not carried in the gut of healthy people. Rather, they are ingested and induce disease. Thus, in most cases the disease is already occurring when a probiotic is administered. The panel needs to define a certain scenario so that anyone wishing to make such a claim knows what studies might be required. 203. I perhaps don’t understand this correctly, but the faster resolution of a disease may not necessarily correlate with reduction in pathogen count in the stool, and why would this be the outcome anyway? It is the clinical evidence that is much more important. 218. There is a danger in defining some "pathogens" such as H. pylori, which may be in some people not pathogenic. 266. The key word here is "could". Companies shouldn’t have to prove that this happens. |
| University of Western     | 4.1 Claims on the function of the immune system   | 271. You are surely not ruling out the role of the immune system in reducing the incidence of infection? This makes no sense, therefore it has to play a role albeit not always the major one. 274. Why always involve physicians? In initial diagnosis yes, but not necessarily more than that. Self-reporting can be reliable. |
| University of Western     | 4.2 Claims on reduction of inflammation           | 294. So, the body does not react to specific antigens? Incorrect. Induction of IL-10 or Tregs are physiological effects which in certain patients could well be beneficial. |
| ORGANISATION               | CHAPTER TEXT                                                      | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                 |
|----------------------------|-------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| University of Western      | 4.3 Claims on reducing a risk factor for infections or allergy     | 308. Why? Surely, the key outcome is shorter duration of disease, not evidence of reduction in some risk factor? Where’s the value in reducing something regarded as a risk factor, when there is no reduction in incidence or duration of disease?                                                                 |
| Ontario                    |                                                                   |                                                                                                                                                                                                                                                                                                                                            |
| Valio Ltd                  | 3.3 Claims on oral and gastrointestinal microbiota                 | Evidence on reduction of pathogens is often mentioned in the document as an appropriate outcome measure. Our concern is that claims will become pathogen specific, e.g. “Reduced risk of infections caused by pathogen X” or “Increased defense against pathogen X”. It is important to note that the number of unidentified intestinal pathogens can be as high as 65% (Karsten et al. 2009). Yet a probiotic can and has been shown to work also when the pathogens have not been identified (Guandalini et al. 2000). In addition, pathogen-related claims on foods are not appealing and most likely not comprehensible to the consumer. References Guandalini S, Pensabene L, Zikri MA et al. Lactobacillus GG administered in oral rehydration solution to children with acute diarrhea: a multicenter European trial. J Pediatr Gastroenterol Nutr 2000;30:54-60. Karsten C, Baumgarte S, Friedrich AW et al. Incidence and risk factors for community-acquired acute gastroenteritis in North-West Germany in 2004. Eur J Clin Microbiol Infect Dis 2009;28:935-43. |

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| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Valio Ltd    | 4.1 Claims on the function of the immune system | Reduction in the numbers of respiratory tract pathogens seems to be an acceptable outcome measure, according to lines 268-70. A list of gastrointestinal pathogens is given earlier in the document, line 211 onwards. Which microbes are considered as pathogens of the respiratory tract? If the length of the study, when showing the reduction of pathogens, is of any importance, could some guidelines be given? Hopefully it is not required that the reduction of pathogens is demonstrated in the same study where clinical evidence on infections is shown. As for studies on allergic diseases, the document states on line 278: “clinical as well as laboratory measures are preferentially shown in the same intervention studies”. Evidence from separate studies should also be accepted. Evidence on reduction of pathogens is given as an appropriate outcome measure for claims of the immune system. Our concern is that claims will become pathogen specific, e.g. “Reduced risk of infections caused by pathogen X” or “Increased defense against pathogen X”. It is important to note that the number of unidentified intestinal pathogens can be as high as 65% (Karsten et al. 2009). Yet a probiotic can and has been shown to work also when the pathogens have not been identified (Guandalini et al. 2000). In addition, pathogen-related claims on foods are not appealing and most likely not comprehensible to the consumer. It should not be required that pathogens are mentioned in the claim. References Guandalini S, Pensabene L, Zikri MA et al. Lactobacillus GG administered in oral rehydration solution to child-ren with acute diarrhea: a multicenter European trial. J Pediatr Gastroenterol Nutr 2000;30:54-60. Karsten C, Baumgarte S, Friedrich AW et al. Incidence and risk factors for community-acquired acute gastroenteritis in North-West Germany in 2004. Eur J Clin Microbiol Infect Dis 2009;28:935-43. |
Wincllove Bio Industries  General comments  Wincllove’s opinion on EFSA’s published guidance (final)
Based on all above mentioned critical notes we come to the conclusion that this guidance is very late however we appreciate this guidance as a positive reaction on all comments the stakeholders gave on the regulation and how EFSA handled it. Nevertheless, this guidance should not be a way whereby EFSA tries to get retrospectively approval from the industry on the judgements they have made the last four years and the underlying basis for their rejections.

All this is a missed chance for a firm assessment process, based on open scientific reasoning. However, this could be overcome when EFSA adopted a procedure wherein the applicant and EFSA can communicate about the claim and the presented data, where scientific arguments can be exchanged and where additional data can be presented. EFSA should in that sense learn from the ways notified bodies judge about medical devices. Such a transparent procedure will prevent the impasse an applicant is faced with and will give EFSA the opportunity to enter in a learning process. As stated above, currently EFSA uses the pharmaceutical paradigm in evaluating the presented evidence. Wincllove does not agree with this on ethical, conceptual and scientific grounds. We would from that perspective highly recommend EFSA, and especially the NDA panel, to recruit more scientists in the field of nutrition and microbiology, since products like probiotics (but also other food supplements and functional foods) have a nutritional approach and should be judged from that perspective and by a team that has knowledge of these products and the way they act.

Both suggestions will benefit the judgement of health claims for nutritional products as well as the quality of EFSA’s opinions.

Wincllove Bio Industries  General comments  Wincllove’s opinion on EFSA’s published guidance (3)
Without going further into detail on all other individual biomarkers, there is one aspect in line with biomarkers we would like to address. One of the main aspects that is lacking in this guidance is the general scientific accepted view that the composition of the intestinal microbiota in general is quite important for the health status of people. Much literature has shown that stability and diversity of the microbiota is beneficial for a healthy life. It is also well described that the relatively stable microbiota is negatively influenced by different factors like antibiotic use, stress, travelling and use of medicines. Restoring these effects is proven to be beneficial. In the guidance, nothing is mentioned concerning this subject. The only adopted biomarker in this field is, according to the guidance, the inhibition of specific pathogens. Adopting this biomarker instead of the support of a healthy, rich and stable microbiota does again confirm the disease-oriented approach EFSA has in executing the health claim regulation. To think further on the aspect of the complete microbiota, preventing people from developing further side effects for example due to disturbances in their microbiota would aim for nutritional products restoring this balance, and thus targeting specific groups of the population (i.e. people taking antibiotics, travelling people, stressed people) that are basically healthy but suffer from side effects of their lifestyle.

In line with that, also people suffering from chronic inflammatory diseases like IBD and IBS and people ‘suffering’ from metabolic syndrome would be considered as relatively healthy people but are just specific target groups. All these people are subgroups of the complete population, and their health will benefit by taking nutritional products.
Outcome of a public consultation on a draft guidance on the scientific requirements for gut and immune function claims

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Outcome of a public consultation on a draft guidance on the scientific requirements for gut and immune function claims

| ORGANISATION                  | CHAPTER TEXT                | COMMENT TEXT                                                                                                                                                                                                 |
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| Winclove Bio Industries       | General comments            | Winclove’s opinion on EFSA’s published guidance (2)                                                                                                                                                        |
|                               |                             | Of course Winclove appreciates the fact that EFSA is finally listening to the concerns from the market, but again a lot of remarks can be made on the guidelines issued. In this letter we will just keep our comments at a more general level, although we also support the more detailed feedback as provided by Dr. Ger Rijkers and the EHPM. |
|                               |                             | The major comment from a scientific point of view is that nutrition (including food supplements, functional foods, etc.) has a complete different working mechanism in the body than pharmaceutical products do. From a pharmaceutical approach, products are developed to target a specific receptor and by that might interfere with a certain mechanism of action. Nutrition is focussed on health and maintenance of the healthy situation by a much more gradual and multifactorial approach. Health claims for nutritional products should therefore not be judged in a medicinal way. To point ‘biomarkers’ for nutritional effects is for that reason quite difficult and maybe impossible (i.e. what would be the biomarker for homeostasis?). EFSA misses this point completely and in our view this is one of the main reasons that its opinions are received by the scientific community with so much comment. The guidance as proposed now is in our opinion therefore too narrow in possibilities. |
|                               |                             | Another major comment on the guidance is that it confuses the applicants and thus still gives no clearness on the evidence that is required to support a health claim. The following quote is an example of the non-information presented in this guidance and clearly illustrates the impasse an applicant is faced with: For disease risk reduction claims studies that show only a reduction in incidence or duration of infection(s) would not constitute evidence for a reduction of the risk factor (e.g. numbers of pathogens). However, clinical outcomes (e.g. number of episodes of infection, severity of symptoms, or duration of infection such as indicated by diarrhoea diagnosed as infection-related using specific criteria), demonstrated in human intervention studies could be supportive of the claimed effect related to pathogens. |
|                               |                             | This quote suggests that a specific product reducing the incidence of infection does not fulfil EFSA’s demand because there is no proof of a reduction of a risk factor while the same product showing reduction in the numbers of episodes of infection could be supportive of the claimed effect related to the product. We do not think there is any expert capable of discriminating between “reducing the incidence of infection” and “reducing the numbers of episodes of infection”. |
|                               |                             | Moreover, in the absence of a clear procedure (where communication is an important part of) the applicant can only guess what EFSA means with this quote and whether the phrase “could be supportive” has any other meaning than its doublespeak character suggests: “will be rejected nevertheless”. |
|                               |                             | More discrepancy in the guidance is in the fact that the guidance states that a health claim only could be approved with health claims. In the guidance the NDA Panel considers that the population group for which health claims are intended is the general (healthy) population. Furthermore it is mentioned that applications that specify target groups other than the general population are the subject of ongoing discussion. By this statement one would exclude thus the subgroups as outlined before (IBS/IBD/metabolic syndrome ‘patients).
when proven effects have been shown on influencing a certain biomarker that is biologically plausible for a certain health effect (clinical results seem to be not even necessary). Nevertheless, when critically reading this guidance, the only ‘biomarkers’ considered to be proven are on bowel function (but even that is only focussing on constipation and what about diarrhoea?) and on inhibition of specific pathogens. Furthermore the guidance stays very reticent and careful in mentioning that certain effects could be beneficial. It seems that EFSA makes hereby use of a catch-22-principle, all the way supporting rejection of the majority if not all claims.

Winckove Bio Industries  General comments
Winckove’s opinion on EFSA’s published guidance (1)
Winckove Bio Industries would hereby like to react on the recently published draft guidance for health claims to gut and immune function, as published in September 2010 in the EFSA Journal.
Principally we support the fact that health- and disease-risk-reduction claims on nutritional products should only be communicated to the consumers when there is evidence for the beneficial effects by those products. In line with that, Winckove Bio Industries (as SME!) has invested a lot in performing research on its bacterial strains and final probiotic formulations and subsequently on writing EFSA dossiers.
During the assessment, EFSA was unclear about the requirements, has changed them during the procedure and was not willing to communicate with us about the evidence a product should have to get its health claim approved. As stressed also in our letter to Mr. Mathioudakis of April this year (which was even accompanied by a support letter of our Ministry of Health, Welfare and Sports) the way the health claim regulation is currently executed results mainly in loss of confidence of the industry and slow their willingness to invest in innovative products with higher health properties.
Besides negatively influencing the industry also other stakeholders and the final consumers, for whom the regulation was initially set up, are harmed by the way the regulation is now executed.
The estimation of today is that over 90% of all health claims will be rejected. Even more alarming is the situation with respect to health claim applications for probiotics and prebiotics, since not a single claim has been approved so far. For the main part health claims on probiotics were purely rejected on the fact that the strains were not characterised sufficiently. Nevertheless, during the whole procedure it is never made clear which were the requirements for ‘sufficiently characterising’ nor was there (until quite a few products were rejected) the possibility to provide EFSA with the additional requested information. To get already ahead of feedback on the EFSA’s draft guidance, not even in that proposed guidance document assistance is given on how to characterize the active ingredients.
After much comments from stakeholders on the way the EFSA judges, EFSA’s rejections based on beforehand unclear requirements and EFSA’s unwillingness to communicate, last month a draft guidance on the scientific requirements for health claims related to gut and immune function was published. The first time a concrete action on many requests from companies is now made, 4 years after launching the claim regulations. From this perspective the
| ORGANISATION          | CHAPTER TEXT     | COMMENT TEXT                                                                                                                                 |
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| Yakult Europe B.V.    | General comments | **This is about the study design of clinical trial. EFSA often gave negative opinions against a number of applications based on incomplete designs/protocols such as low number of subjects and short study periods. However, EFSA did not show any reason of this negative evaluation, and thus we must say it is not faire. EFSA should show the basis of this evaluation clearly. This is also the case in this guidance document. We strongly recommend to describe the actual requirements of an appropriate study design.** |
| Yakult Europe B.V.    | General comments | **1. General considerations**  
(a) Dialogue is essential in case of ‘case by case’ or in case EFSA does not clarify the criteria of assessment. There are instances of the words ‘may’ ‘might’ and ‘can’ in the document, as well as “case by case”, which makes applicants uncertain what are needed for application. We strongly suggest having dialogue with EFSA during the assessment process.  
(b) The guidance should give applicants clear guidance to fulfill EFSA requirements and not just consider examples from dossiers that have already been dealt with by EFSA. We consider that it is essential that a wide range of experts in gut and immune function research are consulted and involved in the amendment of this guidance document after this public consultation and the meeting on 2 December 2010.  
(c) We consider it would be very advisable to collect and combine all learnings from existing guidance in this area (FOSHU, FDA, etc.), and this will enable global harmonization of health claim regulation on food products like pharmaceutical products.  
(d) We believe that claims for foods should be different in several key aspects from those for medicinal products because of a basic difference between medicines and foods. Especially, the benefits of foods in terms of measurable outcome may not always have as great a magnitude as medicinal products, especially when measured in ‘healthy’ people.  
(e) Scientific papers accepted in respected peer review journals should be taken as a clear indication of the quality of the research studies and their findings. Clarification is needed on what value EFSA places on peer-reviewed publication, and why findings from such papers cannot be accepted.** |
| Yakult Europe B.V.    | General comments | **2. Consensus**  
(a) If it is accepted that a state of health of general population is fluctuating, most people who consider themselves healthy experience, at various times in their lives, periods of sub-optimal health due to age, lifestyle, and physical, mental or environmental stresses. Then, is it accepted to use appropriate study population groups with sub-optimal health as representatives of the general population to substantiate health benefits. This enables a clear clinical endpoint to be measured. Examples of groups include the elderly, sports people, smokers, pregnant women. Would populations with common pathologies (diabetes, allergy ...) be also considered part of the general population? Can a population under challenge also be used?** |
(b) For the reasons expressed above, we believe that this guidance should differ from those for medicinal products. In this regard, we need more guidance about what level of evidence is necessary to demonstrate biological plausibility or mechanism of activity and about whether a non-DBPC study can be accepted as convincing evidence of a claim.
(c) Further clarification is needed on what can be considered as beneficial physiological effects relating to gut and immune function, together with studies/outcome measures appropriate for substantiation of gut and immune function claims and disease risk reduction claims.
(d) References for ‘validated’ questionnaire should be provided in the guidance document that can be used to measure health benefits, to avoid any discrepancy in interpretation for the word ‘validation’.

| ORGANISATION | CHAPTER TEXT | COMMENT TEXT |
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| Yakult Europe B.V. | 3.1 Claims on bowel function | As a definition or appearance of constipation, the guidance indicates i) longer transit time, ii) less frequent bowel movements, iii) reduced faecal bulk and iv) harder stools. However, there is no clear indication of the normal range of these bowel functions described. In addition, changes in these parameters do not necessarily mean the beneficial physiological effects judging from the description that ‘Changes in bowel function within the normal range might be considered beneficial physiological effects.’ We definitely need more clarification of the criteria of evaluation by EFSA. For instance, can a group of people with light constipation or with functional constipation be a general population? At least EFSA needs dialogue with applicants if it does not provide the clear guideline. As described in the line 163 of the draft guidance, the sentence in line 167-168 should reads “Appropriate outcome measures of the claimed effect in human studies include transit time, frequency of bowel movement, stool bulk, and stool consistency.” The reference for that is as follow: Lewis SJ, Heaton KW. Scand. J. Gastroenterol. 32, 9: 920-4, 1997. |
| Yakult Europe B.V. | 3.2 Claims on gastrointestinal discomfort | a). Improvement of defecation frequency in constipated subjects. All healthy people experience different periods and severity of constipation through their lives. Such an outcome measure indicates that a food or food ingredient would help maintain a healthy bowel habit. This is the same logic that, in the guidance document, was applied to IBS. b). Concerning the substantiation of claims on gastrointestinal discomfort, what measures other than severity of symptoms (e.g. symptom frequency questionnaires, overall assessment of GI discomfort/comfort, relief of IBS symptoms; quality of life questionnaires) would be considered as appropriate for demonstration of gastrointestinal discomfort benefit claim? |
| ORGANISATION          | CHAPTER TEXT                                      | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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| Yakult Europe B.V.   | 3.3 Claims on oral and gastrointestinal microbiota | a). Reduction of pathogens  
We strongly recommend a thorough consultation with experts of microbiology to re-write this part.  
The guidance does not address the commensal microbiota but pathogens. Many of these pathogens are not normal inhabitants of the gut. Category A “Food born pathogen”(line 211-216) should be clearly distinguished from Category B “Gastrontestinal pathogen (line 217-219), in terms of guideline required.  
In some cases, very low numbers of these pathogens cause disease so their detection in the gut or oral cavity itself is already a disease state. On the other hand, several other pathogens are commensal bacteria. Therefore, the assessment criterion of a decrease of more than 1 log is considered as beneficial can not be applicable to all of these pathogens.  
b). Improvement/maintenance of gut health by maintaining a balanced gut microbiota, particularly levels of bifidobacteria in the young, older people and for people suffering certain minor disorders and by maintaining the gut environment.  
Although there is no ‘optimum’ profile of the intestinal microbiota, several studies show reduced levels of bifidobacteria (and in some case, lactobacilli) are linked to disorders in young children. There is a strong case to argue that maintenance of these bacteria would have health benefits, which are more sustained and long term in a manner appropriate for a functional food.  
Promoting a ‘healthy microbiota’ be considered a health benefit. Similarly, changes in the intestinal microbiota have been linked to many disorders, when comparative analyses have been conducted on healthy and sick people.  
Maintenance of a healthy microbiota can also be considered a health benefit for other population groups, such as the elderly.  
Accumulating evidence shows that the biomarkers such as SCFA, pH in the gut associate with the health status. These biomarkers are obviously the products of gut microbiota, and thus can be linked to the microbiota composition.  
Guidance should be given for the possible health benefits of higher SCFA content and lower pH in the gut.  
c). Improvement/maintenance of gut health by maintaining the intestinal gut barrier/improving gut permeability  
What is the reason for EFSA to consider that ‘intestinal permeability’ in itself not sufficient as a benefit?  
Improvement of mucosal barrier function may be considered as more important for a functional food, in preventing infections than reducing the number of potential pathogens in the gut. If the gut permeability is impaired, one consequence can be diarrhoea. A further consequence, associated with changes in the intestinal microbiota, can be raised levels of circulating endotoxin (from Gram-negative bacteria), which has been linked to the onset of various diseases and inflammation.  
d). Improvement/maintenance of gut health by reducing harmful substances in the gut/ Reduction of microbial metabolites (e.g. in faeces, urine, blood) that are toxigenic or carcinogenic, and therefore could impact on long term health  
Many studies link toxins or carcinogens produced by the commensal gut microbiota to long term illness, such as cancer. There are a range of data showing that certain microbial metabolites in the gut have toxigenic and/or carcinogenic potential (e.g. phenol, p-cresol, deconjugated bile acids, etc.). Excretion of such substances via the gut |
or bladder has been linked to an increased risk of colon and bladder cancer respectively. There are also some data showing that certain gut bacteria can neutralise or absorb such toxins; and also shifts in the proportion of certain bacterial groups affects levels of harmful substances in the gut.

| ORGANISATION          | CHAPTER TEXT                                      | COMMENT TEXT                                                                                                                                                                                                                                                                                                                                 |
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| Yakult Europe B.V.    | 4.1 Claims on the function of the immune system  | It seems that only the reduction of pathogen and stimulation of vaccination against pathogens are recognized evidence to claim a benefit on immune function, and although reduction of allergic manifestation is indicated as beneficial, no clear outcome measurement parameter is indicated. We feel that this is inadequate and insufficient as a guidance. Especially, the description from line 272 to 278 does not indicate any concrete guideline values for applicants to show as benefits, and thus would like to propose the consultation with experts in the field of infection and allergy to clarify and revise the current guidance. We also include a few points as examples for further consideration:

We would like to emphasize that the innate immune response to infection and cancer development should be considered a beneficial immune function if supported by concomitant favorable clinical outcomes or favorable reduced carcinogenic activity in the colonic content. In these cases, would a marker measured in the incubation period of infection and/or during infection and cancer development, such as NK cell activity/cell count, sIgA and gamma-IFN be considered as a relevant function?

Are immunological markers mandatory to substantiate the involvement of the immune system when allergic or infectious manifestations are diagnosed by a trained physician using validated methods within double blind placebo controlled trials? |
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| Yakult Europe B.V. | 4.2 Claims on reduction of inflammation | In line 299 to 300, it is mentioned that “Chronic inflammation is associated with a number of disease, and under certain circumstances reducing levels of markers of inflammation might indicate a beneficial physiological effect.” This does not indicate clear guidance for outcome measures for beneficial immune function for inflammation. We would like to indicate strong requirement for clarification of conditions and markers of inflammation. If it is not available, then EFSA should have more dialogue with applicants to make clear what is the submitted health claim. |
| Yakult Europe B.V. | 4.3 Claims on reducing a risk factor for infections or allergy | Also here, only the reduction of pathogen is recognized evidence to claim a benefit on immune function. We feel that this also needs further consultation with experts of both fields. Whilst the reduction in incidence as an outcome is clearly beneficial for health, it can be difficult to define a function claim to reflect this benefit without being considered as medicinal. What is the reasoning that a risk factor is mandatory even when the clinical outcome as the reduction of the incidence is available? Would it be impossible to consider that such type of results can be extrapolated to a benefit of increasing long term health, and therefore can be extrapolated to substantiate a function claim, with or without a known risk factor? |
| YLFA International | General comments | 1 – YLFA welcome the publication by EFSA’s Panel on dietetic Products, Nutrition and Allergies (NDA panel) of the draft Guidance on the scientific requirements for health claims related to gut and immune function. This communication effort of EFSA is definitively an important step forward. 2 – YLFA request EFSA to provide insight on the approach and reasoning used by the agency not only in the case by case evaluation of applications but in a more global, standard approach which will provide more certainty for the applicants. 3 – Need for scientific dialogue with EFSA is therefore still needed, which can be through allowing applicants to present their dossier and/or strategy for dossier to the NDA panel. 4 – YLFA request further clarification of what “whole body of evidence” will mean. • YLFA need clarification on which type of clinicals will be taken into account and especially with which weight, number of clinicals, value of secondary outcomes when statistically significant, and value of results on the biological plausibility of the effect. • Foods, unlike drugs, are not intended as solutions to specific problems, but as a contribution to health as an overall part of the diet. In that respect, they often address multiple endpoints to fulfil a complex physiological function. Consequently, a claimed effect can be substantiated by complementary data coming from various appropriate outcomes. This multiplicity of relevant endpoints should be taken into account in agreeing studies when the relevant outcome is a secondary criterion, provided the study is adequately powered and the inclusion criteria are appropriate. • The importance of biological plausibility hardly appears in the panel’s opinions on gut health and immunity area whereas they are meaningful parts of the overall consistency of the food effect. We believe that scientific data in both human and non-human supporting the biological plausibility of the effect has to be taken into account in the weighing of the evidence, even if mechanisms of actions are not fully elucidated. • YLFA also need clarification on which population will be considered for clinicals; would populations with common pathologies (diabetes, allergy ...) be considered part of the general population? • YLFA need to know which magnitude of effect will be considered relevant, taking into account that we are dealing with food and general healthy population and |
| ORGANISATION       | CHAPTER TEXT                                                                 | COMMENT TEXT                                                                                                                                                                                                 |
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| YLFA International | 3.2 Claims on gastrointestinal discomfort                                     | therefore cannot expect effect at the level of a drug on diseased people. • YLFA request EFSA to give a list of risk factors and when not available, the proves that will be required to point the predictivity of risk factor. |
| YLFA International | 3.3 Claims on oral and gastrointestinal microbiota                            | Point 3.2. line 169 and next:
Concerning the substantiation of claims on gastrointestinal discomfort, are other measures than severity symptoms (e.g. symptom frequency questionnaires, overall assessment of GI discomfort/comfort, relief of IBS symptoms; quality of life questionnaires) consider as appropriate for gastrointestinal discomfort claim? |
| YLFA International | 4.1 Claims on the function of the immune system                               | Point 3.3 - 183 and next: The guidance does not really address microbiota but pathogens, mainly those which contaminate foods and are not normal gut inhabitants. No reference is made to microbiota composition, metabolites or modification and resistance to infection, and we need some guidance as how such claims, which we believe can be beneficial to human health, can be substantiated. |
|                    |                                                                              | Point 4.1, line 258 and next: Concerning the substantiation of claims on the immune function, a) Do enhanced antibody titres to antigens of a specific pathogen in vaccine substantiate a claim on the function of the immune system related to the defence against natural infection by this pathogen, outside the vaccination context? b) Can the innate immune response to infection be considered a beneficial function if supported by concomitant favourable clinical outcomes? In this case, would a marker measured in the incubation period of infection or during infection, such as NK cell activity/cell count be considered as a relevant function? c) Are immunological markers mandatory to substantiate the involvement of the immune system when allergic or infectious manifestations are diagnosed by a trained physician using validated methods within double blind placebo controlled trials? |
| ORGANISATION          | CHAPTER TEXT                                      | COMMENT TEXT                                                                                                                                 |
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| YLFA International   | 4.3 Claims on reducing a risk factor for infections or allergy | Point 4.3, line 305 and next: The reduction of pathogens in the gastrointestinal tract is recognised as suitable markers to demonstrate a health benefit. A decrease of more than 1 log is proposed as a universal threshold, which is questionable as it depends on the pathogen and characteristics of the infection. |