European Food Safety Authority

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TECHNICAL REPORT

Outcome of a public consultation on the discussion paper for the revision of the guidance on the scientific requirements for health claims related to gut and immune function[1]

European Food Safety Authority[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The European Food Safety Authority (EFSA) carried out a public consultation to receive input from all interested parties on a discussion paper for the revision of the 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). The public consultation for this document was open from 18 June to 10 September 2014. EFSA received comments from 15 interested parties including applicants for health claims, consultants and food industry organisations. EFSA and its NDA Panel wish to thank all stakeholders for their contribution. 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 The NDA Panel prepared a draft guidance document taking into account the questions/comments received. The draft guidance was discussed and endorsed at the NDA Plenary meeting on 10 December 2014, and is now open for public consultation before finalisation.

KEY WORDS

health claims, discussion paper, guidance, gut and immune, microorganisms, consultation

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SUMMARY

The European Food Safety Authority (EFSA) carried out a public consultation on a discussion paper to receive input from all interested parties for the revision of the 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). The document proposed a plan for the revision, outlined the scope and issues to be covered in the revised guidance document, and aimed at collecting comments and suggestions from interested parties before drafting the guidance document. The public consultation for this document was open from 18 June to 10 September 2014. EFSA received comments from 15 interested parties, including applicants for health claims, consultants and food industry organisations. EFSA and its NDA Panel wish to thank all stakeholders for their contribution.

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 a draft guidance document taking into account the questions/comments received. The structure of the guidance has been changed to reflect the comments and the request for clarification received during the public consultation. This draft guidance document was discussed and endorsed at the NDA Plenary meeting on 10 December 2014, and has been released for public consultation before finalisation.

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BACKGROUND AS PROVIDED BY EFSA

Regulation (EC) No 1924/2006[4] harmonises the provisions related to nutrition and health claims and establishes rules governing the Community authorisation of health claims made on foods. According to the Regulation, health claims should be only authorised for use in the Community after a scientific assessment of the highest possible standard to be carried out by EFSA.

Owing to the scientific and technical complexity of health claims, the EFSA Panel on Dietetic products, Nutrition and Allergies (NDA Panel) has placed considerable focus on developing scientific criteria for substantiation of health claims and has published guidance on scientific substantiation of health claims since 2007[5].

To date, over 600 scientific opinions related to health claims have been published and the Panel notes that additional health relationships and outcome measures for specific claimed effects have been considered in the context of specific applications.

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

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

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

Owing to high demand from stakeholders and questions received from applicants requesting clarifications related to gut and immune function claims, it is proposed to start first with updating the existing Guidance document on the scientific requirements for health claims related to gut and immune function[6].

TERMS OF REFERENCE AS PROVIDED BY EFSA

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

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

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

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

[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. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02006R1924-20121129&from=EN

[5] http://www.efsa.europa.eu/en/nda/ndaguidelines.htm

[6] http://www.efsa.europa.eu/en/efsajournal/doc/1984.pdf

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

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 was asked to update the guidance document on the scientific requirements for the substantiation of health claims related to gut and immune function dated 2011. In line with EFSA's policy on openness and transparency, and in order for EFSA to receive comments from the interested parties before updating the guidance document, a discussion paper, which outlined the scope and issues to be covered in the guidance document, was published on the EFSA website for comments (18 June to 10 September 2014)[7]. The NDA Panel prepared a draft guidance document taking into account the relevant questions/comments received. The structure of the guidance document has been changed to reflect the comments and the requests for clarification received during the public consultation. This structure is used in the present technical report to organise and address the comments received, and to explain how these have been considered in the draft guidance document. The draft guidance document was discussed and endorsed at the NDA Plenary meeting in December 2014, and is being released for public consultation before finalisation. EFSA is committed to publishing the comments received during the public consultation on the discussion paper, as well as a report on the outcome of the consultation.

2. Screening and evaluation of the comments received

2.1. Comments received

EFSA received 137 comments from 15 interested parties including applicants for health claims, consultants and food industry associations.

Table 1: List of organisations submitting comments

Organisation	Country
analyse & realize GmbH	DE
Association of the Self-Medication Industry (AESGP)	BE
BENEO-Institute	DE
Biothera	US
Chr Hansen	DK
DANONE	FR
DuPont	DK
Food Supplements Europe	BE
Mondelez International	FR
Morinaga Milk Industry Co., Ltd.	JP
Nestlé S.A.	CH
Sensus	NL
Valio Ltd	FI
Yakult Europe BV	NL
Global Alliance for Probiotics (GAP), the Yogurt Life and Fermented Milk Association (YLFA) and the International Probiotics Association (IPA)	BE

BE, Belgium; CH, Switzerland; DE, Germany; DK, Denmark; FI, Finland; FR, France; JP, Japan; NL, the Netherlands; US, the United States of America.

A summary of the comments is given below, and all written comments received are listed in Appendix B. Several parties submitted identical comments.

[7] http://www.efsa.europa.eu/en/consultationsclosed/call/140618.htm

2.2. General comments

2.2.1. Pre-submission scientific advice

Comment received:

1. Several comments requested the possibility of consulting EFSA on study protocols in order to check whether the outcome measures and measurement tools planned may be appropriate for the scientific substantiation of health claims. There were also requests to set an administrative framework allowing applicants to get advice from the NDA Panel whenever necessary (e.g. in the context of the work of the Applications Desk) through an interactive process in order to: a) avoid repeating similar expensive studies and b) being able to adapt to different requirements in different countries.

Panel consideration of comment received

Ad1. EFSA would like to highlight that pre-submission meetings with individual applicants are not among the services that EFSA offers. EFSA aims, however, to develop new means and procedures to improve the interaction between EFSA and applicants. This aspect has not been addressed in the present guidance document specifically.

2.2.2. Handling of confidential and proprietary data

Comment received:

2. Information on EFSA's handling of confidential data was requested, i.e. on the conditions under which EFSA can make public information which has been classified as confidential by applicants, such as the results of studies which are not yet published; on who has access to the raw data of a clinical study submitted to EFSA, and in which context. It was suggested that EFSA asks the applicant the right to quote confidential data before the opinion is published, as this could lead to competitive disadvantage for the applicant.

Panel consideration of comment received:

Ad2. Many studies submitted for scientific substantiation of health claims have been claimed as confidential by applicants. In this respect, EFSA would like to clarify that, in order to comply with its requirements for transparency as outlined in Article 38 of Regulation (EC) No 178/2002[8] and Article 16 of Regulation (EC) No 1924/2006[9], key data from key studies which are considered essential for the scientific assessment of a health claim may need to be disclosed in the final scientific opinion published by EFSA.

In practice, when applicants submit studies for the scientific substantiation of a health claim that are claimed as confidential, EFSA requests applicants to identify and justify which elements of the studies are claimed as confidential during the completeness check. If the request for confidential treatment for those elements identified by the applicant is accompanied by verifiable justification and this is accepted by EFSA, those elements will be kept confidential. Once a scientific opinion for a health claim is adopted by the NDA Panel, and before its publication on the EFSA website, the scientific opinion is sent to the applicant in order to check whether the scientific opinion discloses any data that EFSA had accepted to keep confidential. EFSA wishes to clarify that confidentiality can only be given to specific parts of a study if duly justified, and not to an entire study. This requirement is to allow EFSA to comply with its requirements for

[8] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety, as last amended.

[9] Corrigendum to 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), as last amended.

transparency as outlined in Articles 38 of Regulation (EC) No 178/2002[10]. However, in principle and without prejudice to Regulation (EC) No 1049/2001 on public access to documents, if a study has not yet been published and its disclosure would undermine the commercial interests and rights of the applicant, EFSA will not make such study available to third parties.

It should be noted that health claim applications submitted via a National Competent Authority will be processed according to Article 15(2) of Regulation (EC) No 1924/2006. The National Competent Authority shall make the application and any supplementary information supplied by the applicant available to EFSA, and EFSA shall make the application and any supplementary information supplied by the applicant available to other Member States and the Commission.

Comment received:

3. Clarifications were asked on the requirements for data exclusivity (e.g. whether data exclusivity can be granted to an applicant-specific strain). In this context, it was suggested that the publication of scientific studies, which is always desirable, should not hamper the possibility of considering them as proprietary.

Panel consideration of comment received:

Ad3. With respect to the handling, use and protection of proprietary data (e.g. requirements needed for data exclusivity), it should be noted that where evidence for substantiation includes a request for the protection of proprietary data, the NDA Panel considers only whether the claim could have been substantiated with or without the data claimed as proprietary by the applicant. As outlined in the general guidance for stakeholders[11], the decision on granting the protection of proprietary data falls within the responsibility of the European Commission when authorising the claims.

Comment received:

4. Being a general topic, it was proposed to deal with issues on confidential and proprietary data under the general guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims.

Panel consideration of comment received:

Ad4. The Panel acknowledges that the handling of confidential data is common to all claims and considers that it is appropriate to clarify this aspect when updating the general guidance for stakeholders in due course. Confidentiality aspects have not been addressed in the draft guidance.

2.2.3. Reporting of human studies

Comment received:

5. It was questioned how a study should be presented within a dossier (list of items to be mentioned), and whether EFSA will refer to existing guidance documents on reporting of human studies and/or EFSA guidance on statistical reporting.

Panel consideration of comment received:

Ad5. Lack of transparent and sufficiently detailed reporting of human studies is a barrier to the scientific evaluation of studies for the substantiation of health claims. Transparent reporting of human studies in a harmonised and standardised way would benefit both EFSA and stakeholders by providing better quality reports of data from which conclusions can be drawn and decisions

[10] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety, as last amended.
[11] http://www.efsa.europa.eu/en/efsajournal/doc/2135.pdf

can be made, and thereby would decrease delays in the review process and improve transparency of the final outcome.

In this context, it is recommended that studies are performed according to scientific standards that are generally accepted by experts in the relevant field, and that they are appropriately reported following, where applicable, EFSA guidelines on statistical reporting[12], or other consensus guidelines published by scientific societies to improve the reporting of human studies[13], e.g. the CONSORT statement[14] and extensions for the reporting of randomised trials; the STROBE statement[15] for the reporting of observational studies; the PRISMA[16] guidelines for reporting on systematic reviews of RCTs; and the MOOSE guidelines (Stroup et al., 2000) for reporting on systematic reviews of cohort data.

Comment received:

6. It was proposed that general recommendations on the reporting of human studies should be covered by the EFSA guidance on statistical reporting. It was suggested to focus only on specific requirements related to health claims on gut health and immune function in this guidance document.

Panel consideration of comment received:

Ad6. The Panel acknowledges that improving the reporting of human studies is applicable to all claims and considers it more appropriate to address this aspect when updating the general guidance for stakeholders in due course. This aspect has not been addressed in the present draft guidance specifically.

2.2.4. Scientific requirements for the scientific substantiation of health claims

Comment received:

7. There were comments emphasizing the discrepancies between Europe and other areas of the world with regard to the evaluation criteria for health claims made on foods.

Panel consideration of comment received:

Ad7. The principles and the criteria for scientific substantiation of health claims made on food in the EU, including the scope and the role of EFSA, are laid down in Regulation (EC) No 1924/2006[17]. According to Regulation No 1924/2006, health claims should be scientifically substantiated by generally accepted scientific evidence (Article 6.1), by taking into account the totality of the available scientific data, and by weighing the evidence (Recital 17). Health claims should only be authorised for use in the Community after a scientific assessment of the highest possible standard (Recital 23).

EFSA would like to reiterate that comments related to different legislative frameworks (EU compared to other regions) are considered to be outside the scope of EFSA, but rather under the remit of risk management, and therefore should be addressed to the European Commission and Member States. Such issues were not taken into account in updating the guidance document.

Comment received:

8. Comments were received suggesting that human studies conducted to assess the effect of food/constituents on health outcomes should not be evaluated under the same standards as human

[12] EFSA Guidance on Statistical Reporting: http://www.efsa.europa.eu/en/efsajournal/doc/3908.pdf
[13] Equator network: http://www.equator-network.org/
[14] http://www.consort-statement.org/
[15] http://www.strobe-statement.org/
[16] http://www.prisma-statement.org/
[17] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02006R1924-20121129&from=EN

studies investigating the effects of medicines on health. There was a request to define the appropriate methodology for the scientific evaluation of human studies in the food area, which would be appropriate for the substantiation of health claims made on foods.

Panel consideration of comment received:

Ad8. The approach and criteria used by the NDA Panel for the scientific evaluation of health claims made on food pursuant to Regulation (EC) No 1924/2006 have been addressed in several guidance documents[18]. Such issues were not taken into account in updating the guidance document.

Comment received:

9. Clarification was requested regarding the scope of claims related to the reduction of the incidence of diseases, e.g. on whether these are medicinal claims and thus cannot be used on food products.

Panel consideration of comment received:

Ad9. It should be noted that the identification of a risk factor is a requirement of Regulation (EC) No 1924/2006 for disease risk reduction claims. Whereas health claims referring to the reduction of the risk of a disease are out of the scope of Regulation (EC) No 1924/2006, data on the reduction of the incidence of a disease can be used for the scientific substantiation of disease risk reduction claims if accompanied by data on a beneficial modification of at least one of the risk factors for the disease. Data on the reduction of the incidence of a disease can also be used for the scientific substantiation of function claims if the disease denotes a clear dysfunction of a particular organ or tissue (e.g. data on the incidence of GI infections can be used for the scientific substantiation of a function claim on defence against pathogens in the GI tract). This aspect has been addressed in Section 3.2.2 of the draft guidance.

Comment received:

10. There were requests to clarify how the NDA Panel considers the following type of studies within the context of the scientific substantiation of health claims, as well as the value that the NDA Panel gives to them while weighing the evidence: a) epidemiological studies/observational studies; b) non-clinical studies in support of overall health benefits; c) open-label studies for claims on food/constituents other than vitamins and minerals. Some comments suggested introducing the use of grading systems (e.g. Jadad scoring system) to evaluate the quality of individual studies.

Panel consideration of comment received:

Ad10. As specified in the general guidance for stakeholders[19], the NDA Panel considers (for all health claims) whether the beneficial effect of the food on the function is substantiated by generally accepted scientific evidence, by taking into account the totality of the available scientific data, and by weighing the evidence. In this context, the NDA Panel evaluates the claim according to consistent criteria on the nature and quality of the totality of the evidence provided.

In assessing each specific food/health relationship which forms the basis of a claim, the NDA Panel makes a scientific judgement on the extent to which a cause and effect is established between the consumption of the food/constituent and the claimed effect (i.e. for the target group under the proposed conditions of use) by considering the strength, consistency, specificity, dose-response, and biological plausibility of the relationship. The design and quality of studies submitted are judged in the context of whether scientific conclusions can be drawn for the substantiation of a specific claim. All the evidence from the pertinent studies from which scientific conclusions can be drawn for the substantiation of the claim (i.e. studies using the

[18] Guidance for applicants on health claims: http://www.efsa.europa.eu/en/nda/ndaguidelines.htm
[19] General guidance for stakeholders: http://www.efsa.europa.eu/en/efsajournal/doc/2170.pdf

food/constituent and with appropriate outcome variables in a study group that is representative of the target group for the claim) is weighed with respect to its overall strength, consistency and biological plausibility, taking into account the quality of individual studies and with particular regard to the population group for which the claim is intended, and to the conditions of use proposed for the claimed effect. A grade is not assigned to the evidence. While studies in animals or *in vitro* may provide supportive evidence (e.g. in support of a mechanism by which a food could exert the claimed effect), human data are central for the substantiation of a claim. This procedure is in agreement with the hierarchy of evidence described in EFSA guidance[20], where human intervention (confirmatory) studies are at the top of the hierarchy that informs decisions on efficacy.

Comment received:

11. There were questions related to the appraisal by the NDA Panel of human studies published years ago ("old published research") which may not meet the quality standards agreed upon by the scientific community thereafter.

Panel consideration of comment received:

Ad11. The NDA Panel would like to reiterate that all the studies submitted by the applicants for the scientific substantiation of health claims are considered in the context of the totality of the evidence provided[21]. EFSA acknowledges, however, that inadequate reporting of human studies may limit the conclusions which can be drawn from such studies for the scientific substantiation of health claims, and that inadequate reporting cannot be solved by the applicants or EFSA when it comes to "old published research". In this context, the NDA Panel considers whether the minimum amount of information which would allow a scientific interpretation of the study has been reported, although details which are considered relevant for reporting may vary depending on the specific nature of the study.

Comment received:

12. It was proposed that meta-analyses should be accepted in their totality and that they should not be dissected down study per study, since the appropriate weighing of supporting studies based on their significance is part of the meta-analysis process.

Panel consideration of comment received:

Ad12. The NDA Panel has used the information derived from meta-analyses to summarise the overall evidence provided by individual human intervention studies and to establish conditions of use (e.g. to define the effective dose) when a cause and effect relationship between the consumption of the food/constituent and the claimed effect has been established[22]. However, the NDA Panel does not solely rely on the results of meta-analyses as key evidence to make a scientific judgement on whether a cause and effect relationship between the consumption of the food/constituent and the claimed effect has been established.

With respect to the use of meta-analyses, in the context of evaluation of health claims made on foods, the EFSA approach is in line with those of other evaluation bodies. For example, the US Food and Drug Administration (FDA) evaluates all pertinent studies individually to decide whether conclusions can be drawn from each single study. Most meta-analyses are used to identify reports of additional studies, and only meta-analyses that review all the publicly available studies on the substance/health relationship are considered as part of the health claim review

[20] Guidance for the preparation and presentation of health claim applications: http://www.efsa.europa.eu/en/efsajournal/doc/2170.pdf
[21] http://www.efsa.europa.eu/en/supporting/doc/569e.pdf
[22] http://www.efsa.europa.eu/en/supporting/doc/569e.pdf

process, as long as the reviewed studies are consistent with the critical elements, quality and other factors set in the FDA guidance and the statistical analyses are adequately conducted[23].

As these comments apply to all claims, they will be considered when updating the general guidance for stakeholders in due course but have not been addressed in the present draft guidance specifically.

Comment received:

13. Clarifications were asked about the reproducibility and consistency of the effect of the food/constituent for which a health claim is proposed (e.g. what can be considered as 'consistency' and 'reproducibility', whether two studies showing the same effect would be considered sufficient).

Panel consideration of comment received:

Ad13. The NDA Panel would like to clarify that reproducibility of the effect means whether the results obtained in one study have been replicated in another (independent) study under similar conditions. When assessing the consistency of the effect, the NDA Panel considers whether the results obtained in different studies (under similar and/or different conditions) are/are not contradictory, and to what extent.

There is no pre-established formula as to how many studies are sufficient to substantiate a claim. Scientific requirements (i.e. to establish a cause and effect relationship between the consumption of the food/constituent and the claimed effect) are considered on a case-by-case basis taking into account the strength, consistency, specificity, dose-response, and biological plausibility of the relationship between the food/constituent and the claimed effect in the context of the totality of the evidence provided. Examples can be found in published opinions on previous applications for health claims[24].

As these comments apply to all claims, they will be considered when updating the general guidance for stakeholders in due course but have not been addressed in the present draft guidance specifically.

Comment received:

14. It was asked, in particular with reference to claims related to the immune system, whether the beneficial effect could be demonstrated by showing a consistent effect on a clinical outcome in repeated trials, as the mechanism which triggers the beneficial effect it is not always known, and validated biomarkers do not exist for every clinical outcome.

Panel consideration of comment received:

Ad14. The Panel acknowledges that, even if evidence on a plausible mechanism of action is an important consideration when concluding on whether a causal relationship between the consumption of the food/constituent and the claimed effect is established, such evidence is not an absolute requirement for the scientific substantiation of health claims made on foods.

Comment received:

15. There were several comments related to the extension of the conditions of use for authorised health claims. Comments mostly related to: a) whether authorised health claims for certain food/constituents could be extended to other food/constituents (or to other molecular forms of the

[23] U.S. Food and Drug Administration (FDA). Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims-Final. http://www.fda.gov/food/guidanceregulation/ucm073332.htm

[24] Nutrition publications: http://www.efsa.europa.eu/en/nda/ndascdocs.htm

same food/constituent) which are "chemically equivalent", "bioequivalent", or "biosimilar"; b) whether authorised health claims for certain food matrices could be extended to other food matrices without the need for replicating efficacy studies; c) the administrative and scientific requirements to obtain an extension of the conditions of use for authorised health claims.

Panel consideration of comment received:

Ad15. According to Article 17(5) of Regulation (EC) No 1924/2006[25], any food business operator can use authorised health claims if the authorised conditions of use (CoU) and any applicable restrictions of use are respected, as specified by the European Commission in the EU Register of Claims[26].

For the extension of the CoU of an authorised claim (e.g. extension of the CoU of a claim related to live yoghurt cultures and improved lactose digestion to food matrices other than yoghurt), applications can be submitted pursuant to Article 19 of Regulation (EC) No 1924/2006. In order to evaluate from a scientific point of view whether the CoU for an already authorised health claim could be modified (e.g. extended to food matrices other than those authorised, to other forms of the food/constituent, to different doses, etc.), the NDA Panel needs to be assured that the claimed effect assessed in the original opinion can also be achieved by the consumption of the food/constituent under the "new" conditions proposed by the applicant. The nature and amount of information needed for that purpose may depend on the food/constituent, the matrix, the claimed effect, and the proposed mechanisms by which the claimed effect may be achieved (short-and long-term efficacy). Each application including the proposed conditions of use will be evaluated by the Panel on a case-by-case basis. Examples of Article 19 applications can be found in EFSA-published opinions[27, 28, 29].

The NDA Panel notes that these comments apply to all claims, and considers it more appropriate to clarify this aspect further when updating the general guidance for stakeholders in due course. This aspect has not been addressed in the draft guidance specifically.

2.3. Specific comments

The main scientific issues raised in the comments received are summarised below, together with the way in which the Panel addressed these comments. EFSA has reviewed all comments carefully and has updated the guidance on the scientific requirements for health claims related to the gastrointestinal tract, the immune system, and defence against pathogenic microorganisms accordingly.

The structure of the draft guidance released for public consultation has changed considerably after taking into consideration the comments received. The draft guidance document aims to further clarify the approach and the criteria used by the NDA Panel for the substantiation of health claims related to the gastrointestinal tract, the immune system, and defence against pathogenic microorganisms, on the basis of the experience gained so far by the NDA Panel with the evaluation of these claims.

2.3.1. Objectives and scope

Comment received:

16. It was proposed to widen the scope of the guidance document, i.e. to extend the guidance document to "new" claimed effects which have not been proposed by applicants in the context of a particular application and which have not been evaluated by the NDA, for companies interested in advancing research and addressing new science. The request was to include an extensive list of

[25] Corrigendum to 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), as last amended.
[26] http://ec.europa.eu/nuhclaims/
[27] http://www.efsa.europa.eu/en/efsajournal/doc/1689.pdf
[28] http://www.efsa.europa.eu/en/efsajournal/doc/3654.pdf
[29] http://www.efsa.europa.eu/en/efsajournal/doc/3577.pdf

"new" claimed effects that are considered beneficial physiological effects, together with the appropriate outcome variables to assess such claimed effects in human studies. In this context: a) it was suggested that "intestinal oxidative stress" has a role in the onset of intestinal diseases/disorders, and that oxidative stress might be eligible as a risk factor for inflammatory bowel disease and/or may be a beneficial physiological effect *per se* (Bhattacharyya et al., 2014; Winter and Baumler, 2014); b) it was noted that claims on the "normal development of gut function", "digestion", "intestinal barrier function", and claims referring to the "function of specific organs, e.g. liver, gut or secretory functions", have not been addressed; c) it was asked to consider claims on e.g. "maintenance of the gut environment by the reduction of the harmful substances", "maintenance of the diversity of the microbiota/reduction of a low diversity of microbiota", "decrease/suppress the harmful bacteria in the gut such as *C. difficile*", or "to enhance the activity of immune factors xxx and xxx, which are important for the activity of xxx part of the human immune system".

Panel consideration of comment received:

Ad16. As stated in Section 2 (Objectives and scope) of the draft guidance, *"The guidance presents examples drawn from past and on-going evaluations to illustrate the approach of the NDA Panel in the evaluation of health relationships and outcome variables which may be acceptable in these areas, as well as the conditions under which they may be acceptable. A better understanding of such an approach could help applicants in preparing applications on health relationships and related outcome variables which have not been evaluated by the Panel so far. The guidance does not intend, however, to provide an exhaustive list of beneficial physiological effects and studies/outcome variables which could be acceptable, or address health relationships and related outcome measures which have not yet been considered by the Panel in the context of a particular application. The reason is that defining the conditions under which health relationships and outcome variables for claimed effects may be acceptable is generally possible only in the context of specific applications, which are often unique and technically complex (e.g. health relationships and outcome variables which may be acceptable in the context of a particular application may not be so in the context of another application with, for example, a different target population)".*

Comment received:

17. It was noted that claims related to the oral cavity had not been addressed.

Panel consideration of comment received:

Ad17. Claims related to the oral cavity (e.g. dental health) have been addressed in the Guidance on the scientific requirements for health claims related to bone, joints, skin and oral health[30].

2.3.2. Characterisation of the food/constituent

Comment received:

18. The need for the characterisation of microorganisms at strain level and the need to deposit strains in internationally recognised culture collections were recognised. However, there was a request to expand the list of methods used for the characterisation of the strains to other widely accepted methods in the field; such methods include amplified fragment length polymorphism (AFLP) and optical mapping. It was found that the ideal characterisation of microorganisms should include a combination of genetic and phenotypic assays, which, collectively, would allow a better understanding of each microorganism at the strain level.

Panel consideration of comment received:

[30] Guidance on the scientific requirements for health claims related to bone, joints, skin and oral health. http://www.efsa.europa.eu/en/efsajournal/doc/2702.pdf

Ad18. Section 3.1.1 (characterisation of microorganisms at strain level) of the draft guidance outlines that the health effects of microorganisms (e.g. bacteria and yeast) are species and strain specific, unless the contrary is demonstrated, and thus the correct identification of the bacterium's and yeast's species and strain for which the claim is proposed is of critical importance. In addition, it has been strongly recommended that strains be deposited in an internationally recognised culture collection (with access number) for control purposes, and the list of methods accepted for the characterisation of bacterial strains has been updated to include other internationally-recognised molecular methods for genetic typing (e.g. AFLP and optical mapping).

Comment received:

19. There were questions on whether the DNA sequence was considered sufficient for the characterisation of strains, or whether other measures *in vivo* (e.g. survival through the gastrointestinal tract) were required. In this context, it was suggested that documentation on the genome sequence should be included whenever possible for the characterisation of a strain, and that "positive attributes" specific to the particular strain could also be included (e.g. genetic regions contributing to a specific health benefit, or even an aspect of survival in the human host).

Panel consideration of comment received:

Ad19. Measures other than DNA sequences of taxonomic markers, such as presence of the microorganism in stools, *in vitro* data on survival of the strain through the gastrointestinal tract or data on genetic regions contributing to a specific function or health benefit, are not strictly required for the taxonomic characterisation of the microorganisms at species and strain level (i.e. to confirm the identity of the food/constituent that is the subject of the health claim, and to establish that the studies provided for substantiation of the health claim were performed with the food/constituent for which the health claim is made). However, such data could be used as evidence for a plausible mechanism by which the consumption of a particular strain could exert the claimed effect, or for the characterisation of microorganisms in relation to the claimed effect whenever a mechanism of action is known (see Section 3.1.2. of the draft guidance). Whole-genome sequencing data could also be useful for providing a more specific genetic characterisation of the microorganism at the strain level.

Comment received:

20. Clarification was asked about the acceptance of claims on general health effects for particular genus, or species (i.e. not strain specific).

Panel consideration of comment received:

Ad20. As outlined in Section 3.1.1 of the draft guidance, "*the observed effects (of microorganisms) in the host are species and strain specific, unless the contrary is demonstrated*". However, there may be exceptions to this rule. As outlined in Section 3.1.2 of the draft guidance (characterisation of microorganisms and other food constituents in relation to the claimed effect) "*in specific circumstances […] the food/constituent(s) could be characterised on the basis of a property which could explain their contribution to the claimed effect (i.e. when the mechanism by which the claimed effect is achieved is known). For example, yoghurt starter cultures contribute to improved lactose digestion*[31] *by producing β-galactosidase. In this case, characterisation of the starter cultures of yoghurt at species level is considered sufficient in relation to the claimed effect because all the strains within the species share the property of producing β-galactosidase, which is the mechanism by which they contribute to improved lactose digestion*".

Comment received:

[31] http://www.efsa.europa.eu/en/search/doc/1763.pdf

21. EFSA was asked for guidance on 'product-based claims', i.e. when the effective component of a mixture cannot be specified. In this context, it was requested to state that, if clinical studies demonstrate the beneficial effect of a food containing a mix of ingredients, the Panel will not "re-qualify" the claim for the active ingredient.

Panel consideration of comment received:

Ad21. As clarified in Section 3.1 of the draft guidance, "*the NDA Panel considers whether the information provided includes those characteristics [of the food/constituent] considered pertinent to the claimed effect, i.e. those characteristics which may influence the specific physiological effect that is the basis of the claim[…]. If the claim is for a specific formulation or a fixed combination of constituents, then studies are needed on this specific formulation or combination. If individual constituent(s) in the specific formulation have an established role on the claimed effect, the NDA Panel also considers whether: i) the effect could be explained by the individual constituent(s), regardless of the source; ii) other constituent(s) in the specific formulation are required for/contribute to the claimed effect*."

2.3.3. Characterisation of the target population for a claim

Comment received:

22. It was asked to define which subjects are considered as part of the "general (healthy) population" and to provide some examples. For example, it was proposed that children should be included in the "general (healthy) population".

Panel consideration of comment received:

Ad22. As explained in Section 3.2.1 (characterisation of the target population for a claim) of the draft guidance "*the NDA Panel considers that the target population for the claim is the **general (healthy) population or specific subgroups thereof**, e.g. men, women, elderly subjects, physically active subjects and pregnant women are part of the general population and as such can be the target population for a claim and the study population. With respect to **children**, the Commission guidance on the implementation of Regulation (EC) 1924/2006*[32] *clarifies the term "children" and the conditions and requirements for health claims targeting children*". The Panel wishes to clarify that the general (healthy) population also includes children.

Comment received:

23. Several comments queried the outcome of the discussions with the European Commission and Member States with regard to the admissibility of target groups for the claim other than the general (healthy) population.

Panel consideration of comment received:

Ad23. Section 3.2.1 (characterisation of the target population for a claim) of the draft guidance informs about the outcome of the discussions with the European Commission with regard to the admissibility of target groups other than the general (healthy) population, which was expressed in the Commission's summary report of the Standing Committee meeting dated 13 June 2014[33]: "*the acceptability of applications for authorisation of claims which target groups under medical treatment and which relate to side effects of the treatment are to be assessed on a case-by-case basis by the Member States*". In this respect, applicants are invited to check the admissibility of the target population for the claim with the Member State to which they intend to submit their application at the earliest possible stage of their consideration regarding the submission of an application for authorisation of a health claim.

[32] http://ec.europa.eu/food/food/labellingnutrition/claims/guidance_claim_14-12-07.pdf
[33] http://ec.europa.eu/food/committees/regulatory/scfcah/general_food/docs/sum_20140613_en.pdf

Comment received:

24. It was questioned whether the reduction of side effects of medications (e.g. claims regarding risks associated with antibiotic use) could be considered as a beneficial effect of a food/constituent, whether the target population for the claim should be the general population or should be limited to the study population (subjects undergoing antibiotic treatment or other widely used drugs, e.g. PPI, aspirin), and what would be needed for the extrapolation of the claim to the general population.

Panel consideration of comment received:

Ad24. For claims referring to the reduction of side effects of medications, applicants are invited to check the admissibility of the target population for the claim with the Member State to which they intend to submit their application at an early stage (see Ad23).

Comment received

25. There were requests to clarify the scientific requirements for the substantiation of health claims related to the "maintenance or restoration of an individual's microbiota under conditions like antibiotic treatment"[34], as well as for claims related to the "maintenance of normal defecation during antibiotic treatment" (decreasing the risk of functional diarrhoea)[35].

Panel consideration of comment received:

Ad25. For claims on the "maintenance or restoration of an individual's microbiota under conditions like antibiotic treatment" and claims on the "maintenance of normal defecation during antibiotic treatment" which target population groups under medical treatment and relate to the side effects of the treatment, please see Ad22 and Ad23.

2.3.4. Characterisation of the claimed effect

2.3.4.1. Characterisation of the claimed effect for function claims

Comments received:

26. Many comments referred to the characterisation of the claimed effect for function claims, either in relation to the definition of the claimed effect to allow a scientific evaluation, to the outcome measures which could be acceptable for specific claims and/or which could be considered as beneficial *per se*, and to the context in which certain outcome measures could be used on their own or as supportive evidence for the substantiation of health claims made on food. The specific comments received are summarised below:

    a) Clarification was requested about the definition of "physiological effect in the context of food".

    b) It was noted that the language used by EFSA for function claims focuses only on the negative side of the benefit (e.g. defence against pathogens), which limits the ability to convey positively potential health benefits (e.g. *"helping you stay healthy").* EFSA was asked to consider the language, which would allow companies to convey immune function benefits based on supporting or maintaining good health.

    c) With respect to claims referring to the immune system, clarifications were requested on whether both symptoms and immune markers or only immune markers could be appropriate outcome measures for these claims; on which immune markers could be accepted for the

[34] Reference was made to: http://www.efsa.europa.eu/en/search/doc/2029.pdf
[35] Reference was made to: http://www.efsa.europa.eu/en/efsajournal/pub/3256.htm

scientific substantiation of claims on the maintenance of a normal immune function without measuring clinical outcomes (Albers et al., 2013); on why immune markers were not acceptable as the only outcome measures for the scientific substantiation of claims on immune function; and on the requirements for the substantiation of claims on "normal function of the immune system" or "maintains a healthy adaptive immune response". It was also asked under what circumstances the restoration of a mildly challenged immune system could be considered *per se* beneficial, and whether these circumstances could include elderly and stressed subjects (e.g. athletes, students during exam period).

d) Several stakeholders queried about the possibility of claiming "beneficial" changes in one or more outcome variables which could be measured *in vivo* in humans (e.g. decrease in stool pH, changes in faecal organic acids, changes in short-chain fatty acid production, intestinal permeability, integrity of intestinal barrier, etc.). In this context, there were requests to develop criteria in order to identify outcome variables which may be sufficient to assume a beneficial effect on the gut (Roberfroid et al., 2010), to allow for claims on "biomarkers" (i.e. which are not a beneficial physiological effect *per se*), and to recognise "physiological intermediaries" (e.g. SCFA production, barrier integrity) as beneficial *per se* as long as they are widely accepted by the scientific community as a risk factors for disease or as beneficial for some specific physiological functions of the body. There were also requests to allow the use of "certain mechanisms of action" (not beneficial *per se*) to substantiate Art 14 children's claims e.g. to allow claims on changes in the characteristics of formula-fed infants which would bring them closer/more similar to the characteristics of human milk-fed infants. It was also suggested that the maintenance of intestinal barrier integrity is a key function in maintaining gut-immune homeostasis, and that strengthening the epithelial barrier function could be considered as a beneficial physiological effect[36].

e) Disagreements were expressed with the NDA Panel's consideration that increasing the amount of bifidobacteria or lactobacilli in the gut was not considered a beneficial physiological effect *per se*. It was requested to update the guidance by listing the "beneficial" bacteria based on scientific expertise and consensus, to give a definition of what constitutes a beneficial microbiota pointing to recent advances in the field of gut microbiota (Kamada et al., 2013; Miquel et al., 2013; Cao et al., 2014), and to clarify whether an increase in the numbers of bifidobacteria or lactobacilli could be considered as a beneficial physiological effect *per se* in subgroups of the general population (e.g. infants or the elderly). In this context, it was requested to address claims such as "maintenance or support of the gastro-intestinal microflora", "maintenance of a diversity of microbiota/reduction of low diversity of microbiota", and "decrease/suppress the harmful bacteria in the gut such as *C. difficile*". It was also requested to consider whether "the bacterial colonisation of the gut (proven via stool analysis)" and "the inhibition of pathogens" could be considered as beneficial effects, and what would be the appropriate outcomes measures for these claims.

f) It was requested to provide a list of relevant biomarkers of inflammation/potential markers of chronic inflammation, to clarify whether reduction of inflammatory markers is considered beneficial, and in what context (e.g. whether a clinical study in diseased subjects with e.g. arthritis or inflammatory bowel disease could be used for substantiation). It was also requested to indicate acceptable models for injury and inflammatory response, to recognise that a decrease in "low-grade inflammation" "may be beneficial for health" (Calder et al., 2009), and to accept that older adults or obese people with low-grade inflammation are considered as appropriate study groups for inflammation-related outcomes (Schiffrin et al., 2010; Lim et al., 2013; Phillips and Perry, 2013). It was questioned whether a body of evidence built on several markers to substantiate a claim on inflammation in the context of chronic diseases could be acceptable, as no marker alone can be considered as a risk factor

[36] Reference was made to: http://www.efsa.europa.eu/en/scdocs/doc/1235.pdf, where the Panel considered that maintaining integrity of the intestinal lining and normal permeability was beneficial to human health.

for metabolic diseases (Calder et al., 2009; Albers et al., 2013; Calder et al., 2013). It was also stated that a decrease in the incidence not only of diseases, but also of associated co-morbidities (e.g. insulin resistance) could be considered as valid and have sufficient outcome variables to show a reduction of inflammation.

Panel consideration of comments received:

Ad26. Section 3.2.2 (characterisation of the claimed effect) of the draft guidance clarifies the meaning of "beneficial physiological effect" in the context of health claims made on foods as follows:

"According to Regulation (EC) No 1924/2006, the use of health claims shall only be permitted if the food/constituent, for which the claim is made, has been shown to have a beneficial physiological effect (i.e. a benefit for a specific function of the body)".

Section 3.2.2.1 of the draft guidance clarifies the requirements for the characterisation of the claimed effect for function claims. Claimed effects should be defined (Section 3.2.2.1.1.), beneficial for the target population (Section 3.2.2.1.2), and refer to a specific function of the body and can be measured *in vivo* in humans (Section 3.2.2.1.3) by generally accepted methods, except for health claims on essential nutrients (as explained in Section 3.4 of this draft guidance). The NDA Panel wishes to reiterate that all three of these requirements need to be met.

In Section 3.2.2.1.1 (the claimed effect is defined), the Panel explains that "*in assessing each specific food/health relationship, which forms the basis of a health claim, the Panel considers whether the claimed effect refers to a specific function of the body (i.e. it is not general and non-specific) as required by Regulation (EC) No 1924/2006. Examples of claims which were not considered by the NDA Panel as sufficiently defined for a scientific evaluation include "gut health", "natural defences", "strengthen the immune system", "maintenance of a normal immune system", "normal development of gut function", "normal digestion"* and other examples are claims such as *"helping you stay healthy",* "*maintenance or support of the gastro-intestinal microflora*", "*maintenance of a diversity of microbiota/reduction of low diversity of microbiota*", *"maintains a normal function of the immune system"* or *"maintains a healthy adaptive immune response".* As outlined in the general guidance for stakeholders, for claims for which a cause and effect relationship has been established, the NDA Panel considers whether the proposed wording reflects the scientific evidence and complies with the criteria laid down in the Regulation (e.g. it should not refer only to general, non-specific health benefits of the food/constituent); if not, the NDA Panel may propose an appropriate wording. However, it should be noted that Regulation (EC) No 1924/2006 allows the use of general and non-specific health claims if accompanied by a specific claim, and that, during the authorisation process (following publication of the EFSA opinion), applicants can negotiate with the European Commission the use of alternative wordings which may also take into account consumer understanding and marketing needs (e.g. *to convey potentially positive health benefits).*

Section 3.2.2.1.2 (the claimed effect is beneficial for the target population) clarifies that "*in assessing each specific food/health relationship, the Panel also considers whether the claimed effect is a beneficial physiological effect for the target population (the general population or population subgroups thereof) for which the claim is intended. For example, "a reduction of gastric acid levels"*[37] *or "a reduction of inflammation"*[38] *could represent therapeutic targets for the treatment of some disease conditions, but are not considered beneficial physiological effects for the general population*".

[37] http://www.efsa.europa.eu/en/efsajournal/doc/1472.pdf
[38] http://www.efsa.europa.eu/en/efsajournal/doc/2059.pdf

Section 3.2.2.1.3 (the claimed effect refers to a specific function of the body and can be measured *in vivo* in humans) addresses in detail the fact that being testable and measurable *in vivo*[39] in humans by generally accepted methods is a necessary, but not sufficient, condition for an outcome variable to form the only basis for the scientific substantiation of a health claim made on foods, as follows:

"*In order to allow a scientific evaluation by the NDA Panel, the claimed effect needs to refer to a function of the body and be specific enough to be testable and measurable in vivo*[40] *in humans by generally accepted methods, except for health claims on essential nutrients (as explained in Section 3.4 of this guidance document). In this context, it should be noted that:*

a) claimed effects, which are considered as beneficial physiological effects, may not allow a scientific evaluation by the NDA Panel in the context of a particular application if no generally accepted methods for the measurement of the outcome variable(s) of interest in vivo in humans have been provided. An example is the lack of generally accepted methods for the measurement of the inhibition of adhesion of P-fimbriated E. coli to uroepithelial cells in vivo in humans, even though this particular effect was considered a beneficial physiological effect in the context of a particular application for a claim on reduction of bacterial colonisation of the urinary tract by inhibition of the adhesion of P-fimbriated E.coli to uroepithelial cells. The reasons for the Panel's conclusions can be found in the published opinion[41].

b) changes in outcome variable(s) which can be measured in vivo in humans by generally accepted methods may not be considered beneficial physiological effects per se if they do not refer to a benefit on a specific function of the body, and thus cannot be the claimed effect (i.e. constitute the only basis for the scientific substantiation of a health claim).

Some examples of outcome variable(s) which can be measured in vivo in humans by generally accepted methods but do not refer to a benefit on specific functions of the body and thus cannot constitute the only basis for the scientific substantiation of a health claim include:

i) changes in stool pH and short-chain fatty acid production (including butyrate) in the gut;

ii) changes in the composition of the gut microbiota;

iii) changes in the structure of the intestinal epithelium;

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

v) changes in immune markers, e.g. numbers of various lymphoid subpopulations in the circulation, proliferative responses of lymphocytes, phagocytic activity of phagocytes, lytic activity of natural killer cells and cytolytic T cells, production of cellular mediators, serum and secretory immunoglobulin levels, delayed-type hypersensitivity responses, etc.

Changes in some of these outcome variables could, however, be proposed as part of the mechanisms by which a food may exert the claimed effect, i.e. induce a beneficial change on a specific function of the body (e.g. maintenance of normal defecation, improved absorption of essential nutrients, or defence against pathogens).

However, in specific circumstances, changes in outcome variable(s) measured in vivo in humans, and which do not refer to a benefit on a specific function of the body directly, may be the claimed

[39] It includes the measurement of functional outcome variables *in vivo* and the measurement (*ex vivo)* of outcome variables in biological samples following an intervention *in vivo.*

[40] It includes the measurement of functional outcome variables *in vivo* and the measurement (*ex vivo)* of outcome variables in biological samples following an intervention *in vivo.*

[41] http://www.efsa.europa.eu/en/efsajournal/doc/3082.pdf

effect if evidence is provided that changes in such variable(s) generally induce a beneficial change in a specific function of the body. An example is the reduction of excessive intestinal gas accumulation, which does not refer directly to a benefit on a specific function of the body, but for which evidence has been provided that the change of the variable generally induces a beneficial change in a specific function of the body, i.e. reducing gastrointestinal discomfort (see Section 4.1.3)".

Section 3.4 (evaluation of claims related to essential nutrients compared to non-essential nutrients) of the draft guidance further clarifies that "*for non-essential nutrients or other substances, claims on the improvement or maintenance of (unspecified) functions of the immune system in general are not sufficiently defined for a scientific evaluation. The specific function of the immune system that is the subject of the claim, together with appropriate outcome variables(s) which may be used for the scientific evaluation of the claimed effect in vivo in humans, must be identified, and it is necessary to review the primary studies submitted and to weigh the evidence for the substantiation of these claims*". In this context, claims such as "*maintaining normal immune function in population groups at risk of immunosuppression*", '*maintenance of the normal function of the immune system*' or "*maintains a healthy adaptive immune response*" are not sufficiently defined to allow a scientific evaluation.

2.3.4.2. Characterisation of the claimed effect for disease risk reduction claims

Comment received:

27. It was requested to clarify what an independent predictor of disease is in the context of disease risk reduction claims made on foods, to provide an extensive list of acceptable independent predictors of disease risk in the context of disease risk reduction claims, or a list of alternatives in their absence.

Panel consideration of comment received:

Ad27. Section 3.2.2.2 (Characterisation of the claimed effect for disease risk reduction claims) of the draft guidance further clarifies the approach applied by the NDA Panel for the scientific evaluation of disease risk reduction claims, including the circumstances in which a variable can be considered as a risk factor for disease in the context of these claims, as follows:

"*For reduction of disease risk claims, the beneficial physiological effect (which Regulation (EC) No 1924/2006 requires to be shown for the claim to be permitted) is the reduction (or beneficial alteration) of a risk factor for the development of a human disease (not reduction of the risk of disease).*

Whether or not the alteration of a factor is considered to be beneficial in the context of a reduction of disease risk claim depends on the extent to which it is established that:

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

If there is strong evidence that there is (i) an independent association between the risk factor and the incidence of the disease, including (ii) a strong evidence for the biological basis through which the risk factor can contribute to the development of the disease, and (iii) evidence that a given modification of the risk factor generally reduces the risk of disease, a given modification of the risk factor may be considered beneficial in the context of a reduction of disease risk claim. In this case, evidence that the dietary intervention induces a given modification on the risk factor for the disease would be sufficient for the scientific substantiation of the claim.

If the evidence is not as strong (e.g. there is evidence for an independent association between the risk factor and the incidence of the disease and for the biological basis through which the risk factor can contribute to the development of the disease, but no evidence that a given modification of the risk factor generally reduces the risk of disease), a given modification of the risk factor may still be considered a beneficial physiological effect in the context of a reduction of disease risk claim. In this case, evidence needs to be provided that a given modification of the risk factor is accompanied by reduced incidence of the disease following a specific dietary intervention, preferably in the same studies (e.g. by consuming the food/constituent for which the claim is made").

A better understanding of this approach should help applicants in preparing applications on disease risk reduction claims which have not been evaluated by the Panel so far. The guidance does not intend, however, to provide an exhaustive list of acceptable risk factors for disease which have not yet been considered by the Panel in the context of a particular application. The reason is that defining the conditions under which a risk factor may be acceptable in the context of a disease risk reduction claim is generally possible only in the context of specific applications, which are often unique and technically complex. Examples can be found in various specific guidance documents[42]. Claims on the reduction (or beneficial alteration) of a risk factor for infections have been addressed in Section 5.1 of the draft guidance.

2.3.5. Human studies submitted for the scientific substantiation of health claims

Comment received:

28. There were questions about the acceptability of studies conducted in non-European populations for the scientific substantiation of health claims.

Panel consideration of comment received:

Ad28. It should be noted that all studies, including those conducted in non-EU populations, submitted to EFSA for scientific substantiation of health claims will be considered by the NDA Panel in the context of the totality of evidence. However, as addressed in Section 3.3 (human studies submitted for the scientific substantiation of health claims) of the draft guidance, "*for studies conducted in non-EU populations, special care should be taken to ensure that intrinsic/extrinsic ethnic characteristics do not influence the physiological response (claimed effect) to the consumption of the food/constituent for which the claim is proposed. Potential confounding factors, such as different dietary habits, should be considered where appropriate. In this respect, it is the responsibility of the applicant to provide a rationale/data which could support the extrapolation of results obtained in non-EU populations to EU populations*".

Comment received:

29. There were questions on the appropriate sample size and study duration for different outcome variables regarding human intervention studies submitted for substantiation of health claims.

Panel consideration of comment received:

Ad29. With respect to the sample size, the number of subjects in a study should always be large enough to provide a reliable answer to the questions addressed with a sufficient statistical power. Sample size is usually determined by the primary outcome of the study, taking into account the estimated dropout rate. This aspect of the planning of clinical trials relies on general scientific knowledge and is not discussed in the draft guidance.

The appropriate study duration in relation to different outcome variables has been discussed in the draft guidance in the context of specific health claims.

[42] Guidance for applicants on health claims: http://www.efsa.europa.eu/en/nda/ndaguidelines.htm

Comment received:

30. There was a request to consider cases where it is not possible to plan human intervention studies using a placebo and/or double-blinded designs due to the technical limitations imposed by the specific characteristics of food products.

Panel consideration of comment received:

Ad30. The Panel acknowledges that when claims are proposed, for example, for whole foods or food categories, rather than, for example, for food ingredients, it may not be possible to plan human intervention studies using a placebo and/or double-blinded designs. The Panel will consider, however, whether efforts have been made to minimise bias. Applicants should also take into account that, as specified in Section 3.3.1 of the draft guidance, "*for self-reported outcome variables (e.g. gastro-intestinal symptoms), which are subjective in nature, adequate blinding of subjects and investigators to the intervention is particularly important*".

Comment received:

31. It was proposed that information on what is clinically relevant and meaningful should be addressed in the human intervention trial and data analysis plans, depending on the targeted claim.

Panel consideration of comment received:

Ad31. The Panel agrees with this comment. This aspect of the planning of clinical trials relies on general scientific knowledge and is not discussed in the draft guidance.

2.3.5.1. Human studies assessing self-reported and composite outcome variables

Comment received:

32. There were requests to define the requirements/criteria/procedures for the validation of questionnaires for self-reported outcomes, and methods for modification of previously validated questionnaires[43]. In this context, it was asked to give an "extensive list of validated questionnaires or tools (e.g. Bristol stool form, Symptom Global Assessment, Rome III or IV criteria)", "examples of validated questionnaires/valid outcome measures for different claims", "examples of not-accepted methods", or of "formally non-validated" tools which are nonetheless generally accepted in the relevant research field, and for the acceptance of "expert accreditation" if no validated questionnaire is available for a particular outcome.

Panel consideration of comment received:

Ad32. Section 3.3.1 (Human studies assessing self-reported and composite outcome variables) and Appendix A of the draft guidance outline issues to consider regarding the validation of questionnaires and the modification of previously validated questionnaires and their use as outcome measures for the scientific substantiation of claims. Questionnaires should have been validated for the study population in the particular study setting and should have been shown to be reliable prior to their use in a confirmatory study. The measurement properties of the questionnaire should be known. The Panel wishes to reiterate that "*there is no single correct way to demonstrate the validity of a questionnaire and that it is a scientific judgement to what extent the information available is sufficient to be confident in the results obtained from the questionnaire. Also, as the appropriateness of a tool will depend on the outcome variable to be measured, the study population, the study design and the study setting, no exhaustive list of acceptable questionnaires can be given*". This aspect is addressed in Section 3.3.1 (human studies assessing self-reported and composite outcomes variables) of the draft guidance.

[43] Reference was made to: http://www.efsa.europa.eu/en/efsajournal/doc/3756.pdf

Comment received:

33. Comments were received related to: a) the use of validated questionnaires for diseased populations which have been adapted and validated for the target population, in the absence of validated questionnaires for the general (healthy) population, and b) the acceptance of new questionnaires validated for the appropriate target population but not widely used in the scientific community.

Panel consideration of comment received:

Ad33. The Panel considers that in both cases the questionnaires would be acceptable, as long as they have been validated for the study population in the particular study setting, have been shown to be reliable, and the measurement properties are known (see Section 3.3.1 and Appendix A of the draft guidance for details on the validation of questionnaires for self-reported outcomes).

Comment received:

34. There were requests for consideration of e.g. PAC-SYM (Patient Assessment of Constipation Symptoms); validated QoL (Quality of Life) questionnaires specific for a given conditions such as the PAC-QoL (Patient Assessment of Constipation Quality of Life) questionnaire for constipation; generic Health-Related Quality of Life outcome measures such as the Infant Toddler Quality of Life Questionnaire© (Camilleri et al., 2008).

Panel consideration of comment received:

Ad34. Questionnaires such as PAC-SYM, PAC-QoL, or Infant Toddler QoL Questionnaire, have not been evaluated by the NDA Panel in the context of a specific health claim application.

PAC-SYM (Patient Assessment of Constipation Symptoms) may be used in the context of claims on maintenance of normal defecation. Validated "quality of life questionnaires" may be used to provide supportive evidence for claims on gastro-intestinal discomfort. However, the appropriateness of these questionnaires will depend on the outcome variable to be measured, the study population, the study design and the study setting, and their validity within a study will need to be considered on a case-by-case basis in the context of specific applications. These questionnaires have not been specifically considered in the draft guidance.

Comment received:

35. Clarification was requested on the meaning of "generally accepted in the relevant research fields" (e.g. Bristol stool scale, Rome criteria).

Panel consideration of comment received:

Ad35. As a general point for all claims, the NDA Panel considers what is generally accepted in the relevant research fields (e.g. guidelines published by scientific societies based on rigorous methodological approaches) when evaluating the studies provided for substantiation of the claimed effect (e.g. use of appropriate statistical analyses of data; validation of tools used for assessing self-reported and composite outcome variables; Rome III criteria for the characterisation of the study population for claims on gastro-intestinal discomfort; Bristol stool scale for studies on stool characteristics for claims on maintenance of normal defecation).

Section 2 (Objective and scope) of the draft guidance document has been updated to highlight this point.

2.3.5.2. Extrapolation of results from the study population to the target population

Comment received:

36. It was pointed out that information on the suitability of human studies conducted on a particular study population or on subjects "at-risk" (Albers et al., 2013) for the substantiation of claims intended for the general population is missing. In this context, it was requested to give: examples of how the results from a study group other than the general population (specific subgroups or subjects with a disease) can be extrapolated to the general population; an extensive list of suitable study populations (including their conditions of use); a statement about the suitability of e.g. subjects with infections, hospitalised subjects, outpatients, for claims on defence against pathogens, as considered by the Panel in its opinion dated 2011[44]. It was suggested not to limit the study population to a specific category of health status, but to allow study subjects to be on the basis of their ability to demonstrate the health benefit to support the desired claim. There were also queries on the suitability of specific population sub-groups as study groups, e.g.: (a) symptomatic uncomplicated diverticular disease (SUDD), self-claimed constipation and functional gastrointestinal symptoms, obesity (e.g. BMI >30 kg/m^2); (b) populations at higher risk e.g. with poor diets or food intolerances, occasional diarrhoea, healthy people travelling to high risk countries, or receiving attenuated pathogenic bacterial or viral strains, experiencing physical or psychological stress (e.g. endurance exercise); or (c) subjects with a pathology unrelated to the claimed effect but which increases their susceptibility to the targeted disease.

Panel consideration of comment received:

Ad36. Section 3.3.2 (Extrapolation of results from the study population to the target population) of the draft guidance provides general guidelines on the circumstances in which results obtained in certain study groups, including subjects at high risk for a disease and subjects with a disease, can/cannot be extrapolated to the target population for a claim (the general population or sub-groups thereof).

It should be noted that the suitability of the study population for the scientific substantiation of a claim has to be considered in the context of the specific claim and the target population for which the claim is intended. The NDA Panel considers on a case-by-case basis the extent to which it is established that extrapolation from the study population (e.g. subjects with a disease) to the target population (e.g. subjects without the disease) is biologically plausible. In this respect, applicants should provide the rationale or data which could support such extrapolation. Therefore, no extensive list of suitable study populations and the conditions of use of the food can be given. However, examples of suitable study populations other than the target population can be found in the context of specific health claims addressed in the draft guidance.

Comment received:

37. It was questioned why irritable bowel syndrome (IBS) patients are an appropriate study group for claims for the general population.

Panel consideration of comment received:

Ad37. This question is addressed in Section 4.1 (claims on gastro-intestinal discomfort) of the draft guidance as follows: "*IBS is a functional bowel disorder characterised by chronic or recurrent abdominal pain or discomfort, mostly associated with defecation abnormalities (consistency and frequency of stools) in the absence of a detectable organic or pathological cause. Episodes of abdominal pain or discomfort occur both in healthy people and in individuals suffering from IBS, the difference being the higher frequency and/or greater severity of the symptoms in IBS patients. IBS patients or subgroups of IBS patients (Rome III criteria) are generally considered an appropriate study group to substantiate claims on gastro-intestinal discomfort intended for the general population*". Subjects with IBS are also appropriate study groups for claims on maintenance of normal defecation (see also Section 4.2 of the draft guidance).

[44] *L. rhamnosus* GG and defence against pathogenic gastrointestinal microorganisms http://www.efsa.europa.eu/en/efsajournal/doc/2167.pdf

Comment received:

38. It was suggested that, under certain circumstances, it should be possible to extrapolate a benefit demonstrated in adults to children, when there is no reason to assume that age has an influence or risk.

Panel consideration of comment received:

Ad38. Section 3.3.2 (Extrapolation of results from the study population to the target population) of the draft guidance clarifies that: "*In general, results obtained in infants and young children cannot be used for the scientific substantiation of health claims involving the gastrointestinal tract and/or the immune system, including claims related to (immune) defence against pathogens, for which the target population are adults, and vice versa. Evidence or a rationale for extrapolation of the results from a sub-group of the population (study group) to the target population, if the target group is wider or different from the study group, should be provided, and will be considered by the Panel on a case-by-case basis*". Whether the results obtained in adults could be extrapolated to children will be considered by the NDA Panel on a case-by-case basis in the context of specific applications, where applicants should provide evidence/a rationale to clarify under which circumstances there is no reason to assume that age has an influence on the claimed effect.

2.3.6. Evaluation of claims related to essential nutrients compared to non-essential nutrients

Comment received:

39. There were comments and requests for clarification regarding the requirements for the scientific substantiation of health claims on essential nutrients *vs.* non-essential nutrients. It was noted that, whereas some authorised health claims for essential nutrients (e.g. various vitamins, zinc, copper, calcium) relied on claimed effects such as, for example, maintenance of the normal function of the immune system and inflammatory response, and thus it could be assumed they were sufficiently defined for a scientific evaluation (and thus could be measured *in vivo* in humans), the same claimed effects were considered as general and non-specific (not sufficiently defined for a scientific evaluation) when the claim was requested for non-essential nutrients or other substances. On the other hand, it was questioned whether this aspect (requirements for the substantiation of health claims for essential nutrients *vs.* non-essential nutrients and other substances) was needed in this specific guidance document or whether it could just be addressed in the general guidance for stakeholders and/or to issue a specific guidance for claims on essential nutrients.

Panel consideration of comment received:

Ad39. The Panel acknowledges that claims proposed for well-established functions of essential nutrients (vitamins and minerals) are treated in a different way to claims proposed for non-established functions of essential nutrients, for non-essential nutrients or for other substances. Section 3.4 (Evaluation of claims related to essential nutrients compared to non-essential nutrients) of the draft guidance clarifies these differences as follows:

"*Claims proposed for established functions of essential nutrients (vitamins and minerals) are treated differently from claims proposed for functions of non-essential nutrients or other substances. The requirements for the definition of the claimed effect, for the scientific substantiation of the claim, and for establishing conditions of use, differ.*

Some vitamins and essential minerals have established roles in physiological processes based on a large body of scientific evidence including deficiency symptoms in humans. For claims for which there is well-established consensus among scientific experts as indicated by authoritative scientific sources as to their substantiation by generally accepted scientific evidence (e.g. many of the

functions of essential nutrients), the NDA Panel may rely on such consensus for substantiation of the claim. In such cases it may not be necessary to review the primary scientific studies submitted on the relationship between the food/constituent and the claimed effect. For these claims, conditions of use are set on the basis that any amount of the essential nutrient will contribute to the claimed effect (e.g. conditions of use can be linked to nutrition claims).

Claims on the maintenance of (unspecified) functions of the immune system have been evaluated by the NDA Panel with a positive outcome for some essential nutrients[45, 46]. The scientific substantiation of these claims was based on the well-established biochemical role of such nutrients, and/or on deficiency symptoms involving the immune system, rather than on weighing the evidence. The use of unspecified functions of the immune system to substantiate such claims is because symptoms of deficiency of a nutrient can result from effects on multiple physiological functions, and it is sometimes not possible or appropriate to single out a precise function that is affected by deficiency of that nutrient in a particular organ or system (e.g. copper contributes to the normal function of the immune system[47]; vitamin D and contribution to the normal function of the immune system and healthy inflammatory response[48]).

For non-essential nutrients or other substances, claims on the improvement or maintenance of (unspecified) functions of the immune system in general are not sufficiently defined for a scientific evaluation. The specific function of the immune system that is the subject of the claim, together with appropriate outcome variables(s) which may be used for the scientific evaluation of the claimed effect in vivo in humans, must be identified, and it is necessary to review the primary studies submitted and to weigh the evidence for the substantiation of these claims. For these claims, conditions of use are set on the basis of the human studies submitted for substantiation by considering the minimum amount of the non-essential nutrient or other substance, which consistently exerts an effect on the function targeted by the claim.

Claims proposed for essential nutrients which do not have an established role on the particular function that the claim mentions (e.g. vitamin C and function of the immune system assessed as reduction of the incidence of common cold during and after extreme physical exercise[49]) will be treated as non-essential for that function. In this context, the particular function of the immune system that the claim is targeting must be identified, and it is necessary to review the primary studies submitted and to weigh the evidence for the substantiation of these claims"

Although the above applies to all claims, the NDA Panel considers it important to clarify this aspect in this draft guidance, and to provide examples in the specific areas covered by this document, particularly in relation to claims related to the normal function of the immune system and inflammatory responses.

2.3.7. Claims on gastro-intestinal discomfort

2.3.7.1. Claims on gastro-intestinal discomfort in adults

Comment received:

40. Some questions were related to claims on gastro-intestinal discomfort *vs.* claims on the reduction of a specific gastrointestinal symptom (e.g. bloating, flatulence), as well as to the outcome measures which could be appropriate to assess each of these claims. It was proposed that specific symptoms should be measured as primary outcomes of specific claims (e.g. reduction in bloating, flatulence), and that objective measures, for example abdominal distension or number of daily flatulence should be accompanied by Patient-Reported Outcomes (PRO) (e.g. sensation of

[45] http://www.efsa.europa.eu/en/efsajournal/doc/1226.pdf
[46] http://www.efsa.europa.eu/en/efsajournal/doc/1229.pdf
[47] http://www.efsa.europa.eu/en/efsajournal/doc/1211.pdf
[48] http://www.efsa.europa.eu/en/efsajournal/doc/1468.pdf
[49] http://www.efsa.europa.eu/en/efsajournal/doc/1226.pdf

abdominal bloating or flatulence). It was also suggested that, for claims on GI discomfort, changes in a composite score of gastrointestinal symptoms seemed to be more appropriate as an outcome measure than changes of a single symptom[50]. It was also asked: (a) why "validated general quality of life questionnaires" are not appropriate outcome variables for these claims but "validated questionnaire(s) on severity and frequency of symptoms" are considered appropriate; (b) whether the Birmingham IBS symptom questionnaire (Roalfe et al., 2008; Spiegel et al., 2010), Likert scales, or visual analogue scales (VAS) (e.g. to measure pain severity) could be used, provided that a significant (pre-defined) reduction of symptoms severity is reached (e.g. ≥ 30% decrease in abdominal pain).

Panel consideration of comment received:

Ad40. Section 4.1.1 (claims on gastro-intestinal discomfort in adults) of the draft guidance addressed the appropriate outcome variables for the evaluation of claims on gastro-intestinal discomfort, as follows: "*Gastro-intestinal discomfort may be measured by using validated subjective global symptom severity questionnaires (such as described in the consensus opinions by Veldhuyzen van Zanten et al. (1999) and Irvine et al. (2006)). Changes in one or more of the individual symptoms (e.g. representing different domains of the questionnaire), as well as changes in bowel habits, may be used as supportive evidence for mechanisms by which the food/constituent could exert the claimed effect, but cannot be used alone for the substantiation of a claim on the reduction of gastro-intestinal discomfort. Validated "quality of life questionnaires" may also provide supportive evidence for claims on gastro-intestinal discomfort.*"

As outlined in Section 3.3.1 of the draft guidance and in Ad32, the appropriateness of a tool or questionnaire will depend on the outcome variable to be measured, the study population, the study design and the study setting, and will need to be considered on a case-by-case basis by the NDA Panel in the context of specific applications. The Panel wishes to reiterate that it is not possible to provide an exhaustive list of questionnaires or other appropriate outcome measures for claims on the reduction of gastrointestinal discomfort without considering the context in which these are to be used.

Comment received:

41. There were queries about appropriate study groups**,** e.g. IBS patients (adults or children), study groups other than IBS patients, and about the extrapolation of evidence from constipated subjects to the general population. It was also suggested that subjects meeting only a subset of official disease criteria (e.g. Rome III) could be considered an appropriate study group provided that the improvement in symptoms are shown using validated evaluation methods.

Panel consideration of comment received:

Ad41. Section 4.1.1 (claims on gastro-intestinal discomfort in adults) of the draft guidance also clarifies that: "*Irritable bowel syndrome (IBS) patients or subgroups of IBS patients (Rome III criteria) are generally considered an appropriate study group to substantiate claims on gastro-intestinal discomfort intended for the general population (adults and children).*"

For other study groups (e.g. constipated subjects), information on the selection criteria and on the characterisation of the study population in relation to the claimed effect should be provided, and will be considered on a case-by case basis (see also Section 3.3.2 of the draft guidance).

Comment received:

42. It was proposed to differentiate between "weight of or average symptoms" and "other signs, such as hard stools symptoms" in claims on GI discomfort.

[50] http://www.efsa.europa.eu/en/efsajournal/pub/3259.htm

Panel consideration of comment received:

Ad42. Section 4.1.1 (claims on gastro-intestinal discomfort in adults) of the draft guidance outlines that "*changes in one or more of the individual symptoms (e.g. representing different domains of the questionnaire), as well as changes in bowel habits, may be used as supportive evidence for mechanisms by which the food/constituent could exert the claimed effect, but cannot be used alone for the substantiation of a claim on the reduction of gastro-intestinal discomfort*".

Comment received:

43. It was suggested that "reduction of gastro-oesophageal discomfort", assessed by a reduction in the frequency or severity of symptoms such as heartburn or reflux, could be considered a beneficial physiological effect and could be a sub-set of claims on gastro-intestinal discomfort. It was requested to consider whether subjects with "functional heartburn" could be a suitable study group for claims on the "reduction of gastro-oesophageal discomfort". Questions were also received in relation to claims on "other GI symptoms" (e.g. "indigestion, fullness").

Panel consideration of comment received:

Ad43. No claims on the "reduction of gastro-oesophageal discomfort" or studies targeting subjects with "functional heartburn" for the scientific substantiation of such claims have been submitted to EFSA for a scientific evaluation. Given the contextual nature of specific claims, whether or not the claimed effect may be a beneficial physiological effect, the context in which it may be considered beneficial, the outcome variables which may be appropriate for its evaluation and the study groups from which results could be extrapolated to the target population of the claim can only be defined during the evaluation of specific applications. The guidance may be updated in the future in light of additional experience gained with the evaluation of such a claim.

Claims on e.g. "indigestion, fullness" are not sufficiently defined to allow a scientific evaluation (see Section 3.2.2 (Characterisation of the claimed effect) of the draft guidance).

2.3.7.2. Claims on gastro-intestinal discomfort in infants and young children

Comment received:

44. Clarification was asked on whether reducing gastro-intestinal discomfort is a beneficial physiological effect for young children.

Panel consideration of comment received:

Ad44. Section 4.1.2 (Claims on gastro-intestinal discomfort in infants and young children) of the draft guidance specifies that: "*reduction of gastrointestinal discomfort is a beneficial physiological effect for infants and young children*". Appropriate outcome measures for this claim, which targets infants and young children specifically, are also addressed in Section 4.1.2 of the draft guidance.

2.3.7.3. Claims on the reduction of excessive intestinal gas accumulation

Comment received:

45. There were comments proposing objective measures as valid outcomes for claims related to intestinal gas, such as breath tests, intestinal gas volume (imaging methods such as CT scans or Functional Magnetic Resonance Imaging), or the collection of gas evacuated through the anus. In

this context, it was asked whether all these outcomes would refer to the same beneficial effect (i.e. reduction of intestinal gas accumulation), and whether these outcomes could be considered alone or should be interpreted in the context of an improvement of symptoms as reported by the subject.

Panel consideration of comment received:

Ad45. Section 4.1.3. (Claim on the reduction of excessive intestinal gas accumulation) of the draft guidance specifies the appropriate outcome variables for the reduction of excessive intestinal gas accumulation. Such variables include, for example, "*breath hydrogen levels measured by hydrogen breath test, intestinal gas volume assessed by imaging techniques (e.g. functional magnetic resonance imaging)*". Subjective outcomes could be provided as supportive evidence.

2.3.8. Claims on maintenance of normal defecation

Comment received:

46. There were questions on the number of outcome variables needed to substantiate health claims related to bowel function and on the type of claims which were possible in this field. For example, it was asked: a) whether improvement of at least one outcome variable could be enough for a specific claim (e.g. increase in faecal bulk); b) whether improvement of two or more outcome variables would be needed for a claim related to the improvement of bowel function in general. In this context, it was suggested to give examples on the design, outcome variables and methods of measurement to be used in human intervention studies which could be appropriate for the scientific substantiation of claims on bowel function. Reference was made to standard methodologies currently used to measure transit time, e.g. radiopaque markers, wireless motility capsules (like SmartPill) and colonic scintigraphy (Rao et al., 2011).

Panel consideration of comment received:

Ad46. Section 4.2. (Claims on maintenance of normal defecation) of the draft guidance clarifies that previous claims proposed on the maintenance of normal bowel function actually related to the maintenance of normal defecation (a bowel function), both in the context of functional diarrhoea and in the context of functional constipation, as follows:

"*The scientific evidence for the substantiation of health claims on the maintenance of normal defecation can be obtained from human intervention studies showing an increase in the frequency of defecations and/or a beneficial change in the consistency of stools (lower) and faecal bulk (higher) in subjects with functional constipation at baseline, provided that such changes do not lead to diarrhoea, as compared to an appropriate food/constituent which is neutral with respect to the claimed effect, or to no treatment (e.g. control group on usual diet) if duly justified. The scientific evidence for the substantiation of health claims on the maintenance of normal defecation can also be obtained from human intervention studies showing a decrease in the frequency of defecations in subjects with functional diarrhoea at baseline which does not lead to constipation under the same conditions. In this context, beneficial changes in the consistency of stools (higher) and faecal bulk (lower) can be used as supportive evidence for the claim. Evidence for a sustained effect with continuous consumption of the food/constituent over periods of time of at least 4 to 8 weeks should also be provided, owing to the chronic nature of functional constipation/diarrhoea*.

Frequency of defecations, stool consistency and faecal bulk can be assessed directly by the investigators or by using validated questionnaires for self-reported outcomes. Changes in transit time (e.g. by using radio-opaque markers) may be used as supportive evidence for a mechanism by which changes in the frequency of defecations are achieved".

Comment received:

47. Clarification was requested about the meaning of "*within the normal range*" in the context of changes in bowel function.

Panel consideration of comment received:

Ad47. The requirement of showing changes in bowel function "within the normal range" has been addressed in the draft guidance by explicitly mentioning that such changes should not lead to diarrhoea or constipation.

Comment received:

48. It was proposed that an improvement of diarrhoea that does not result in constipation should be considered as a beneficial physiological effect, that the same variables used to assess claims related to the improvement of constipation could be used to assess claims on the improvement of diarrhoea (e.g. stool consistency or stool frequency), and that patients with IBS-D should be an appropriate study group, as well as patients with functional diarrhoea.

Panel consideration of comment received:

Ad48. Section 4.2. (Claims on maintenance of normal defecation) of the draft guidance also covers health claims related to functional diarrhoea. Please see Ad46.

Comment received:

49. There were questions about whether certain study groups could be appropriate for the scientific substantiation of claims on normal bowel function (e.g. subjects with symptomatic uncomplicated diverticular disease (SUDD), with self-claimed constipation, with self-claimed functional gastrointestinal (GI) symptoms, obese subjects, populations at higher risk of functional constipation and/or diarrhoea (e.g. with poor diets or food intolerances), subjects with self-claimed occasional diarrhoea and/or traveller's diarrhoea, subjects with diverticulitis.

Panel consideration of comment received:

Ad49. Section 4.2. (Claims on maintenance of normal defecation) of the draft guidance clarifies that: "*results from studies conducted in subjects with functional (chronic) diarrhoea and/or with functional (chronic) constipation, including subjects with IBS, could be used for the scientific substantiation of these claims. However, the rationale for extrapolation of results obtained in subjects with chronic diarrhoea or constipation under pharmacological treatment to the target population for the claim should be provided, and will be considered on a case-by-case basis (e.g. evidence for a lack of interaction between the food and the medications used on the claimed effect)*".

For other study groups, information on the selection and characterisation of the study population in relation to the claimed effect should be provided, and will be considered on a case-by-case basis in the context of specific applications.

2.3.9. Claims on digestion and/or absorption of nutrients

Comment received:

50. It was proposed that a decrease in severity of most frequently reported symptoms of lactose intolerance (diarrhoea, abdominal cramping, vomiting, audible bowel sounds, flatulence or gas) experienced after lactose ingestion, evaluated by a visual analogue scale (VAS) score, should be considered a valid outcome measure for the scientific substantiation of claims on improved lactose tolerance/digestion (Casellas et al., 2009).

Panel consideration of comment received:

Ad50. Claims on improved lactose digestion, including appropriate outcome variables for the scientific substantiation of these claims, have been addressed in Section 4.3.1.1. of the draft guidance as follows: "*To assess lactose digestion, studies in susceptible populations or lactose intolerant subjects, defined either by clinical symptoms or by genotyping lactase non persistence polymorphism, with appropriate assessment of symptoms of gastrointestinal discomfort, and/or measurement of breath hydrogen and methane, are required*". What could be an appropriate assessment of symptoms of gastro-intestinal discomfort is clarified in section 4.1 (claims on gastro-intestinal discomfort) of the draft guidance.

Comment received:

51. It was commented that the new guidance should also mention other nutrients, such as calcium ("an increase in calcium absorption leading to an increase in calcium retention might be a beneficial physiological effect"[51]).

Panel consideration of comment received:

Ad51. Claims on an increase in calcium absorption have been addressed in Section 4.3.2 (Claims on digestion and/or absorption of micronutrients) of the draft guidance.

2.3.10. Claims on (immune) defence against pathogens

Comment received:

52. Clarifications were requested about the appropriate outcome variable(s) which could be used to substantiate health claims on defence against pathogens. In this context, it was asked: (a) whether a reduction in the incidence/ duration/ severity of symptoms of infection assessed by a clinician based on stool diaries (filled in by the volunteer/patient) could be an appropriate outcome measure; (b) whether self-reported data could be sufficient to establish the diagnosis of infections or whether microbiological data would be required as well for confirmation; (c) whether a diagnosis by a physician following general medical practice could be sufficient for establishing the infectious nature of the disease at different sites of the body (e.g. whether what is being used in the clinical practice is in principle acceptable as a validated methodology, under what circumstances a physician-diagnosis of infection of the respiratory tract would be acceptable). It was also suggested to clarify explicitly that a reduction in the number of infectious episodes, their severity, or their duration could be considered a beneficial effect and thus a sufficient requirement for the substantiation of health claims on defence against pathogens.

Panel consideration of comment received:

Ad52. Section 4.4 (Claims on (immune) defence against pathogens) of the guidance clarifies that: "*The scientific evidence for the substantiation of health claims related to defence against pathogens can be obtained from human intervention studies showing an effect on clinical outcomes related to infections (e.g. incidence, severity and/or duration of symptoms). The infectious nature of the disease should be established, e.g. by clinical differential diagnosis and/or microbiological data and/or the use of validated questionnaires, depending on the study context and type of infection*".

As an example, incidence of diarrhoeal episodes may be used as an outcome variable for claims related to defence against pathogens in the gastro-intestinal tract. The infectious aetiology of diarrhoeal episodes should be ascertained. In this context, gastro-intestinal infections clinically

[51] Reference was made to: http://www.efsa.europa.eu/en/efsajournal/doc/2234.pdf

diagnosed by the primary care or hospital physician following well-defined criteria can be used as an appropriate outcome measure for the scientific substantiation of the claim, provided that adequate exclusion criteria for the most common non-infectious causes of diarrhoea have been applied.

The Panel wishes to clarify that, even if a reduction in either the number of infectious episodes, their severity, or their duration (i.e. the severity or duration of symptoms) are all appropriate outcome variables for claims on defence against pathogens and beneficial changes in any of these outcomes could be used for their scientific substantiation, it should be kept in mind that a scientific judgement will be made on the extent to which a cause and effect is established between the consumption of the food/constituent and the claimed effect (i.e. for the target group under the proposed conditions of use) by considering the strength, consistency, specificity, dose-response, and biological plausibility of the relationship. In this context, consistency across studies regarding the outcome variable that is modified by the intervention and the biological plausibility for a change in one but not in other outcome variables which would be appropriate for the substantiation of health claims on defence against pathogens will be carefully considered by the Panel on a case-by-case basis.

The requirements for validation of questionnaires are outlined in Section 3.3.1 of the draft guidance.

Comment received:

53. Many comments pointed out the practical difficulties in identifying/characterising specific pathogenic organisms/their toxins (e.g. traveller's diarrhoea), and in interpreting/fulfilling the scientific requirements regarding the "relevant/magnitude of reduction of the presence of specific pathogens, their toxins or other virulence factors" as outlined in the 2011 guidance document. Questions were received: (a) about acceptable cut off values to demonstrate the presence or a decrease in pathogens or pathogen metabolites; (b) on whether "pathogens, their toxins or other virulence factors" include "commensal" pathogens in healthy carriers, potentially responsible for opportunistic infections, such as *C. difficile;* (c) on whether both qualitative and quantitative reductions of the presence of specific pathogens/their toxins/or other virulence factors could be considered physiologically relevant and acceptable. In this context, there were proposals to modify/extend/limit the list of foodborne pathogens provided in the first version of the guidance (2011), and requests to provide a similar (and exhaustive) lists of pathogenic or toxicogenic microorganisms for other sites of the body.

Panel consideration of comment received:

Ad53. The NDA Panel notes the comments received and acknowledges the technical difficulties encountered in interpreting the context in which the above-mentioned outcome variables could be used for the scientific substantiation of function claims related to defence against pathogens.

The NDA Panel has clarified in the draft guidance (Section 4.4) that: "*the (transient) presence of microorganisms and/or their toxins at a particular body site or in the circulation may or may not reflect a clinical infection. In this context, microbiological data could be used instead of (i.e. replace) clinical outcomes related to infections (e.g. incidence of, severity and/or duration of symptoms) if evidence is provided that the presence of a particular microorganism (and/or their toxins) at a particular body site, or the presence of a certain amount of the microorganism, would eventually lead to a clinical infection in the target population for which the claim is made (general population or subgroups thereof). The evidence provided will be evaluated by the NDA Panel on a case-by-case basis*".

Acknowledging that the presence of a particular microorganism (and/or its toxins) may or may not reflect a clinical infection depending on a number of factors related to both the microorganism and the host, including the site of the body in which the microorganism is present, the NDA Panel

considered that providing an exhaustive list of "pathogenic" or "toxicogenic" microorganisms for each site of the body was out of the scope of this document. However, whenever evidence is provided by applicants that the presence of a particular microorganism (and/or their toxins) at a particular body site, or the presence of a certain amount of the microorganism, lead to a clinical infection in the target population for which the claim is made in the context of a particular application, this guidance document will be updated accordingly to reflect such examples.

Comment received:

54. It was proposed that for claims on defence against pathogens, cohort studies could be used to establish an association between the reduction of specific pathogens, toxins or virulence factors and reduction in a clinical outcome.

Panel consideration of comment received:

Ad54. The Panel will consider different types of cohort studies (prospective cohort studies, retrospective cohort studies, combined prospective and retrospective) within the hierarchy described in the EFSA guidance[52] and in the context of all the evidence provided to assess whether an association between the reduction of the presence of specific pathogens, toxins or virulence factors and the reduction in a clinical outcome is established. This aspect has not been specifically considered in the draft guidance.

Comment received:

55. Clarifications were requested on whether the use of a claim on defence against pathogens which has been substantiated for a specific pathogen (e.g. rotavirus) should be restricted to that pathogen (e.g. rotavirus), to the type of pathogen (e.g. viruses) or could be extended to pathogens in general, within a particular body site (e.g. viral gastro-intestinal infections or gastro-intestinal infections).

Panel consideration of comment received:

Ad55. Section 4.4 of the draft guidance specifies that: "*For function claims on defence against pathogens, the claim should specify the site of infection (e.g. defence against pathogens in the gastro-intestinal tract, in the upper respiratory tract or in the urinary tract), the type of pathogenic microorganism (e.g. bacteria, virus, fungi), and the target population*".

It should be noted that the NDA Panel considers whether the proposed wording reflects the scientific evidence for claims for which a cause and effect relationship has been established. However, it should also be noted that the final wording of the claim adopted by the European Commission during the authorisation process may have to take into account aspects other than agreement with the scientific evidence, for example consumer understanding (see also Ad26).

Comment received:

56. There was a question on whether intervention studies assessing the effects of the food/constituent on experimental models of infection in humans with either live viruses/bacteria or their attenuated versions could be used as the only source of evidence for the scientific substantiation of claims related to defence against pathogens (e.g. human studies in which an experimental infection is induced through exposure to rhinovirus (Peterson et al., 2009; Mallia et al., 2011) or an attenuated *Escherichia Coli* vaccine (Ouwehand et al., 2014). There were also questions on whether, for example: subjects with a "sub-optimal immune" status (e.g. stressed individuals or those doing heavy physical exercise/athletes) and healthy subjects who are challenged with pathogenic

[52] Guidance for the preparation and presentation of health claim applications: http://www.efsa.europa.eu/en/efsajournal/doc/2170.pdf

bacterial or viral strains or their attenuated versions) could be appropriate study populations for claims on (immune) defence against pathogens.

Panel consideration of comment received:

Ad56. Section 4.4 (claims on immune defence against pathogens) clarifies that healthy subjects challenged with attenuated viruses/bacteria could be a suitable study population for claims related to defence against pathogens, as follows: *"higher responses to vaccination (as measured by increased numbers of individuals attaining protective levels of antibody titres) are appropriate outcome variables for the scientific substantiation of claims related to the immune defence against pathogens".* In addition, it has been specified that subjects challenged with live viruses/bacteria could be a suitable study population for claims related to defence against pathogens, as follows: "*subjects without an infection at baseline, including subjects at high risk for infection (e.g. travellers to high risk countries, subjects under heavy physical exercise, elderly individuals in nursing homes, children attending day-care centres, subjects challenged with live viruses/bacteria) could be suitable study groups for the scientific substantiation of claims on (immune) defence against pathogens for the general population […]".*

Comment received:

57. Comment 26(c) related to claims on immune function was also made in relation to claims on immune defence against pathogens.

Panel consideration of comment received:

Ad57. For the substantiation of Article 13(5) claims on immune defence against pathogens, Section 4.4 of the draft guidance clarifies that: "*Outcome variables, such as changes in immune markers, may provide supportive evidence on the biological plausibility and on the mechanism by which the food/constituent could exert the claimed effect (e.g. through the activation of the immune system), but cannot be used alone for the scientific substantiation of these claims*".

Comment received:

58. For the scientific substantiation of claims on immune defence against pathogens, some comments asked for clarification as to whether evidence on beneficial changes in immune markers and evidence for beneficial changes on clinical outcomes of infections had to be obtained within the same human studies or not.

Panel consideration of comment received:

Ad58. For claims related to immune defence against pathogens, the NDA Panel considers that changes in clinical outcomes related to infections together with concomitant changes in relevant immunological parameters, preferably shown in the same intervention studies, would provide the strongest evidence for a role of the immune system on the claimed effect. However, it is not an absolute requirement for the scientific substantiation of these claims (i.e. beneficial changes in clinical outcomes and beneficial changes in relevant immune markers could also be demonstrated in separate studies conducted under similar conditions).

Comment received:

59. Clarification was requested on the use of increments in antibody titres for the substantiation of claims on immune defence against pathogens, and on whether this could be a "sufficient" outcome measure in the absence of clinical outcomes related to infections.

Panel consideration of comment received:

Ad59. This point has been addressed in Section 4.4. (Claims on (immune) defence against pathogens) of the draft guidance as follows "*vaccination confers immunity to certain infectious diseases. Even if a strict correlation between titres in response to vaccination and protection against infection is not always evident, cut-off values of antibody-titres in response to vaccination indicating protection have been established for many vaccines. Higher responses to vaccination (as measured by increased numbers of individuals attaining protective levels of antibody titres) are appropriate outcome variables for the scientific substantiation of claims related to immune defence against pathogens*". In this context, evidence for an effect of the food/constituent on clinical outcomes related to infections is not required.

Comment received:

60. There were queries about the assessment of the incidence/severity/duration of upper respiratory tract infections in different subgroups of the population including children. Questions related to whether clinical diagnosis could be an appropriate outcome measure, and to whether specific questionnaires/tools could be acceptable (e.g. the Wisconsin Upper Respiratory Symptom Survey for assessing the severity of a common cold (WURSS-11, WURSS-21 and WURSS) (Barrett et al., 2005), the Jackson Score for the assessment of common cold incidence and severity (Jackson et al., 1958). It was also suggested that for claims related to upper respiratory tract infections, influenza infections should be excluded in the differential diagnosis because they cause similar symptoms as common cold but they are not upper respiratory tract infections.

Panel consideration of comment received:

Ad60. Section 4.4.2 of the draft guidance specifically addresses appropriate outcome variables for claims on defence against pathogens in the (upper and/or lower) respiratory tract, and the particular circumstances, as follows: "*The scientific evidence for the substantiation of health claims related to defence against pathogens in the respiratory tract can be obtained from human intervention studies showing an effect on clinical outcomes related to respiratory infections (e.g. incidence of, severity and/or duration of symptoms), either of the upper respiratory tract (such as rhinitis, pharyngitis, sinusitis, otitis, and common cold), of the lower respiratory tract (such as pneumonia, bronchitis, and bronchiolitis), or both. For instance, upper or lower respiratory tract infections clinically diagnosed by the primary care or hospital physician following well-defined criteria can be used as an appropriate outcome measure for the scientific substantiation of the claim, provided that adequate exclusion criteria for the most common non-infectious causes (e.g. allergic diseases) of the signs and symptoms used for diagnosis of the respiratory infection have been applied (i.e. differential diagnosis). Microbiological data could also be used to ascertain the infectious aetiology of clinical episodes*".

Regarding the validity of questionnaires for the assessment of common cold or other respiratory tract infections, please refer to Section 3.3.1 of the draft guidance and to Ad32.

Regarding the question on whether or not influenza infections are/are not upper respiratory infections, the Panel wishes to clarify that the guidance document does not intend to replace textbook knowledge or define specific claims which have not been evaluated so far in the context of a specific application.

Comment received:

61. There was a question on the age at which the immune system can be considered to be mature in children, and thus on the age at which extrapolation of results from adults to children and *vice versa* could be possible for claims on immune defence against pathogens.

Panel consideration of comment received:

Ad61. Please refer to Ad38.

2.3.11. Claims on a beneficial change in response to allergens

Comment received:

62. It was questioned whether claims on a beneficial change in response to allergens can be addressed specifically to people with allergy symptoms and what type of claims would be possible.

Panel consideration of comment received:

Ad62. It should be noted that, as outlined in Section 3.2.1 of the draft guidance, health claims made on foods cannot refer to the treatment of a disease, thus subjects with the disease cannot be the target population for a claim on beneficial changes in response to an allergen. However, the Panel considers that "*the general healthy population comprises persons with an increased risk of developing allergic (atopic) reactions such as allergic rhinitis, allergic asthma, atopic dermatitis and food allergy*", and "*a beneficial change in response to allergens is a beneficial physiological effect for subjects at risk of allergic reactions*".

Comment received:

63. There were suggestions to consider as valid outcome variable(s) for claims in response to allergens, for example: (a) the duration of an allergic manifestation; (b) the decrease in the use of anti-allergy medication or the improvement of symptoms over standard of care (i.e. anti-histaminics); (c) certain % improvement in the Rhino-conjunctivitis Quality of Life Questionnaire [RQLQ] symptom scores.

Panel consideration of comment received:

Ad63. Section 4.5 of the draft guidance specifies that "*the scientific evidence for the substantiation of function claims related to a beneficial change in response to allergens can be obtained from human studies showing a decreased incidence, severity and/or duration of allergic manifestations in subjects at risk of allergic reactions but free of symptoms at baseline*".

Other outcome variables would need to be considered in the context of specific applications, and particularly within the context of the study population which could be appropriate for the scientific substantiation of these claims (i.e. "*subjects at risk of allergic reactions but free of symptoms at baseline"* and thus not under pharmacological treatment for allergy symptoms).

Comment received:

64. There was a question on which clinically relevant immune markers could be used alone without measuring clinical outcomes to substantiate a health claim related to resistance against allergens (Lambert et al., 2003; Kosnik et al., 2005; Rueff et al., 2009; Albers et al., 2013). It was proposed to accept a reduction of the allergic response as measured by changes in specific biomarkers (Actis-Goretta et al., 2012; Singh et al., 2013) as an appropriate and standalone outcome measure for the assessment of these claims.

Panel consideration of comment received:

Ad64. Section 4.5 of the draft guidance clarifies the outcome variables which are considered appropriate for the scientific substantiation of claims related to beneficial changes in response to allergens as follows:

"*The scientific evidence for the substantiation of function claims related to a beneficial change in response to allergens can be obtained from human studies showing a decreased incidence, severity and/or duration of allergic manifestations in subjects at risk of allergic reactions but free of symptoms at baseline. Allergic symptoms are not always easy to distinguish from non-allergic phenomena, and data from self-reported allergies are usually unreliable and insufficient for a diagnosis of allergy. In addition, differences in exposure to the triggering allergen(s) in the intervention and control groups should be carefully considered.*

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

Comment received:

65. Clarity was requested on how studies should be designed in order to address quality of life and symptom improvement in subjects with allergy.

Panel consideration of comment received:

Ad65. The guidance is intended to provide a general framework on the type of studies which can provide evidence for the scientific substantiation of health claims made on foods. It is not intended to set requirements on how studies should be designed (e.g. to address quality of life and symptom improvement in subjects with allergy). It is the responsibility of the applicant to ensure that the studies are performed according to standards that are generally accepted by experts in the relevant field. This aspect has not been addressed in the draft guidance. However, applicants should consider that "*the scientific evidence for the substantiation of function claims related to a beneficial change in response to allergens can be obtained from human studies showing a decreased incidence, severity and/or duration of allergic manifestations in subjects at risk of allergic reactions but free of symptoms at baseline*".

Comment received:

66. In relation to respiratory allergy, it was suggested that a benefit demonstrated for pollen allergy could also be used to substantiate a general claim on aero-allergens.

Panel consideration of comment received:

Ad66. From a scientific point of view, a benefit demonstrated for pollen allergy could only be used to substantiate a general claim on aero-allergens if evidence is provided that results obtained for pollen allergy could be extrapolated to all aero-allergens. However, as specified in Ad26., Regulation (EC) No 1924/2006 allows the use of general and non-specific health claims (e.g. beneficial changes in response to aero-allergens) if accompanied by a specific claim (e.g. beneficial changes in response to pollen), and that, during the authorisation process (following publication of the EFSA opinion), applicants can negotiate with the European Commission on the use of alternative wordings which may also take into account consumer understanding and marketing needs.

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

Comment received:

67. Many comments were received regarding acceptable outcome variables for the scientific substantiation of health claims on the reduction (or beneficial alteration) of a risk factor for infections. Specific comments referred to:

a) The variables which could be accepted as risk factors for infections as long as evidence is provided for an effect of the food/constituent in reducing the risk of infections (e.g. "dysbalance of gut microbiota", changes in "groups/communities of intestinal microbiota", changes in relevant immune markers).

b) The variables which could be accepted as risk factors for infections even in the absence of evidence for an effect of the food/constituent in reducing the risk of infections (e.g. number of persons being colonised with pathogenic microorganisms after an intervention *vs.* placebo).

c) Could evidence for an effect of the food/constituent in reducing the risk of infections (clinical outcomes) be sufficient for the substantiation of these claims or should evidence on the reduction (or beneficial alteration) of a risk factor be provided as well? In this context, what to do if a risk factor for infections cannot be identified/measured (e.g. difficult to isolate and to measure the pathogenic agent responsible for upper respiratory tract infections)?

d) If evidence is provided for an effect of the food/constituent in reducing the risk of infections (clinical outcomes), could the health claim target the reduction in the incidence of disease (infections) directly?

Panel consideration of comment received:

Ad67. Section 3.2.2.2 of the draft guidance addresses general aspects to consider for the characterisation of the claimed effect for disease risk reduction claims, and Section 2.3.4.2 of this technical report addresses the comments received during the public consultation and how these have been considered in the guidance. In addition, Section 5.1 of the draft guidance provides extensive clarification regarding the scientific requirements for the substantiation of claims on the reduction (or beneficial alteration) of a risk factor for infections as follows:

"The scientific substantiation of health claims on the reduction (or beneficial alteration) of a risk factor for infections can be obtained from human intervention studies showing an effect on clinical outcomes related to infections (e.g. incidence, severity and/or duration of symptoms), together with the reduction (or beneficial alteration) of a risk factor for infections, preferably in the same studies (see Section 3.2.2.2).

In this context, evidence for an independent association between the risk factor and the incidence of infections and for the biological basis through which the risk factor can contribute to the development of infections needs to be provided. Such evidence will be evaluated by the NDA Panel on a case by case basis.

The presence of certain microorganisms (or an increase in the number of certain microorganisms) or their toxins at particular sites of the body has been independently associated with an increased risk of infections and there is evidence for the biological basis through which the risk factor can contribute to the development of infections. Examples include, but are not limited to, presence of toxigenic Clostridium difficile in the GI tract[53]*, and of uropathogenic E. coli strains in the urinary tract*[54, 55, 56]*.*

The scientific substantiation of health claims on the reduction (or beneficial alteration) of a well-established risk factor for infections could also be obtained from human intervention studies showing a reduction (or beneficial alteration) of a risk factor for infections by dietary

[53] http://www.efsa.europa.eu/en/efsajournal/doc/1903.pdf
[54] http://www.efsa.europa.eu/en/efsajournal/doc/943.pdf
[55] http://www.efsa.europa.eu/en/efsajournal/doc/1421.pdf
[56] http://www.efsa.europa.eu/en/efsajournal/doc/3657.pdf

intervention, and not necessarily on clinical outcomes related to infections (e.g. incidence, severity and/or duration of symptoms).

For less well established risk factors, additional evidence needs to be provided that a given modification by dietary intervention of the risk factor generally reduces the risk of infections. Such evidence will be evaluated by the NDA Panel on a case by case basis".

The NDA Panel acknowledges that a clear identification of pathogens responsible for a particular infectious disease is frequently hard to obtain, and that in practice clinical outcome variables are generally used such as incidence and/or severity of a well-characterised infectious disease in a well-described cohort of subjects receiving a particular nutritional intervention. However, it should be noted that for reduction of disease risk claims, the beneficial physiological effect (which Regulation (EC) No 1924/2006 requires to be shown for the claim to be permitted) is the reduction (or beneficial alteration) of a risk factor for the development of a human disease (not reduction of the risk of disease) (Section 3.2.2.2).

Alternatively, if evidence on the clinical outcome (e.g. incidence of, severity and/or duration of symptoms) related to infections is established, an Article 13(5) function claim (e.g. defence against pathogens) could be considered instead of a disease risk reduction claim.

As per Article 7(3) of Regulation (EU) No 1169/2011[57], the food information to consumers shall not attribute to any foodstuff the property of preventing, treating or curing a human disease; therefore health claims made on foods cannot refer to the prevention or treatment of a disease. In this regard, the clinical outcome itself (e.g. reduction of incidence of infections, such as common cold/upper respiratory tract infections) cannot be mentioned in a health claim. However, clinical outcomes related to infections may be used for substantiation of function claims on, for example, defence against pathogens, and for disease risk reduction claims if accompanied by evidence for the reduction (or beneficial alteration) of a risk factor for disease.

2.3.13. Claims on the reduction (or beneficial alteration) of a risk factor for allergy

Comments received:

68. It was asked whether circulating IgE levels such as skin prick test, degranulation responses (mast cells, basophil reactivity), as well as the level of sensitization to a number of allergens are considered valid 'risk factors' (if accompanied by an improvement in a clinical outcome). It was also asked why EFSA only plans to address risk factors for infection and allergy (as mentioned in the discussion paper).

Panel consideration of comment received:

Ad68. Circulating total or specific anti-food antigens IgE levels, skin prick tests, atopy patch tests, degranulation responses (mast cells, basophil reactivity), or other biomarkers of food sensitisation may be considered as risk factors for allergy if evidence is provided that a given modification of the risk factor (e.g. IgE, or degranulation responses) is accompanied by reduced incidence of the allergy following a specific dietary intervention, preferably in the same studies. However, no applications for claims on the reduction (or beneficial alteration) of a risk factor for allergy have been received by EFSA or considered by the Panel so far. The reason why EFSA has only addressed in the draft guidance claims on the reduction (or beneficial alteration) of a risk factor for infections is that only this type of claim has been submitted to EFSA to date.

[57] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011R1169&from=EN

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APPENDIX

Appendix A. EXPLANATORY TEXT FOR THE PUBLIC CONSULTATION ON A DRAFT DISCUSSION PAPER ON THE REVISION OF THE GUIDANCE ON THE SCIENTIFIC REQUIREMENTS FOR HEALTH CLAIMS RELATED TO GUT AND IMMUNE FUNCTION

EFSA has launched an open consultation on the Discussion paper on the revision of the guidance on the scientific requirements for health claims related to gut and immune function.

This document is a discussion paper released with the aim of collecting comments and suggestions from interested parties before drafting the guidance document. It proposes a plan for the revision, outlines the scope and issues to be covered in the revised guidance document, and proposes a timetable for finalising the guidance. The outcome of the public consultation together with new scientific evidence available to the NDA Panel and the experience gained with the evaluation of health claims will serve as a basis for revising the guidance document.

In line with EFSA's policy on openness and transparency and in order for EFSA to receive comments from the scientific community and stakeholders, EFSA has launched a public consultation on the draft document developed by the NDA Panel of EFSA.

Interested parties are invited to submit written comments by 10 September 2014. Please use exclusively the electronic template provided with the documents to submit comments and refer to the line and page numbers. Please note that comments submitted by e-mail or by post cannot be taken into account and that a submission will not be considered if it is:

- submitted after the deadline set out in the call
- presented in any form other than what is provided for in the instructions and template
- not related to the contents of the document
- contains complaints against institutions, personal accusations, irrelevant or offensive statements or material
- is related to policy or risk management aspects, which is out of the scope of EFSA's activity.

EFSA will assess all comments from interested parties which are submitted in line with the criteria above. The comments will be further considered by the relevant EFSA Panel and taken into consideration if found to be relevant.

All comments submitted will be published. Comments submitted by individuals in a personal capacity will be presented anonymously. Comments submitted formally on behalf of an organisation will appear with the name of the organisation.

Appendix B. FULL LIST OF COMMENTS RECEIVED ON DISCUSSION PAPER ON THE REVISION OF THE GUIDANCE ON THE SCIENTIFIC REQUIREMENTS FOR HEALTH CLAIMS RELATED TO GUT AND IMMUNE FUNCTION

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
BENEO-Institute	1. General considerations	Beneo welcomes EFSA's plan to revise the Guidance on the scientific requirements for health claims related to gut and immune function as well as the opportunity to provide comments and suggestions before drafting the guidance document. As pointed out in the corresponding Discussion paper for the revision (EFSA supporting publication 2014:EN-NNNN), the revision shall not be aimed at addressing and proposing new possible beneficial effects and/or studies/outcome measures which may be acceptable beyond those evaluated so far. Rather, it will be restricted to what has been evaluated to date. Clarifying the claimed effects already submitted and the scientific requirements for the scientific substantiation of those claims will be useful by itself. However, not addressing areas where new science has opened possibilities for new beneficial effects or outcome measures as well as approaches to assessing strength of data, seems to miss an opportunity. It is therefore suggested that the proposed scope of the revised guidance document is less restrictive and broadened in order to provide a clear guidance for those companies interested in advancing research in the area of gut and immune function and respective health claims. The Guidance document will presumably also after its revision not be intended to include an exhaustive list of beneficial effects and studies/outcome measures which are acceptable. In order to enable companies to gain feedback from the NDA panel on a research approach before launching expensive and time-consuming studies, an open pre-dialogue with EFSA to discuss scientific planning, methodologies, end points, study population etc is needed. This would help to decrease uncertainty for companies active in research and guide research and development in the desired direction. Hence, next to a revised Guidance document, an administrative framework allowing applicants to "troubleshoot" and get advice from the NDA panel whenever necessary needs to be created, e.g. in the context of the work of the Applications Desk.

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
DuPont	1. General considerations	We would like to emphasize the discrepancies between Europe and other areas of the world with regard to the evaluation criteria for nutrition and health claim on foods. The effort of food companies to get health claims on foods is a global activity, and we would like to avoid repeating similar expensive studies to adapt different requirements in different countries. Of equal importance, a guidance document of this type can only be properly implemented when interactive process for application and evaluation is made possible. Therefore we urge to include the concrete plan for procedural improvement in the revised guidance document, which in our opinion is a prerequisite for any substantial improvement.
Food Supplements Europe	1. General considerations	Food Supplements Europe welcomes the revision on this guidance and the opportunity to be consulted in a two-step approach.
Food Supplements Europe	1. General considerations	Food Supplements Europe would like to ask EFSA to take the opportunity of this revision to address the practicability of some of the criteria of the current guidance (e.g. relating to pathogens and infection) and to include in the accepted approach clarification on the value of non-clinical data in support of overall health benefits. Since this is of a general nature we think it is highly appropriate and would strongly support the development of new guidance documents on the scientific requirements for the substantiation of health claims.
Food Supplements Europe	1. General considerations	We would ask EFSA to illustrate every aspect of the guidance with relevant examples to increase the clarity. Although not specific for gut and immune function claims, the topic of appropriate validation requirements for questionnaires is important to be addressed.

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
Yakult Europe BV	1. General considerations	1. GENERAL COMMENTS PRIOR TO REVISION OF THE GUIDANCE DOCUMENT We greatly appreciate the initiative to revise the existing guidance document and we also realize, as indicated by EFSA, that it will be a step-by-step undertaking. We would like to emphasize that several fundamental points must be addressed and discussed prior to the technical revision of the guidance document. First of all, we consider it very essential that characteristics (i.e. differences and similarities) of food and medicine are precisely compared and appropriate methodology for evaluation a food study to be defined within the scope of HC. EU health claim (HC) regulation initiative is a regulation for food, aiming at protecting consumers from misleading and stimulating initiatives for food innovation and fair competition. Since GCP standard for medical products has been often referred to as the current standard for conducting human studies on food products. Such a comparison between food and medicine can form a matrix with the existing standard for 'evidence based medicine' to facilitate the definition to the standard for the 'evidence based food'. Otherwise EFSA would encounter in the process of revising and implementing the guidance document the repetition of earlier occurred problems. In the concrete comments here below, we also elaborate on this point with concrete examples. In addition, we would like to emphasize the discrepancies between Europe and other areas of the world with regard to the evaluation criteria for nutrition and health claim on foods. The effort of food companies to get health claims on foods is a global activity, and we would like to avoid repeating similar expensive studies to adapt different requirements in different countries. Of equal importance, a guidance document of this type can only be properly implemented when interactive process for application and evaluation is made possible. Therefore we urge to include the concrete plan for procedural improvement in the revised guidance document, which in our opinion is a prerequisite for any substantial improvement. 2. GENERAL COMMENTS ON EFSA STATEMENT DOCUMENT We think that a careful extension of the current statement document first needs take place on the basis of the reactions sent to EFSA by the stakeholders by 10 September, before EFSA proceeds with the actual revision of the guidance document.

ORGANISATION	CHAPTER TEXT	COMMENT TEXT
		The current statement document for discussion has a different structure than the original EFSA guidance document. In addition, we find some parts of the current document too abstract (for instance the part General Considerations which only includes titles without any explanation) to properly understand the intended scope and to give specific feedback for further discussion. The following parts are the concrete comments we have now on the current document. In principle we followed the structure of the statement document, but also added comments relevant for the content of the original guidance document 2011.
GAP/IPA/YLFA	1. General considerations	1. GENERAL COMMENTS PRIOR TO REVISION OF THE GUIDANCE DOCUMENT We greatly appreciate the initiative to revise the existing guidance document and we realise, as indicated by EFSA, that it will be a step-by-step undertaking. We would like to emphasise that several fundamental points must be addressed and discussed prior to the technical revision of the guidance document. First of all, we consider it very essential that characteristics (i.e. differences and similarities) of food and medicine are precisely compared, and appropriate methodology for the evaluation of a food study should be defined within the scope of a health claim (HC). The EU HC regulation initiative is a regulation for food, aimed at protecting consumers from misleading information and stimulating initiatives for food innovation and fair competition. Since the GCP standard for medical products has often been referred to as the current standard for conducting human studies on food products, such a comparison between food and medicine can form a matrix with the existing standard for 'evidence-based medicine' to facilitate the definition of the standard for 'evidence-based food'. Otherwise, in the process of revising and implementing the guidance document EFSA would encounter the repetition of previously experienced problems. In the concrete comments here below, we also elaborate on this point with concrete examples. In addition, we would like to emphasise the discrepancies between Europe and other areas of the world with regard to the evaluation criteria for nutrition and health claim on foods. The efforts of food companies to obtain health claims on foods is a global activity, and we would like to avoid repeating similar expensive studies to adapt different requirements in different countries. Of equal importance, a guidance document of this type can only be properly implemented when interactive processes for application and evaluation are made possible. Therefore, we urge the inclusion of a concrete plan for procedural improvements in the revised guidance document, which, in our opinion, is a prerequisite for any substantial improvement.

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		2. COMMENTS ON EFSA STATEMENT DOCUMENT We think that a careful extension of the current statement document first needs to take place on the basis of reactions received by EFSA from stakeholders, before EFSA proceeds with the actual revision of the guidance document. The current statement document for discussion has a different structure to the original EFSA guidance document. In addition, we find some parts of the current document too abstract (for instance, the section 'General Considerations', which only includes titles without any explanation) to properly understand the intended scope and to give specific feedback for further discussion. The following parts are concrete comments we have now on the current document. In principle, we followed the structure of the statement document, but also added comments relevant to the content of the original guidance document of 2011.
analyze&realize GmbH	1.1. Suitability of the study population	Esophageal discomfort describes a group of conditions that is presented with symptoms presumed to originate in the esophagus such as reflux and heartburn. Heartburn is usually associated with regurgitation of gastric acid (gastric reflux), which is the major symptom of gastro-esophageal reflux disease (GERD). While GERD is a collective term embracing all disorders caused by gastro-esophageal reflux (Vakil et al., Am J Gastroenterol, 101, 2006), heartburn describes symptoms of gastro-oesophageal discomfort induced by reflux of distinct origin. Based on ROME III criteria functional heartburn is defined as a burning retrosternal discomfort or pain in the absence of evidence that gastro-esophageal acid reflux is the cause of the symptom. Would subjects with functional heartburn be a suitable study group?
Association of the Self-Medication Industry (AESGP)	1.1. Suitability of the study population	Reference: 'EFSA Guidance on the scientific requirements for health claims related to gut and immune function', section 2.1, page 5: "The NDA panel considers that the population group for which the claims are intended is the general (healthy) population or specific subgroups thereof, for example, elderly people, physically active subjects, or pregnant women." Reference: 'EFSA Guidance on the scientific requirements for health claims related to gut and immune function', section 3.1, page 6: "Irritable Bowel Syndrome (IBS) patients or subgroups of IBS patients with constipation are generally considered an appropriate study group to substantiate claims on bowel function intended for the general population (adults and children)."

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		Comment: EFSA is kindly requested to clarify why IBS patients are considered an appropriate study group for claims for the general population and whether the following subgroups are also considered appropriate in this context: symptomatic uncomplicated diverticular disease (SUDD), self-claimed constipation and functional gastrointestinal (GI) symptoms, obese (e.g. BMI >30), populations at higher risk e.g. with poor diets or food intolerances, occasional diarrhoea, traveller's diarrhoea.
BENEO-Institute	1.1. Suitability of the study population	The current Guidance document (EFSA Journal 2011; 9(4):1984) identifies patients with IBS (or subgroups) as an appropriate study group to substantiate claims on bowel function and gastrointestinal discomfort intended for the general population (adults and children). Concerning Claims related to other health benefits, such as defence against pathogens, reduction of a risk factor for infection or claims on the function of the immune system, however, information on the suitability of a particular study population or a selected at-risk subpopulation (see e.g. Albers et al Br J Nutr 2013) for claims intended for the general population is largely missing. It would thus be helpful to include in the revised Guidance document further examples on what study population group is sufficient or suitable. For instance, whether or not a) healthy people that are challenged (e.g. by travelling to high risk countries, by receiving attenuated pathogenic bacterial or viral strains, by experiencing physical stress (e.g. endurance exercise)), or b) non-healthy people receiving antibiotics (as in case of C. diff. associated diarrhea) are a suitable model system and study population to show a health benefit for the general population.
Biothera	1.1. Suitability of the study population	Biothera believes that use of a subset of a normal healthy population that is "enriched" should be considered appropriate as a model of the general population when studying the effect of immune enhancing ingredients. Selecting for healthy normal adults who experience elevated levels of either physical or psychological stress, for example, results in a population that is more prone to the occurrence of cold symptoms and allows a study to be properly powered to measure a reduction in those symptoms based on a smaller overall sample size compared to a "general" population. This is analogous to the way in which data was generated on the roles of Vitamins A, C, D & E in supporting immune function were based on measuring their effects in vitamin deficient populations. The US FDA supports the use of enriched study populations to support claims for functional ingredient and in drug efficacy studies. (US FDA, Enrichment Strategies for Clinical Trials Dec 2012)

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Chr Hansen	1.1. Suitability of the study population	1.1. 1.Clarity is needed regarding populations under antibiotic treatment. How can effects on diarrhea in a population under antibiotic treatment be translated into a health claim? Will a health claim be limited to the study population? What is needed to allow for extrapolation to the general population. In addition to clinical effects, which parameters should be addressed? 2.Athletes. If the study target is of relevance to the general population, can athletes be used as a model for the general population for claims related to the immune function? 3.Allergy. Clarity is needed on how studies should be designed in order to address quality of life and symptom improvement in people with allergy. Can claims be addressed specifically to people with allergy symptoms and what type of claims would be possible. 1.3 1. Clarity is needed regarding the use of questionnaires for establishment of the infectious nature of a disease. Which existing questionnaires are considered appropriate for this use?
DANONE	1.1. Suitability of the study population	1.1. In the current guidance, NDA panel considers that where a health claim relates to a function/effect which may be associated with a disease, subjects with the disease are not the target population for the claim. However guidance also indicates that Irritable Bowel Syndrome (IBS) patients or subgroups of IBS patients with constipation are generally considered an appropriate study group to substantiate claims on bowel function intended for the general population. The guidance finally indicates that some dedicated discussions are on going in Europe on the subject. the subject of ongoing discussions with the Commission and Member States with regard to their admissibility. The new guidance should provide information on the results of discussions and indicate which others specific populations with associated criteria for eligibility are relevant for claims on the general population. New guideline should indicate whether a study is pertinent when performed on subjects with a pathology unrelated to the claimed effect but which increases their susceptibility to the targeted disease and therefore ease the clinical demonstration of the product effect. In that case, could this population be used for a claim on the general population? In an opinion on maintaining normal defecation the target population was adults and children healthy outpatient on oral antibiotic treatment (EFSA Journal 2013;11(6):3256). Panel noted that from two of the studies (Szajewska 2009, Arvola 1999) conclusions could have been drawn if they had shown a significant effect on the incidence of diarrhea resulting from antibiotic treatment. This intends that the populations included in these studies, i.e. children under triple therapy for Helicobacter pylori eradication (Szajewska

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		2009) or under antibiotics treatment for respiratory infections (Arvola 1999), and hospitalized (Szajewska 2009) or outpatients (Arvola 1999), were suitable for a claim substantiation on healthy outpatients on oral antibiotic treatment. This possibility of transposition from study diseased (infected) population to healthy population and from hospitalized to outpatients population should be clearly stated in the new guidelines, even if restricted to this specific claim. New guidance should also confirm whether the same approach could be used for adult population. It may be mentioned whether the targeted population should be restricted to subjects under antibiotic treatment or whether general population can be targeted considering that antibiotic-associated diarrhea has been described to be due to alteration of the gut microbiota which is subsequently responsible for both infectious and osmotic diarrheal episodes, a sequence of mechanistic events that may occur in other conditions in the absence of drug intake. In another scientific opinion (EFSA Journal 2011;9(6):2167), panel noted that, out of the five human intervention studies from which conclusions could be drawn for the scientific substantiation of the health claim, only one showed an effect on the incidence or duration of GI infections in hospitalized children. This last opinion further supports the possibility in specific cases to include hospitalized population in studies for claim substantiation on the general population. This case should be clearly described as an opportunity in the new guidanceAt last, during the last EFSA consultation, NDA panel indicated that extrapolation from studies conducted in non-European populations are in principle acceptable if biologically justifiable and that it is the responsibility of the applicant to provide justification on e.g. extrapolation of study population and that provided references are taken into account in the judgment of the Panel. This statement should be added in the new guidance.
Mondelez International	1.1. Suitability of the study population	• Could the EFSA clarify in which conditions subjects with a disease are considered as an appropriate study group to demonstrate a claim intended for the general population? • Could the EFSA provide some example on how the results from a study group other than the general population (specific subgroups of the general population or disease subjects) can be extrapolated to the general population? • Could the EFSA provide a clear definition of which subjects are considered as part of the “general (healthy) population” and provide some examples? • Has the admissibility of applications for claims intended for specific target groups other than the general population been clarified?

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Morinaga Milk Industry Co., Ltd.	1.1. Suitability of the study population	1.1. Suitability of the study population < Collection of clinical data > At present, only data on healthy subjects is considered. However, healthy subjects possess a proper immune balance giving them adequate immune functions. It is basically thought not possible to collect clinical data with relation to immune functions from such subjects and clinical trials on immune function derived from probiotics are largely conducted with the elderly, hospital patients and those whose immune balance is disrupted. We wish that such data can be included for evaluation. < Number of subjects for clinical trial > Though there is some discussion of using 1000 subjects for the clinical trial, we believe is not best to focus on the number. Even if we included only 100 subjects and followed a well designed approach, this would provide meaningful clinical data that provide sufficient information for proper evaluation. Further, rather than conducting one large scale trial, we believe that several medium scale trials would provide the opportunity to reconfirm results lending more credence to the data. < Ethnic group > We also would like to ask NDA panel member simultaneously to accept not only clinical data of European people but also other ethnic group, such as data on Japanese subjects, to clarify the biomarkers, application procedures and evaluation criteria and etc..
Yakult Europe BV	1.1. Suitability of the study population	In the 2011 document, it is stated as 'case-by-case', when subjects with a disease would be the study group. We strongly propose EFSA to provide a more extensive list of examples for possible study populations for health claim and the condition of use of these population in the new document, i.e. otherwise healthy/general population, diseased population, hospitalized population, non-European population etc. As a concrete example, can we discuss that a disease risk reduction proven in a study group consisting of patients but not having the disease which is the target of the claim should be accepted? For instance, hospitalized patients due to injury who are undergoing antibiotic treatment. Can this study population be used for health claims re risks associated with antibiotic use? Can other widely used drugs be considered in this

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		category – e.g. PPI, aspirin (stomach damage), etc? Suitability of target groups other than the general (healthy) population to substantiate a claim on general population were going to be subject of ongoing discussions with the EU Commission. What has been the outcome of such discussions initiated in 2011?
GAP/IPA/YLFA	1.1. Suitability of the study population	In the current guidance, it is stated as 'case-by-case', when subjects with a disease would be the study group. We strongly propose that EFSA provide a more extensive list of examples for possible study populations to be used for health claims and the conditions of use of these populations in the new document, i.e. otherwise healthy/general population, diseased population, hospitalised population, non-European population, etc. The guidance finally indicates that *applications for claims which specify target groups other than the general (healthy) population are the subject of ongoing discussions with the Commission and Member States with regard to their admissibility*. **The new guidance should provide information on the results of these discussions and indicate which other specific populations, with associated criteria for eligibility, are relevant for claims on the general population.** New guidelines should indicate whether a study is pertinent when performed on subjects with a pathology unrelated to the claimed effect but which increases their susceptibility to the targeted disease and **therefore ease** the clinical demonstration of the product effect**.** Study populations should not be limited to a specific category of health status, but instead should be chosen based on their ability to effectively demonstrate the health benefit most appropriate to support the desired claim. **In that case, could this population be used for a claim on the general population?** For instance, patients hospitalised due to injury who are undergoing antibiotic treatment. Can this study population be used for health claims regarding risks associated with antibiotic use? Can other widely used drugs be considered in this category – e.g. PPI, aspirin (stomach damage), etc? EFSA should elaborate on where other populations may function as models for the general population; e.g. elderly and immune function (notwithstanding, of course, that we have a lack of validated biomarkers for immune). Comments on specific populations: - Athletes: If the study target is of relevance to the general population, can athletes be used as a model for the general population for claims related to the immune function?

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		- Allergy: Clarity is needed on how studies should be designed in order to address quality of life and symptom improvement in people with allergy. Can claims be addressed specifically to people with allergy symptoms and what type of claims would be possible?
DANONE	1.2. Evaluation of claims related to essential nutrients compared to non-essential nutrients	1.2.1.2. Evaluation of claims related to essential nutrients compared to non-essential nutrients It is indicated by EFSA that the NDA Panel adopts a similar approach for its evaluation of health claims under articles 13(5) and 14(1) and under article 13(1) of Regulation (EC) 1924/2006, with some differences in the procedural section. Equally, EFSA has indicated that it does not differentiate its assessment between essential and non-essential nutrients, However, the practice from EFSA for many of the health claims authorized for essential nutrients included in the Article 13(1) list (Regulation 432/2012) have been accepted despite the related opinions of the NDA-Panel stating that the evidence provided does not establish that inadequate intake of the substance leading to the health-related benefit occurs in the general EU population but also substantiated by generally accepted scientific evidence (extensive body of knowledge of the role and mechanisms played by these nutrients in various metabolically importa nt processes), as opposed to well-controlled clinical intervention studies in humans. - Manganese and protection of DNA, proteins and lipids from oxidative damage (ID 309, 310, 311,340) - Manganese and maintenance of bone - Copper and the normal function of the immune system - Chromium and contribution to normal macronutrient metabolism Chromium and maintenance of normal blood glucose concentrations Considering the positioning of NDA panel on these opinions, The new guidance should clarify the apparent contradictions in the positions between essentials and non essentials evaluation process.
DuPont	1.2. Evaluation of claims related to essential nutrients compared to non-essential nutrients	• Suitability of target groups other than the general (healthy) population to substantiate a claim on general population were going to be a subject of ongoing discussions with the EU Commission. What has been the outcome of such discussions initiated in 2011? We ask EFSA to include the outcome of this discussion in the renewed guidance document. • We strongly propose EFSA to provide a more extensive list of examples for possible study populations to be used for health claim and the condition of use of these populations in the new document • What does "other than general (healthy) population" mean: Diseased population?, hospitalised population?,

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		non-European populations? • Clarity is needed regarding populations under antibiotic treatment. How can effects on diarrhea in a population under antibiotic treatment be translated into a health claim? Will a health claim be limited to the study population? What is needed to allow for extrapolation to the general population? In addition to clinical effects, which parameters should be addressed? • Athletes. If the study target is of relevance to the general population, can athletes be used as a model for the general population for claims related to the immune function? • Allergy. Clarity is needed on how studies should be designed in order to address quality of life and symptom improvement in people with allergy. Can claims be addressed specifically to people with allergy symptoms and what type of claims would be possible. • Children should be included in the definition of "general healthy population". Meaning that it should, under certain circumstances, be possible to extrapolate a benefit demonstrated in adults to children, when there is no reason to assume age has an influence or risk. • Study populations should not be limited to a specific category of health status, but instead should be chosen based on their ability to effectively demonstrate the health benefit most appropriate to the support the desired claim
DuPont	1.2. Evaluation of claims related to essential nutrients compared to non-essential nutrients	We would strongly propose for a guidance document dedicated for non-essential nutrient claims, which should sufficiently acknowledge the characteristics of this category in relation to the health maintenance to base the new guidance document on. - Essential nutrients and non-essential nutrients have different contribution to the health. Lack of essential nutrients result in deficiencies, while it is not the case with non-essential nutrients. However, non-essential nutrients whose effects are mostly subtle and needs longer period of intake to manifest a potential way of maintaining health/reducing disease risk.

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Mondelez International	1.2. Evaluation of claims related to essential nutrients compared to non-essential nutrients	Could the EFSA clarify if scientific dossiers and scientific requirements will differ between these 2 categories of claim subjects?
Nestlé S.A.	1.2. Evaluation of claims related to essential nutrients compared to non-essential nutrients	It is not apparent which issue EFSA wishes to address by having a chapter relating to essential nutrients compared to non-essential nutrients in the upcoming revised guidance on scientific requirements for health claims related to gut and immune function. The EU regulation (EC) No 1924/2006 does not differentiate between essential and non-essential nutrients. Health Claims can be made for a food category, a food or one if its constituents. According to Article 2(2) No 2 and 3 respectively, "nutrients" are "protein, carbohydrate, fat, fibre, sodium, vitamins and minerals (…)" and "other substance" is a substance other than a nutrient that has a nutritional or physiological effect. If this chapter indeed relates to nutrients as defined by the regulation, the substantiation of a health claim should in principle follow similar criteria, independent of essentiality. Having a "beneficial effect" is leading. This beneficial effect is not limited to vital functions only, but includes effects that can improve health status. If the topic is rather related to the permissibility of a claim (relating to optional / mandatory ingredients), Nestlé is of the opinion that this should be addressed by policy makers, not EFSA. In essence, Nestlé questions the necessity of this chapter to be included in this specific guidance on the scientific substantiation of Health Claims related to gut health. If EFSA considers this topic vital, it could be addressed in the EFSA's "General guidance for stakeholders on the evaluation of 13.1., 13.5 and 14 health claims" – unless specific guidance for gut health and immune function can be given that is also in line with the regulation.

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Yakult Europe BV	1.2. Evaluation of claims related to essential nutrients compared to non-essential nutrients	We would strongly propose for a guidance document dedicated for non-essential nutrient claims, which should sufficiently acknowledge the characteristics of this category in relation to the health maintenance to base the new guidance document on. Our proposal is based on the following considerations: - While the scope of essential nutrient claims has been mostly established (similar to medicinal products), that for non-essential nutrients is relatively new. - Essential nutrients and non-essential nutrients have different contribution to the health. Lack of essential nutrients result in severe health problems/diseases, while it is not the case with non-essential nutrients. However, non-essential nutrients whose effects are mostly subtle and needs long period of intake to manifest represent a potential proactive way of maintaining health/reducing disease risk.
GAP/IPA/YLFA	1.2. Evaluation of claims related to essential nutrients compared to non-essential nutrients	It is indicated by EFSA that the NDA Panel adopts a similar approach for its evaluation of health claims under articles 13(5) and 14(1) and under article 13(1) of Regulation (EC) 1924/2006, with some differences in the procedural section. Equally, EFSA has indicated that it does not differentiate its assessment between essential and non-essential nutrients. We would strongly suggest a guidance document dedicated to non-essential nutrient claims, which should sufficiently acknowledge the characteristics of this category in relation to the health maintenance, on which the new guidance document would be based. Our proposal is based on the following considerations: - While the scope of essential nutrient claims has been mostly established (similar to medicinal products), that for non-essential nutrients is relatively new - Essential nutrients and non-essential nutrients have different contributions to health. Lack of essential nutrients results in severe health problems/diseases, while it is not the case with non-essential nutrients. However, non-essential nutrients whose effects are mostly subtle and needs long period of intake to manifest itself represent a potential proactive way of maintaining health/reducing disease risk.

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analyze&realize GmbH	1.3. Considerations on the validity of tools used to measure outcomes (e.g. questionnaire)	There is still uncertainty about validated and appropriate tools for function claims related to defence against pathogens particularly with regards to the identification of common cold episode and severity. The Wisconsin Upper Respiratory Symptom Survey (WURSS) is an illness-specific health-related quality of life questionnaire outcome instrument designed to assess symptomatic and functional impairment caused by URTI but not the incidence. Both, the long (WURSS-44) and short (WURSS-21) versions have been validated and are reliable and responsive (Barrett et al., J Clin Epidemiol, 58, 2005). Another widely used questionnaire is the so-called Jackson scale assessing eight common cold related symptoms but the validity, reliability and responsiveness have not been thoroughly assessed (Jackson et al., AMA Arch Intern Med, 101, 1958) We assume that, WURSS-11, WURSS-21 and WURSS-44 could be a suitable method assessing the severity of a common cold? Would EFSA accept the Jackson Score as a reliable and valid to ol for the assessment of common cold incidence and severity?
Association of the Self-Medication Industry (AESGP)	1.3. Considerations on the validity of tools used to measure outcomes (e.g. questionnaire)	Reference: 'EFSA Guidance on the scientific requirements for health claims related to gut and immune function', section 2.2, page 6: "Whether the studies used (an) appropriate outcome measure(s) of the claimed effect. For this, the NDA Panel considers what is generally accepted in the relevant research fields, and consults experts from various disciplines, as appropriate." Comment: EFSA is kindly requested to further clarify the meaning of "generally accepted" and whether the following tools and methods would be considered as "generally accepted": Bristol stool scale, Rome criteria. The applicants would find helpful if some examples of not-accepted methods are provided together with reasons for their non-acceptance. Reference: 'EFSA Guidance on the scientific requirements for health claims related to gut and immune function', section 3.2, page 7: "Validated general "quality of life questionnaires" alone are insufficient as outcome measures, but may provide indirect evidence for claims on gastro-intestinal discomfort. Comment: EFSA is kindly requested to clarify why validated general "quality of life questionnaires" are not accepted as appropriate outcome measures.

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		Reference: 'EFSA Guidance on the scientific requirements for health claims related to gut and immune function', section 3.1, page 7: "Diarrhoea is not considered in the context of claims related to bowel function for the general population, but may be used as an outcome measure for other claims, for example, claims related to defence against pathogens in the gastro-intestinal tract." Comment: EFSA is kindly requested to clarify why diarrhoea is not considered in the context of bowel function claims.
Biothera	1.3. Considerations on the validity of tools used to measure outcomes (e.g. questionnaire)	Choosing specific outcome measures in a study designed to demonstrate a risk reduction for an infectious event is difficult and past EFSA opinions have not clarified the selection of outcome measures in this area (EFSA NDA Panel Scientific Opinions on Yestimun Claims 2010 and 2013). Is EFSA willing to provide a specific list of approved outcome measures that can be used to substantiate a risk reduction claim?
DANONE	1.3. Considerations o n the validity of tools used to measure outcomes (e.g. questionnaire)	1.3. 1.3. Considerations on the validity of tools used to measure outcomes (e.g. questionnaire) In the current guidance, NDA panel provides a list of appropriate outcomes related to claims on bowel function, gastro-intestinal discomfort and defense against pathogens.The guidance specifies that these outcomes should be measured by generally accepted methods including validated questionnaire-based assessments. Several scientific opinion from NDA panel rejected claims arguing, among other criticisms, that the applicant did not establish the validity of the questionnaire used (most recent opinions: EFSA Journal 2013;11(4):3159, EFSA Journal 2014;12(5):3658, EFSA Journal 2014;12(5):3659). NDA panel also emphasized that the previous use of a questionnaire/scale is not necessarily a proof of validity (EFSA Journal 2014;12(5):3658). On the other hand, it might be acceptable that clinical outcomes frequency be measured based on self-reporting of well-defined and sufficiently objective parameters such as daily stool frequency and consistency in the case of diarrhea. In the absence of appropriate validated biological markers for the reduction of GI discomfort, Patient-Reported Outcomes (PRO) (e.g. questionnaires) have been reported as an appropriate measure for symptom assessment because they are subject to lower measurement error than physician reported assessment (Irvine et al., 2006). Nevertheless, they should not be used as a stand-alone measure. In any case, the used PRO questionnaires should be valid, responsive and relevant for the population of interest (eg population type, language). Theoretically, PROs should be completely and rigorously validated, but there is a lack of instruments to make

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		such validation, including in the IBS field and even more when considering PRO for the general population. Therefore, to use at least partially validated instruments may be the best option, provided that the use of such PROs is justified on the basis of the adequacy of the outcomes to fit with the target claim (e.g. reduc tion of GI discomfort). To this end FDA (2006) and EMA (2005) have issued guidelines on PRO validation, use and interpretation. Such documents dealt with medicinal products and indicate a preference for instruments focused on disease-specific measures of symptom severity rather than on assessing functions and other aspects of health (Coon et al., 2013: FDA guidance on IBS, 2010), which may limit their applicability in the context of foods. The validity of tools being a key aspect of the demonstration of the health relationship and the development and qualification of new P.R.O. (for example in the case of diarrhea), as well as for objective measure (eg measure of intestinal gas with breath test or imaging methods), taking time and evolving with time. We believe that while waiting for the publication of a positive list, applicants must be allowed to discuss with EFSA about the validity of the PRO they are planning to use in human studies before the launch of these studies. This process used since many years in pharmacology will avoid the use of inappropriate outcomes and ensure adequate study design vs. ESFA‘s expectations.
DuPont	1.3. Considerations on the validity of tools used to measure outcomes (e.g. questionnaire)	• A wealth of literature exists on probiotics, that was published before the requirement of validated questionnaire existed. It must be possible to utilise these 30 years of studies to substantiate claims similarly as was done for e.g. vitamins and minerals.. • There should be an emphasis on evaluating the totality of evidence. This would include weighting of data not necessarily conforming to current 'best practice', as proposed by the World Health Organization. It is important that we do not reject a vast majority of the data generated during the last 30 years of research into digestive and immune health • How is EFSA evaluating Post hoc analysis (old studies not on line with the current standards)? Can EFSA formalise its position on that regard?
DuPont	1.3. Considerations on the validity of tools used to measure outcomes (e.g. questionnaire)	What is needed to validate a questionnaire? Are there "validated" questionnaires recognized as acceptable by EFSA in previous guidelines and/or opinions? We strongly propose EFSA to provide an extensive list for validated questionnaires or/and clear criteria/procedure for validation. Due to the lack of objective biomarkers in this area, we also propose to allow expert accreditation of any new

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		tool in case no validated questionnaire is available.
Mondelez International	1.3. Considerations on the validity of tools used to measure outcomes (e.g. questionnaire)	• If no validated questionnaire exists on the general (healthy) population, would the EFSA consider validated and recognized questionnaires for diseased population? If not should we create adapted questionnaires validated on the target population? • Will the EFSA accept new questionnaire validated on the appropriate target population but not widely used in the scientific community at the time of the dossier submission?
Nestlé S.A.	1.3. Considerations on the validity of tools used to measure outcomes (e.g. questionnaire)	Nestlé suggests that EFSA specify the criteria it applies to decide whether a questionnaire is considered validated and provides examples of validated questionnaires for different types of claims, like PAC-SYM for constipation (Camilleri et al., 2008). We also suggest that different validated questionnaires in successive studies are acceptable if they evaluate the same benefit. Furthermore EFSA considers validated Quality of Life (QoL) questionnaires specific for a given conditions as valid outcome measures, such as the PAC-QoL questionnaire for constipation (Camilleri et al., 2008), and considers generic Health-Related Quality of Life outcome measures such as the Infant Toddler Quality of Life Questionnaire© (HealthActCHQ Inc., Boston, MA, USA). Camilleri M, Kerstens R, Rykx A, Vandeplassche L (2008). A placebo-controlled trial of prucalopride for severe chronic constipation. N Engl J Med. 358(22):2344-2354.

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Yakult Europe BV	1.3. Considerations on the validity of tools used to measure outcomes (e.g. questionnaire)	What is needed to validate a questionnaire? Are there "validated" questionnaires recognized as acceptable by EFSA in previous guidelines and/or opinions? We strongly propose EFSA to provide an extensive list for validated questionnaires or/and a clear criteria/procedure for validation. Due to the lack of objective biomarkers in this area, We also propose to allow expert accreditation of any new tool in case no validated questionnaire is available.
GAP/IPA/YLFA	1.3. Considerations on the validity of tools used to measure outcomes (e.g. questionnaire)	In the current guidance, the NDA panel provides a list of appropriate outcomes related to claims on bowel function, gastro-intestinal discomfort and defence against pathogens. The guidance specifies that these outcomes should be measured by generally accepted methods, including validated questionnaire-based assessments. However, several scientific opinions from the NDA panel have rejected claims arguing, among other criticisms, that the applicant did not establish the validity of the questionnaire used. Therefore, the new guidance should indicate what type of validation is needed for questionnaires to be considered acceptable measures in support of health claims. Moreover, considering the fact that a wealth of literature exists on probiotics, which was published before the requirement of validated questionnaires existed, it must be possible to utilise these 30 years of studies to substantiate claims, similarly as was done for, e.g., vitamins and minerals conforming to current 'best practice', as proposed by the World Health Organisation. It is important that we do not reject a vast majority of the data generated during the last 30 years of research into digestive and immune health. Nevertheless, while regarding the acceptance of a claim on lactose, where post hoc analysis (old studies not in line with the current standards) were accepted to substantiate the claim, the **new guidance should formalise a position in that regard**.
Association of the Self-Medication Industry (AESGP)	1.4. Appropriate reporting of human studies	Reference: 'EFSA Scientific and technical guidance for the preparation and presentation of an application for authorisation of a health claim (revision 1)', section 3.3, page 21: "(…) the study population in which the effect has been observed and whether it is representative of the target population (…)" Comment: It would be useful to indicate what the required minimum size of the study group and minimum duration of the study would be considered as appropriate. Comment: It would be useful to indicate whether the studies among the following groups can be used for claims for the general population: self-claimed constipation, obese subjects (e.g. BMI >30), populations at

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		higher risk e.g. with poor diets or food intolerances, claimed occasional diarrhoea and claimed occasional traveller's diarrhoea. Reference: 'EFSA Scientific and technical guidance for the preparation and presentation of an application for authorisation of a health claim (revision 1)', section 3.3, page 21: "(…) the sustainability of such effect over time (…)." Comment: EFSA is kindly requested to further clarify what period of time would be considered as sustainable, preferably illustrated with some examples.
DANONE	1.4. Appropriate reporting of human studies	Not commented
DuPont	1.4. Appropriate reporting of human studies	We would propose EFSA to give a guidance as to how a study should be presented for a dossier. A list of items that must be mentioned when reporting the study would be very useful. In this regard, it would be very useful if EFSA could introduce grading/scoring system (eg Jadad scoring system) to evaluate individual studies and to base the final conclusion on. Meta-analyses should be accepted in their totality, and should not be dissected down per study. Appropriate weighing of supporting studies based on their significance is part of the meta-analysis process. In addition, we would like to address the following items (which are not mentioned in the current document but was addressed in the guidance document of 2011): • Physiological effect We would like to have more clarification as to what is the exact definition of 'physiological effect', in particular in the context for food? • Independent predictor

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		What does the word "independent" mean exactly? We would strongly propose EFSA to provide an extensive list of 'independent predictors' that are acceptable for EFSA and what the alternatives are in absence of such predictors. Handling of data claimed as confidential Can EFSA make public information classified by the applicant as confidential and in affirmative case under which conditions? This is mainly relevant when submitting results of studies not yet published. Publication of studies is desirable from a transparency standpoint. It must be possible to use published studies in a dossier and still claim proprietary data.
Mondelez International	1.4. Appropriate reporting of human studies	• Does it mean that the EFSA will refer to the EFSA report on the "Technical meeting on the reporting of human studies submitted for the scientific substantiation of health claims" held in Parma on 20 November 2013 and to the guidance document on statistical reporting?
Nestlé S.A.	1.4. Appropriate reporting of human studies	Similar to handling of confidential data (see Nestlé comments in chapter 1.5.), Nestlé recommends that general recommendation on the reporting of human studies should be covered by the EFSA guidance on statistical reporting. Guidance on reporting of human studies in relation to this consultation should focus on specific requirements relating to health claims on gut health and immune function only. In this context, Nestlé suggests that when dealing with micro-organisms, publications and clinical trial protocols should refer to the deposit number of the strain in an internationally recognised culture collection.
Yakult Europe BV	1.4. Appropriate reporting of human studies	We would propose EFSA to give a guidance as to how a study should be presented for a dossier. A list of items that must be mentioned when reporting the study would be very useful.

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		In this regard, it would be very useful if EFSA could introduce grading/scoring system (eg Jadad scoring system) to evaluate individual studies and to base the final conclusion on. How will the past studies that have once been submitted be treated, in particular when companies did not have the chance to submit the full data or when one part of a human study is considered not sufficient as evidence? In addition, we would like to address the following items (which are not mentioned in the current document but was address in the guidance document of 2011): • Physiological effect We would like to have more clarification as to what is the exact definition of 'physiological effect', in particular in the context for food? The explanation for this proposal: Except for the examples indicated by EFSA like IBS, constipation, reduction of incidence of diseases (physiological effect) could easily fall outside the scope of health claim, because of its 'medicinal character'. At the same time, changes of biomarkers, unless they are proven to be 'independent predictor' for diseases are also not entitle for the health claim. In this way, very little possibility remains for a food product to claim a health effect. What is the concrete solution of EFSA to this? •Independent predictor What does the word "independent" mean exactly? We would strongly propose EFSA to provide an extensive list of 'independent predictors' that are acceptable for EFSA. In this regard, we also would like EFSA to take into consideration the limited number of such predictors and the differences between food and medicine in this regards. • Appropriate study and study outcomes We propose EFSA to properly address the importance of epidemiological studies, observational studies and studies in the past which do not meet the modern standard but peer-reviewed and demonstrated unequivocal effect of the product. We expect more specific guidance in this regard than only 'case by case' approach.

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		The explanation for this proposal: Randomised (placebo-)controlled interventional trial (RCT) has been considered in general as the highest in the hierarchy of studies by EFSA to substantiate a claim (with exception of essential nutrients like vitamins). RCT could be true for a medicinal product, as long as it is ethically approved, to demonstrate a clinical outcome. However, In case of food consumed by a 'general population' other than patients, the effect is mostly mild and often manifests itself over a long period of consumption. Epidemiological studies and observational studies are as important. In addition, due to the texture of the food product, it is not always possible to have a double-blinded trial design. EFSA treated open label trials as valid in case of vitamin and minerals. We think that such consideration should also be given to other categories as well.
GAP/IPA/YLFA	1.4. Appropriate reporting of human studies	We would propose that EFSA give guidance as to how a study should be presented for a dossier. A list of items that must be mentioned when reporting the study would be very useful. In this regard, it would be very useful if EFSA could introduce a grading/scoring system (e.g. Jadad scoring system) to evaluate individual studies and on which to base the final conclusion. During the last plenary session in Parma, most recent standards for assessing quality of reporting were discussed (Prisma, Probe, …) but questions remain as to how past studies that have once been submitted will be treated, in particular when companies did not have the chance to submit the full data or when one part of a human study is considered not sufficient as evidence. The new guidance should also clarify how a meta-analysis made under Prisma statement will be analyzed by the panel: it should be accepted in its totality, and should not be dissected down per study. Appropriate weighing of supporting studies based on their significance is part of the meta-analysis process. Guidance on EFSA's position vis-à-vis epidemiological studies, observational studies is required, particularly when such studies have been peer-reviewed and have demonstrated an unequivocal beneficial effect of the product/substance. A case-by-case approach does not provide guidance on EFSA's criteria for accepting the same or not. EFSA treated open label trials as valid in the case of vitamins and minerals. We think that such consideration should also be given to other categories, as well assuming that the NDA Panel adopts a similar approach for its evaluation of health claims under articles 13(5) and 14(1) and under article 13(1) of Regulation (EC) 1924/2006.

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Association of the Self-Medication Industry (AESGP)	1.5. Handling of data which are claimed as confidential	Reference: 'EFSA General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims', section 12.2.2, page 21: "The decision on the protection of proprietary data falls within the responsibility of the European Commission." Comment: Although a decision on the protection of proprietary data falls within the responsibility of the European Commission, it would be appreciated to have a more detailed clarification on the requirements needed for data exclusivity, e.g. whether data exclusivity can be granted to an applicant-specific strain. It should be noted in this context that production of consistent and reproducible results to prove a beneficial physiological effect involves significant financial investments and a robust system of protection of proprietary data is needed to further stimulate research and innovation in the EU.
Biothera	1.5. Handling of data which are claimed as confidential	Well-designed research studies that could support immune health claims are very expensive often in the range of hundreds of thousands to millions of euros per study. To support this level of investment, companies need to gain a corresponding advantage in marketing their products after a claim is approved. One potential mechanism that would both recognize the investment and further protect consumers would be to approve the initial claim for only the active agent used in the studies that supported the claim application rather than requiring submission of "confidential data" in order to obtain a proprietary claims. Other manufacturers would be required to submit data to EFSA showing chemical equivalence or (in the case of biologically derived materials) biosimilarity with respect to the same immune function on which the claim was approved. This would align with the requirement to prove biosimilarity used for both medicinal and drug active agents. (US FDA Scientific Considerations in Demonstrating Biosimilari ty, Feb. 2012) Publication of all data used to substantiate claims makes the claims process more transparent and benefits both consumers and industry.
DANONE	1.5. Handling of data which are claimed as confidential	Title: Lack of information on handling of information classified as confidential by the applicant Providing raw clinical study data to EFSA panel, in a scope of a regulatory dossier, is a good practice, with respect to the Data Transparency Initiative. The debate isn't whether or not data will be made available: it's about who will have access to this data and in what context. This question is key, especially vs publication of data prior to dossier submission but also on the potential data access restriction (qualified professionals should be the only ones). The new guidance should provide information on this topic.

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DuPont	1.5. Handling of data which are claimed as confidential	Can EFSA make public information classified by the applicant as confidential and in affirmative case under which conditions? This is mainly relevant when submitting results of studies not yet published. Publication of studies is desirable from a transparency standpoint. It must be possible to use published studies in a dossier and still claim proprietary data.
Mondelez International	1.5. Handling of data which are claimed as confidential	• According to the EFSA General guidance for Article 13.1, 13.5 and 14 health claims evaluation, data claimed as confidential by the applicant in the scientific dossier and which are considered essential for the scientific assessment are released in the opinion. We would like that the EFSA ask the applicant the right to quote confidential data before the publication of the opinion as this could lead to competitive disadvantage for the applicant.
Nestlé S.A.	1.5. Handling of data which are claimed as confidential	Taking into consideration that the current EFSA "Guidance on the scientific requirements for health claims related to gut and immune function" of 2011 does not contain any statements on confidential/proprietary data this topic should not be addressed in the revised guidance, too. Being a general topic it is appropriate to continue dealing with it under the existing EFSA "General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims" of 2011 where respective statements are already addressed. Any modifications of these general approaches on the handling of confidential/proprietary data should be reserved to a revision of this general guidance.
GAP/IPA/YLFA	1.5. Handling of data which are claimed as confidential	Can EFSA make public information classified by the applicant as confidential, and in the affirmative case under which conditions? This is relevant mainly when submitting results of studies not yet published. Publication of studies is desirable from a transparency standpoint. It must be possible to use published studies in a dossier and still claim proprietary data, but the new guidance needs to clarify who will have access to the raw data.

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DANONE	2. Characterisation of microorganisms and other food constituents in relation to claims on gut and immune function	The requirement for the demonstration of a health relationship for a food containing a mix of ingredients is unclear and needs clarification, it must clearly state that if clinical studies demonstrate the beneficial effect of this food, the panel will not re-qualify the claim for the active ingredient. In order to extent the possibility of the claim usage for different forms of food products, the applicant should provide scientific "bioequivalence" data to sustain this possibility. As bioequivalence is a complex scientific question, it could be useful that EFSA propose a scientific working session on it.
Mondelez International	2. Characterisation of microorganisms and other food constituents in relation to claims on gut and immune function	• Does it mean that for each thematic guidance for health claims the EFSA will include a specific part relating to the characterization of the subject of the claim in relation to the thematic of claims detailed in the guidance document?
GAP/IPA/YLFA	2. Characterisation of microorganisms and other food constituents in relation to claims on gut and immune function	The requirement for the demonstration of a health relationship for a food containing a mix of ingredients is unclear and needs clarification. Indeed, it is in the charge of the applicant to identify and demonstrate this relationship, but how can EFSA structure rules for bioequivalence models? One of the key questions is how we can transfer a claim on the active component in one product to be used for other products that contain this component without repeating the trials and applications Moreover, we support the concept that the characterisation of microorganisms should be done at the strain level for the claim effect. Unambiguous characterisation of a microorganism is an essential element in establishing a health benefit mediated by the microorganism in question. General health benefits may be attributed to some microbial species whilst other benefits are believed to be strain-specific. Therefore, characterisation at the strain level is critical, especially when considering a beneficial effect which is considered to be strain specific. Essentially, ideal characterisation should include a combination of genetic and phenotypic assays that collectively allow as complete an understanding as possible of each microorganism, at the strain level as it was suggested for example in the FAO/WHO guidelines for microorganisms (WHO, 2002).

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DuPont	2.1. Characterisation of microorganisms at the strain level	Unambiguous characterisation of a microorganism is an essential element in establishing a health benefit mediated by the microorganism in question. General health benefits may be attributed to some microbial species whilst other benefits are considered to be strain-specific. Therefore characterisation to the strain level is critical, especially when considering a beneficial effect which is considered to be strain specific. Characterisation of a specific microorganism should include the documentation of the genome sequence where possible. Furthermore, any additional characterisation can include positive attributes specific to the strain itself. This can include genetic regions contributing to a specific health benefit, or even an aspect of survival in the human host. Essentially, ideal characterisation should include a combination of genetic and phenotypic assays that collectively allow as complete an understanding as possible of each microorganism, at the strain level.
Nestlé S.A.	2.1. Characterisation of microorganisms at the strain level	Nestlé suggests that the current list of characterisation methods is made more extensive by appending it with other internationally recognized methods, such as AFLP and optical mapping.
Yakult Europe BV	2.1. Characterisation of microorganisms at the strain level	We support the concept that the characterisation of microorganism should be done at strain level for the claim effect.
Association of the Self-Medication Industry (AESGP)	2.2. Characterisation of microorganisms and other food constituents in relation to the claimed effect	Reference: 'EFSA Guidance on the scientific requirements for health claims related to gut and immune function', section 2.2, page 6: "Whether the design and quality of the studies allow conclusions to be drawn for the scientific substantiation of the claim." Reference: 'EFSA Guidance on the scientific requirements for health claims related to gut and immune function', section 3.1, page 6: "Appropriate outcome measures of the claimed effect in human studies include transit time, frequency of bowel movements, stool bulk and stool consistency." Comment: It would be useful to include more clarification on the following aspects, ideally illustrated with

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		some examples: - What study duration would be required e.g. for acute and long term improvement to bowel movement? - What minimum size of the study group would be acceptable? Reference: 'EFSA Guidance on the scientific requirements for health claims related to gut and immune function', section 2.2, page 6: "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." Comment: It would be helpful to provide further clarifications on what can be considered as 'consistency' and 'reproducibility', ideally illustrated by some examples (e.g. whether two studies showing the same effect would be considered sufficient). Comment: It would be helpful to clarify whether a meta-analysis would be accepted as primary evidence for general health effect of a probiotic genus, or genus and species (not strain specific)? Reference: 'EFSA General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims', section 7, page 12: "For microorganisms (e.g. bacteria and yeast), the NDA Panel considers whether, in addition to species identification, sufficient information is provided for characterisation (genetic typing) at strain level by internationally accepted molecular methods, and regarding the naming of strains according to the International Code of Nomenclature." Comment: It would be useful to clarify whether for a probiotic strain characterisation, the DNA sequence is considered sufficient, or is it required to produce in-vivo measures such as bioavailability (in stool) and/or other measures.
DuPont	2.2. Characterisation of microorganisms and other food constituents in relation to the claimed effect	• We would like to propose EFSA to make clear guideline for so-called 'product-based claim' when effective component can't be specified) and for cases when a placebo and double-blinded design is not possible due to the characteristics and technical limitation of food products. • Can a claim on the active component in one product be used for other products that contain this component without repeating the trials and applications? Can EFSA provide the condition of use? Food component need to be clearly characterised. A method of detection might be desired for enforcement

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		purposes.
Nestlé S.A.	2.2. Characterisation of microorganisms and other food constituents in relation to the claimed effect	Nestlé suggests that EFSA strongly recommends (and not only consider as 'desirable') to have strains deposited in an internationally recognised culture collection (with restricted access to the culture collection).
Yakult Europe BV	2.2. Characterisation of microorganisms and other food constituents in relation to the claimed effect	• We would like to propose EFSA to make clear guideline for so-called 'product-based claim' when effective component can't be specified) and for cases when a placebo and double-blinded design is not possible due to the characteristics and technical limitation of food products. Explanation for this proposal: ideally the cause and effect relation between the claim effect and specific the microorganisms or the active food constituents should be demonstrated with placebo controlled trial. However, it is not always possible to achieve a stable placebo when the microorganism and active food constituents are isolated from the product. In such a case, a 'product-based' claim should also be possible. • Can a claim on the active component in one production be used for other products that contain this component without repeating the trials and applications? Can EFSA provide the condition of use?
Food Supplements Europe	3. Function claims	The section on function claims highlights the fields of health that will be considered in the revision. We would strongly support EFSA to address the possibilities for a claim relating to the maintenance or support of the gastro-intestinal microflora. There is growing consensus that this microflora is of primordial importance for the functioning of the immune system and the development of allergenic susceptibility. It is important that consumer information on the role of products containing pro- and prebiotics are not undermined solely because of the lack of effects on physiological or clinical outcomes. Appreciation of the increase in beneficial

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		bacteria should be possible on the basis of the evidence available, as indicated below. We note that aspects of normal development of gut function, digestion, intestinal barrier function are not covered. These are nevertheless important topic that merit inclusion. The same holds true for claims that refer to the functioning of specific organs, such are liver, gut or secretory functions. In the absence of guidance, many of these fields of health remain unclear and research may not be initiated.
BENEO-Institute	3.1. Claims that are insufficiently defined for a scientific evaluation	The Discussion paper for the revision (EFSA supporting publication 2014:EN-NNNN) lists under the bullet point "Claims that are insufficiently defined for scientific evaluation" as an example "maintenance of normal immune function". A recent scientific opinion on Zinc (EFSA Journal 2014;12(5):3653) confirms that "normal function of the immune system" is a beneficial physiological effect and "zinc contributes to normal function of the immune system" as appropriate wording. This seems to be conflicting and further clarification on what is considered as sufficiently defined (and why) and what is not (and why not) should be addressed in the revised Guidance document.
Biothera	3.1. Claims that are insufficiently defined for a scientific evaluation	The Function claims section (Discussion paper for the revision of guidance for health claims related to gut and immune function) indicates a bias against presenting immune function claims based on helping to maintain health (insufficiently defined for scientific evaluation or not considered beneficial physiological effects per se) and a push toward defining immune claims in a negative context (defense against pathogens). This is a concern because it appears to limit the ability to convey potential health benefits in a positive manner (helping you stay healthy) and forces use of a negative approach (disease defense). The primary function of the immune system is to maintain health (homeostasis), but the language EFSA uses to describe "appropriate" function claim areas focuses only on the negative side of the benefit. Biothera's consumer research indicates food and beverage customers are more interested in products that promote health and are much less interested in messages about avoiding a negative health condition. It would be very useful if in addition to defining outcome measures and biomarkers to support an immune function claim, that EFSA also consider and address language which would allow companies to convey immune function benefits based on supporting or maintaining good health. The data used to substantiate such a claim should be based on the same type of well-defined health outcomes that are proposed for "disease defense" claims, supported by defined mechanisms of action and biomarker data. The difference would be allowing claim language that expresses the health benefits in positive terms rather than negative.

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DANONE	3.1. Claims that are insufficiently defined for a scientific evaluation	Title: Discrepancies between scientific evaluations of 13.5 and 13.1 health claims on immune function The technical report provided by EFSA in view of the consultation indicates that a claim like "maintenance of a normal immune function" is insufficiently defined for a scientific evaluation. However in the current guidance (EFSA Journal 2011;9(4):1984) NDA panel considers that maintaining a normal immune function is a beneficial physiological effect. Given the multiple roles of the immune system, it is also requested that the specific aspect of immune function which is the subject of the claim be indicated. Recently, some positive opinion has been issued by the panel on zinc effect (EFSA Journal 2014;12(5):3653): "zinc contributes to normal function of the immune system". The new guidance should reflect better this new position. Title: Lack of clarity on whether both symptoms and immune markers outcomes, or only immune markers, have to be measured for claims on maintaining normal immune function The current guidance (EFSA Journal 2011;9(4):1984) also indicates that for claims on maintaining normal immune function in population groups considered to be at risk of immunosuppression (e.g. older adults, individuals experiencing stress or engaging in heavy physical exercise, or after exposure to ultraviolet radiation), studies on subjects with immunosuppression (confirmed by symptoms and/or immune markers) showing improvement of those symptoms and/or immune markers may be considered appropriate. Here the words "and/or" are quite confusing. They suggest that immunosuppression could be established on the basis of only immune markers assessment and that improvement of only these immune markers could be sufficient to substantiate claims on maintaining normal immune function. It must be clarified in the new guidance whether both symptoms and immune markers outcomes should be measured or whether each outcome is considered alone as appropriate.
DuPont	3.1. Claims that are insufficiently defined for a scientific evaluation	What are possible relevant markers for health claims on maintaining normal immune function, taking that EFSA has validated 13.1 claims without data on immune markers? It is not always known what mechanism triggers the beneficial effect. Also, validated biomarkers do not exist for every clinical outcome. Still, if the beneficial effect could be demonstrated as clinical outcome in repeated trials, it should be possible to approve this claim. • We propose a more extensive list of defined claims to be provided by EFSA. • "Maintenance of a normal immune function" was considered as a beneficial physiological effect (page 9, guidance document 2011). Then on page 10, with the further explanation about this point: "For claims on

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		maintaining normal immune function in population groups considered to be at risk of immunosuppression (e.g. older adults, individuals experiencing stress or engaging in heavy physical exercise, or after exposure to ultraviolet radiation), studies on subjects with immunosuppression (confirmed by symptoms and/or immune markers) showing improvement of those symptoms and/or immune markers may be considered appropriate". Can we consider 'maintenance of a normal immune function' a function claim as long as clearly defined as described in the 2011 document or should we now consider this phrasing as insufficiently defined?
Food Supplements Europe	3.1. Claims that are insufficiently defined for a scientific evaluation	Although we understand why EFSA considers some claims to be insufficiently defined, we would ask EFSA to consider ways to address the totality of the evidence available in support of a more general, but better understandable claims wording. I addition, we would support EFSA to accept a more consumer-friendly wording accompanied by the more specific aspect that was demonstrated by the scientific evidence (E.g. This food supports gut health by [specific effect []).
Mondelez International	3.1. Claims that are insufficiently defined for a scientific evaluation	• Several claims related to the "normal function of the immune system" have been authorized on the art 13 positive list of claims (Regulation (EU) 432/2012). Could the EFSA explain the difference with "maintenance of a normal immune function" which is considered as insufficiently defined according to this document? • Could the EFSA provide example(s) of beneficial physiological or clinical outcome(s) which are appropriate for the substantiation of claims related to the normal function of the immune system?
Yakult Europe BV	3.1. Claims that are insufficiently defined for a scientific evaluation	• We propose a more extensive list of defined claims to be provided by EFSA. • "Maintenance of a normal immune function" was considered as a beneficial physiological effect (page 9, guidance document 2011). Then on page 10, with the further explanation about this point: "For claims on maintaining normal immune function in population groups considered to be at risk of immunosuppression (e.g. older adults, individuals experiencing stress or engaging in heavy physical exercise, or after exposure to ultraviolet radiation), studies on subjects with immunosuppression (confirmed by symptoms and/or immune markers) showing improvement of those symptoms and/or immune markers may be considered appropriate". Can we consider 'maintenance of a normal immune function' a function claim as long as clearly defined as described in the 2011 document or should we now consider this phrasing as insufficiently defined?

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SENSUS	3.1. Claims that are insufficiently defined for a scientific evaluation	In many authorized generic health claims for vitamins or minerals "contribution to the normal function of the immune system" or similar wording is used. It seems puzzling that now this is included as insufficiently defined for immune health claims. This issue should be addressed. A claim for Vitamin D is based on the relationship of this vitamin and Normal function of immune system and inflammation response is allowed. This suggests that the normal function of the inflammation response is known and can be measured and that changes in inflammation markers may thus be beneficial. From the authorized generic claims it follows that normal bowel function, normal function of the immune system (e.g. various vitamins, copper), normal function of digestive enzymes (calcium) are known and can be measured. There seems to be a discrepancy between the wording of the Article 13.1 claims and the topics to be addressed in the Guidance. i.e. what constitutes normal gut or immune health.
GAP/IPA/YLFA	3.1. Claims that are insufficiently defined for a scientific evaluation	"Maintenance of a normal immune function" is considered as a beneficial physiological effect in the current guidance: "*For claims on maintaining normal immune function in population groups considered to be at risk of immunosuppression (e.g. older adults, individuals experiencing stress or engaging in heavy physical exercise, or after exposure to ultraviolet radiation), studies on subjects with immunosuppression (confirmed by symptoms and/or immune markers) showing improvement of those symptoms and/or immune markers may be considered appropriate*". Can we consider 'maintenance of a normal immune function' a function claim as long as clearly defined as described in the 2011 document or should **we now consider this phrasing as insufficiently defined?**
Association of the Self-Medication Industry (AESGP)	3.2. Claims which are not considered to have beneficial physiological effects per se	Reference: 'EFSA Guidance on the scientific requirements for health claims related to gut and immune function', section 3.2: "Appropriate outcome measures of the claimed effect in human studies include validated questionnaire(s) on severity and frequency of symptoms (e.g. abdominal pain, cramp, bloating, straining, borborygmi [rumbling] and sensation of incomplete evacuation)."; "Validated general "quality of life questionnaires" alone are insufficient as outcome measures, but may provide indirect evidence for claims on gastro-intestinal discomfort." Comment: EFSA is kindly requested to clarify why "validated general "quality of life questionnaires" are not accepted as appropriate outcome measures but "validated questionnaire(s) on severity and frequency of symptoms" are considered appropriate. It would be also helpful to clarify whether the list of symptoms given

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		is non-exhaustive and whether other symptoms would be considered appropriate and why, e.g.: indigestion, heartburn, fullness. Reference: 'EFSA Guidance on the scientific requirements for health claims related to gut and immune function', section 2.1, page 5: "A risk factor is a factor associated with the risk of a disease that may serve as a predictor of development of that disease." Comment: Some examples of risk factors are listed in the 'EFSA General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims', section 9, page 15. More examples of risk factors, especially in the context of gut and immune health effects would be helpful.
BENEO-Institute	3.2. Claims which are not considered to have beneficial physiological effects per se	The Discussion paper lists a couple of "Claims which are not considered beneficial physiological effects per se". In addition, the current Guidance document contains further outcome measures (e.g. decrease in stool pH, changes in short-chain fatty acid production etc) that accordingly are not considered beneficial physiological effects per se. As no scientific rationale and criteria are provided in the current Guidance document on which the NDA panel concludes/concluded that claimed effects/outcome measures are accepted as beneficial physiological effects or not, the revised and updated Guidance document should also provide here a clear rationale to help applicants understanding.
DANONE	3.2. Claims which are not considered to have beneficial physiological effects per se	According to 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. For function claims, a beneficial effect may relate to the maintenance or improvement of a function. Till today, the NDA panel position doesn't accept any type of claims around some physiological functions although they are more and more widely recognized as essential for maintenance of Health, or linked to emergence of digestive disorders, pathologies and/or complications as SCFA production within the colon, barrier integrity, …The new EFSA guidance should recognize the impact on such physiological intermediaries as beneficial per se and subject of specific allegations, as long as it is widely accepted by the scientific worldwide community as a risk factor reduction or beneficial for some specific physiological functions of the body demonstrated according to the best and relevant experimental & clinical standards. For example, there is a growing consensus that butyrate is considered as the preferential energy source of colonocytes (Canani et al, 2011, World J Gastoenterol, 17(12): 1519-1528). Therefore, the butyrate can be

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		considered as an essential nutrient for the human body. The energization of colonocytes by butyrate leads to other essential features as epithelial cell proliferation and differentiation, tight junction strengthening and mucus production which contribute to the maintenance and the functioning of normal gut mucosal membrane. An another point is the integrity of the intestinal barrier, constantly challenged by stress, inflammation, uptake of drugs, food intolerance, pathogens and other foreign antigens. Therefore, the maintenance of this barrier integrity is a key function in maintaining gut-immune homeostasis, strengthening the epithelial barrier function could be considered as a beneficial physiological effect. In an EFSA opinion (EFSA Journal 2009; 7(9):1235) the Panel considers that maintaining integrity of the intestinal lining and normal permeability is beneficial to human health. Health relevance of specific immune markers have been recently discussed by a group of experts (Albers et al. 2013, BJN, Vol. 110 No. 2 August 2013). Some markers were classified to be both clinically relevant and indicative of the involvement of immune function(s) (see for more details section 3.6 and section 3.7). New EFSA guidance should clearly indicates which immune markers modulation will be regarded as beneficial physiological effects per se, without measuring clinical outcomes, to substantiate a health claim related to immune functions. In the current guidance EFSA acknowledged that "Based on current scientific knowledge, it is not possible to define the exact numbers of the different microbial groups which constitute a normal microbiota". Recent advances in the field of gut microbiota helped in reaching a scientific consensus on the principle that some bacteria of the gut microbiota are favorable for the host while others are detrimental (amada et al., 2013, Nature immunology; PMID: 23618829). The authors of this review listed potential beneficial or indigenous opportunistic pathogens (=pathobionts) bacteria. *Faecalibacterium prauznitizii* is today consensually recognized as a protective species for human intestinal health (Miquel et al; PMID:23831042; Cao et al; 2014; PMID: 24799893). The data available may qualify the increase of Faecalibacterium prauznitizii has a beneficial effect per se or a decrease of a risk factor for IBD. New guidance should give a definition of beneficial microbe in the microbiota and the criteria that would make a specie eligible for such status, able to define a well microbiota composition.

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DuPont	3.2. Claims which are not considered to have beneficial physiological effects per se	Microbiota We would like to have appropriate discussion on 'microbiota' related claim and to seek for possible claims for it. - Maintain the gut environment by reduction of the harmful substance - Maintenance of a diversity of microbiota/reduction of low diversity of microbiota. - Decrease/suppress the harmful bacteria in the gut such as C. difficile. - Maintaining or restoring an individuals microbiota under the condition like antibiotics treatment (which other conditions?) to it's original composition and/or activity Immune system and immune markers We strongly urge EFSA to include an extensive list of biomarkers of this category, based on i.e. quality reviews by the experts of this field such as what has been published by the ILSI workgroup of PASSCLAIM. Would it be possible to define a way to make claims about these factors? For example, would EFSA allow a claim like: "has shown to enhance the activity of immune factors xxx and xxx which are important for the activity of xxx part of the human immune system"? Similarly, we would like to propose to EFSA to provide a list of the most relevant biomarkers for inflammation. Recent development of research on this field defines several biomarkers related to inflammation.
Food Supplements Europe	3.2. Claims which are not considered to have beneficial physiological effects per se	Judging whether an effect is beneficial or not is a matter of appreciation based on the evidence available. We note that in the area of pro- and prebiotics the leading experts in the field may not share EFSA's view on the fact that increasing numbers of 'beneficial' bacteria (mainly bifidobacteria and lactobacilli) in the gastrointestinal tract is not beneficial per se. We would welcome that the guidance document provides an updated vision on this aspect based on scientific expertise and consensus. The fact that this effect is not considered to be beneficial per se has resulted in the prohibition to communicate on these effects that have been demonstrated by studies for many products, at a moment that the important role of these bacteria in the development and priming of the immune system gets growing consensus. We would support that criteria are developed to identify outcomes in gut parameters that are sufficient to assume a beneficial effect on the gut (e.g. decrease of gut pH, production of metabolites (sF A, etc). Such criteria have been published before

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		(Roberfroid et al. 2010 Brit J Nutr 104: S1-63). This should also cover methodologies to consider the totality of the evidence available, giving appropriate value to observational, animal and experimental data in support of plausible mechanisms and expert opinion.
Mondelez International	3.2. Claims which are not considered to have beneficial physiological effects per se	• This is the only section of this document referring to claims on reduction of inflammation. Does it mean that it will not be possible to claim on reduction of inflammation? • Many pathologies are now recognized as mediated by inflammatory processes. Low-grade inflammation has been recognized as one important risk factors for the development of chronic diseases (Calder et al., 2009). Therefore, low-grade inflammation should be recognized as "may be beneficial for health". As no marker alone can be considered as a risk factor (Albers et al., 2013;Calder et al., 2013;Calder et al., 2009) for metabolic diseases would you accept a body of evidence built on several markers to substantiate a claim on inflammation in the context of chronic diseases? Calder PC, Albers R, Antoine JM et al. (2009). Inflammatory disease processes and interactions with nutrition. The British Journal Of Nutrition 101 Suppl 1, S1-S45. Albers R, Bourdet-Sicard Rl, Braun D et al. (2013). Monitoring immune modulation by nutrition in the general population: identifying and substantiating effects on human health. The British Journal Of Nutrition 110 Suppl 2, S1-S30. Calder PC, Ahluwalia N, Albers R et al. (2013). A consideration of biomarkers to be used for evaluation of inflammation in human nutritional studies. The British Journal Of Nutrition 109 Suppl 1, S1-S34.
Nestlé S.A.	3.2. Claims which are not considered to have beneficial physiological effects per se	Nestlé suggests that EFSA makes it clear in their guidance that certain mechanisms of action (not considered per se to be beneficial), such as a reduction of intestinal permeability or changes in the production of fecal organic acids can be used as risk factors. Human milk-fed infants are recognized as the gold standard in infant (-12 mo) nutrition. For article 14 claims referring to children's development and health, Nestlé suggests allowing certain mechanisms of action (not considered to be beneficial per se), such as a reduction of intestinal permeability, reduction of fecal pH, changes in fecal organic acids to be used in substantiation of these health claims when these changes alter the

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		characteristics of formula-fed infants to be closer / more similar to the characteristics of human milk-fed infants.
Yakult Europe BV	3.2. Claims which are not considered to have beneficial physiological effects per se	General comments We would like to strongly propose to EFSA when evidence is available, to define criteria and methodology of making a claim about biomarkers which are not per se beneficial physiological effect on its own. Explanation about this proposal: Science is a continuum: we are far from understanding all physiological processes. Various biomarkers have been demonstrated to play an important role in physiological processes, even if the exact mechanism is not known. Without claiming health improvement (alternative: the physiological processes), we consider it highly necessary to find ways to make claims about these biomarkers possible. Here below we would like to elaborated on this point with specific examples as followings: 1. Microbiota We would like to have appropriate discussion on 'microbiota' related claim and to seek for possible claims for it. Explanation about the proposal: The importance of the commensal gut microbiota to health (particularly long term) is now generally acknowledged by medical experts, thus a claim based on the profile or function of this should be possible, and is entirely different from claims about pathogens in the gut. There is mounting evidence that (a) the gut microbiota performs essential health-protective functions and (b) a microbiota of low diversity is associated with poor health. In terms of (a) this could include improved metabolism in the gut, including reduction of toxic/proteolytic/carcinogenic metabolites – either by reduced production (through a shift in the proportions of the gut species) and/or showing an increase in numbers of strains/species that absorb toxic substances (either ingested or produced in the gut).

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		These toxic substances are not necessarily related to a certain infectious disease, however they do constitute disease risk factor. If one can show the decrease of such toxic substances, should not it be accepted as a health benefit without speculating the possibly related disease, as such toxic substance is in any cases harmful for the health? The following examples (not exhaustive) are suggested as physiological benefits: - Maintain the gut environment by reduction of the harmful substance - Increase of intestinal bifidobacteria can decrease of pH in the gut, which can prohibit growth of harmful bacteria in the gut - Maintenance of a diversity of microbiota/reduction of low diversity of microbiota. - Decrease/suppress the harmful bacteria in the gut such as c-difficile. - Maintaining a normal microbiota under the condition like antibiotics treatment (which other conditions?) 2. Immune system and immune markers We strongly urge EFSA to include an extensive list of biomarkers of this category, based on i.e. quality reviews by the experts of this field such as what has been published by the ILSI workgroup of PASSCLAIM. Explanation about the proposal: An immune parameter can be proven clearly to be beneficial based on current understanding of the immune system, even if it is not “in itself a beneficial physio logical effect”, the data showing the relative change and maintenance of this activity or cell numbers should be accepted (eg NK cell, sIgA). Would it be possible to define a way to make claims about these factors? For example, would EFSA allow a claim like: “has shown to enhance the activity of immune factors xxx and xxx which are important for the activity of xxx part of the human immune system”? In addition, it is difficult to argue against the current stipulation for trials showing clinical benefit in conjunction with a change in immune parameter, but could there be more consideration for studies that do this separately? 3. Similarly, we would like to propose to EFSA to provide a list of the most relevant biomarkers for

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		inflammation.
GAP/IPA/YLFA	3.2. Claims which are not considered to have beneficial physiological effects per se	Science is a continuum: we are far from understanding all physiological processes. Various biomarkers have been demonstrated to play an important role in physiological processes, even if the exact mechanism is not known. Without claiming health improvement (*alternative: the physiological processes)*, we consider it highly necessary to find ways to make claims about these biomarkers possible. The new guidance should take into account scientific developments since the 2011 guidance was written and should propose new possible beneficial effects that would be acceptable beyond those evaluated so far or stipulated in the 2011 guidance. For example, during the last years metagenomic analyses have provided information about differences in gut microbiota composition between healthy and diseased individuals. Generally, microbial diversity is thought to be associated with a healthy gut microbiota while loss of diversity correlates with diseases. The importance of the commensal gut microbiota to health (particularly long term) is now generally acknowledged by medical experts, thus a claim based on the profile or function of this should be possible, and is entirely different from claims about pathogens in the gut. The physiological function of the maintenance of the integrity of the gut barrier also directly contributes to several beneficial functions related to immune homeostasis, digestion/absorption of nutrients or defense against pathogens. Any defect in IECs-specific process can cause the breakdown in gut barrier and i) disruption of normal mucosal immune homeostasis; ii) impaired nutriments absorption; iii) commensals and pathogen translocation. Therefore, the following examples (not exhaustive) are suggested as physiological benefits: - Maintain the gut environment by reduction of the harmful substance - Increase of intestinal bifidobacteria can decrease of pH in the gut, which can prohibit growth of harmful bacteria in the gut - Maintenance of a diversity of microbiota/reduction of low diversity of microbiota - Decrease/suppress the harmful bacteria in the gut such as *c-difficile* - Maintain a normal microbiota under the condition like antibiotics treatment - Increase or decrease of a group of immune parameters can be proven clearly to be beneficial based on current understanding of the immune system, even though EFSA stated in its guidance document and opinions on

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		various HC applications that the event is not "in itself a beneficial physiological effect". The data showing the relative change and maintenance of this activity or cell numbers should be accepted (e.g. NK cell, sIgA. Albers et al. 2013, British Journal of Nutrition, Vol. 110 Supplement No. 2 August 2013.
Association of the Self-Medication Industry (AESGP)	3.3. Claims on bowel function	Reference: 'EFSA Guidance on the scientific requirements for health claims related to gut and immune function', section 3.1, pages 6-7: "Irritable Bowel Syndrome (IBS) patients or subgroups of IBS patients with constipation are generally considered an appropriate study group to substantiate claims on bowel function intended for the general population (adults and children)." Comment: EFSA is kindly requested to clarify why IBS patients are considered an appropriate study group for claims for the general population and whether the following subgroups are also considered appropriate in this context: symptomatic uncomplicated diverticular disease (SUDD), self-claimed constipation and functional gastrointestinal (GI) symptoms, obese subjects (e.g. BMI >30), populations at higher risk e.g. with poor diets or food intolerances, claimed occasional diarrhoea and claimed occasional traveller's diarrhoea.
BENEO-Institute	3.3. Claims on bowel function	The Guidance document will - presumably also after its revision - not be intended to include an exhaustive list of acceptable studies/outcome measures and corresponding methods. Nevertheless, it would be helpful to have, beyond what is included in the Guidance document so far, non-exhaustive examples for measures / methodologies, study designs etc. that are to date considered as appropriate (or not) by the EFSA NDA Panel in order to substantiate claims on bowel function.
DANONE	3.3. Claims on bowel function	Title: Lack of consideration, in the current guidance, of diarrhea improvement as a beneficial effect per se 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. We therefore believe that improvement of diarrhea that does not result in constipation should be considered as a beneficial effect. Effect on diarrhea is measured with the same valid outcomes (eg stool consistency or stool frequency) than for constipation. Patients with IBS-D should be considered an appropriate study group as well as patients with functional diarrhea. Considering the multiple outcome measures associated with bowel function, we believe that the improvement

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		of at least one valid outcome measure is sufficient to support a beneficial effect on bowel function. In that case, claim should be related to this specific effect (increase faecal bulk). When two or more valid outcome measures are improved, we suggest that the claim is related to improvement of bowel function. These points need to be clarified in the revised guidance.
DuPont	3.3. Claims on bowel function	• Is it possible to address not only constipation but also functional diarrhoea for claims on maintenance of normal defecation during antibiotic treatment with studies demonstrating an effect on AAD occurrence, duration or severity? • As IBS patients can be used, can this be extended to people with diverticulitis since diverticula develop with age and risk of developing the disorder can develop? A biological extrapolation can be made to healthy people. • The totality of evidence and multiple symptoms should be considered, so we would like to propose that a claim could be allowed by studies in a range of endpoints that add up to one benefit.
Nestlé S.A.	3.3. Claims on bowel function	Nestlé recommends that the upcoming guidance is clear on the principles and criteria that are considered appropriate for making claims on bowel function. Examples for appropriate study population, beneficial effects, and effect sizes, tools and markers considered validated will be welcomed, while ensuring lists are not exhaustive. Information about what is clinically relevant and meaningful can and should be addressed in the human intervention trial and data analysis plans, depending on the targeted claim. Please find below some specific examples that Nestlé suggest to consider: - EFSA accepts as valid, methodologies currently used to measure transit time, including radiopaque markers, wireless motility capsules (like SmartPill) and colonic scintigraphy (Rao et al., 2011); - While relevance of an effect, a population meeting only a subset of official disease criteria (e.g. Rome III) can be considered an appropriate study group provided that the improvements in symptoms are shown using validated evaluation methods (e.g. improved stool consistency measured by the Bristol scale).

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		Rao SS1, Camilleri M, Hasler WL, Maurer AH, Parkman HP, Saad R, Scott MS, Simren M, Soffer E, Szarka L (2011). Evaluation of gastrointestinal transit in clinical practice: position paper of the American and European Neurogastroenterology and Motility Societies. Neurogastroenterol Motil. 23(1):8-23.
Yakult Europe BV	3.3. Claims on bowel function	• Is it possible to address not only constipation but also functional diarrhea for claims on maintenance of normal defecation during antibiotic treatment with studies demonstrating an effect on AAD occurrence, duration or severity? • As IBS patients can be used, can this be extended to people with diverticulitis since diverticula develop with age and risk of developing the disorder can develop? A biological extrapolation can be made to healthy people. • The totality of evidence and multiple symptoms should be considered, so we would like to propose that a claim could be allowed by studies in a range of endpoints that add up to one benefit.
GAP/IPA/YLFA	3.3. Claims on bowel function	Is it possible to address not only constipation but also functional diarrhea for claims on maintenance of normal defecation during antibiotic treatment with studies demonstrating an effect on AAD occurrence, duration or severity?
analyze&realize GmbH	3.4. Claims on gastro-intestinal discomfort	Upper gastrointestinal symptoms affect up to 40% of adults in any one year (Stanghellini, Scand J Gastroenterol Suppl, 231, 1999). Esophageal discomfort describes a group of conditions that is presented with symptoms presumed to originate in the esophagus such as reflux and heartburn. Reflux symptoms are one of the most common gastro-intestinal complaints, which may impact quality of life. Even mild symptoms of heartburn or abdominal pain have been shown to reduce well-being (Wiklund et al., Am J Gastroenterol, 101, 2006). Within one year, about 25 to 33% of the population suffer from heartburn. Moreover, 6-27% of the general population experience symptoms once a week and 4-11% even daily (Pehl and Schepp, Dtsch Arztebl 99(44): A-2941 / B-2495 / C-2339, 2002). Does the panel confirm that the reduction of gastro-esophageal discomfort including heartburn or reflux (e.g.

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		frequency or severity) could be considered a beneficial physiological effect with regards to claims on gastro-intestinal discomfort?
Association of the Self-Medication Industry (AESGP)	3.4. Claims on gastro-intestinal discomfort	Reference: 'EFSA Guidance on the scientific requirements for health claims related to gut and immune function', section 3.5, page 8: "The evidence available to the Panel does not establish that increasing the number of any groups of microorganisms, including lactobacilli and/or bifidobacteria, is in itself a beneficial physiological effect." Comment: EFSA is kindly requested to clarify whether the following effects would be considered as beneficial effects: (a) the bacteria colonise in the gut (proven via stool analysis); (b) inhibition of pathogens occurs. It would be also helpful to clarify what outcome measures for these effects would be considered appropriate.
BENEO-Institute	3.4. Claims on gastro-intestinal discomfort	In the current guidance document, severity and frequency of symptoms (e.g. abdominal pain, cramp, bloating, straining, etc.) are indicated as appropriate outcome measures for gastrointestinal discomfort when assessed by validated questionnaires. However, the validity of questionnaires is often questioned in scientific opinions by the EFSA NDA panel and thus noted as major limitation of studies. The revised Guidance document should thus give non-exhaustive examples for accepted questionnaires / instruments, validated ones and those which are "formally not validated" but still are generally accepted in the relevant research fields as tools to measure respective outcomes. It is further suggested to address in this respect also what kind of modifications of previously validated questionnaires as well as their mode of administration are considered acceptable (e.g. on-line use of a previously validated questionnaire was recently questioned (EFSA Journal 2014; 12(7): 3756)).
DANONE	3.4. Claims on gastro-intestinal discomfort	A recent application claimed on the effect of LGG on maintenance of normal defecation during antibiotic treatment (EFSA Journal 2013;11(6):3256) with a target population as adults and children healthy outpatient on oral antibiotic treatment. In his opinion, NDA panel validated that maintenance of normal defecation during antibiotic treatment is a beneficial physiological effect. Although the claim was rejected, panel also noted that from two of the studies (Szajewska 2009, Arvola 1999) conclusions could have been drawn for the scientific substantiation of the claim, if they had shown an effect on the incidence of diarrhoea resulting from antibiotic treatment. Both studies investigated on the Antibiotic Associated Diarrhea (AAD) as primary or secondary

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		criteria in children treated for H. pylori eradication (Szajewska 2009) or for respiratory infections (Arvola 1999) and included hospitalized (Szajewska 2009, Arvola 1999) or not hospitalized patients (Arvola 1999). The above panel position is a clear evolution from the current guidance (EFSA Journal 2011;9(4):1984), where effect on diarrhea symptoms could be used only to substantiate claims on defense against pathogens. The new guidance should mention this new type of claim opportunity and clearly indicate the possibility to substantiate a claim on maintenance of normal defecation during antibiotic treatment with studies demonstrating an effect on AAD occurrence, duration or severity. For claim related to overall GI discomfort, PRO should capture the different aspects of discomfort. Single question allowing the patient to weight or average either symptoms (eg bloating, abdominal pain, borborygmi) or other signs of discomfort (eg hard stool) is an appropriate way to capture such information. The measure of the key digestive symptoms (e.g. abdominal pain/discomfort, bloating, flatulence, rumbling) may also be considered relevant as they could be collectively described as intestinal discomfort (EFSA opinion on Bimuno). When considering overall GI discomfort a composite score of these symptoms seems to be more appropriate than looking at single symptom changes. For claim related to the reduction of a specific symptom (eg bloating, flatulence), the measurement of a specific symptom as primary outcome is recommended. When a simple objective measure, such as measure of abdominal distension (Lewis et al., 2001) or number of daily flatulence, is applicable it should be used in connexion with PRO assessing a relevant endpoint (e.g. sensation of abdominal bloating or flatulence). Including PRO measures would always be valuable if aspects that are both important to patients and likely influenced by the treatment are measured (Guyatt et al., 2007). For claim related to intestinal gas, the effect should be assessed through different methods such as breath tests, intestinal gas volume (imaging method such CT scan or Functional Magnetic Resonance Imaging) or collecting gas evacuated by anus. These objective measures are valid outcomes for intestinal gas and are appropriate study ou tcomes for claims on the reduction of excessive intestinal gas accumulation (eg Opinion on active charcoal). This must be included in the revised guidance and whether all these outcomes will refer to the same beneficial effect (ie reduction of intestinal gas accumulation). It should be stated whether these study outcomes are considered alone or if there is a need of reporting improvement as perceived by the subject in parallel. Symptoms arising in the upper GI tract are also highly prevalent and should be considered under GI discomfort claim. The revised guidance should describe this aspect of GI discomfort including which study outcomes and study population are appropriate.

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DuPont	3.4. Claims on gastro-intestinal discomfort	Is it possible to differentiate GI discomfort claim into different categories: • Weight or average symptoms • Other signs such as hard stools symptoms? Is EFSA planning to integrate symptoms in the upper GI tract as relevant markers to measure GI discomfort ?
Food Supplements Europe	3.4. Claims on gastro-intestinal discomfort	In terms of acceptable assessment questionnaires, EFSA will have reviewed scientific studies using a variety of validated questionnaires. It would be useful to list the instruments that EFSA has accepted as valid in the studies reviewed so far (e.g Bristol stool form, Symptom Global Assessment, Rome III or IV criteria,
Mondelez International	3.4. Claims on gastro-intestinal discomfort	• The sentence: "Episodes of abdominal pain or discomfort (e.g. bloating, abdominal pain/cramp and borborygmi [rumbling]), in the absence of organic diseases or biochemical abnormalities, are commonly associated with food or drug intake or with alterations of bowel habit and vary between individuals in frequency and severity." mentions 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? • As constipated subjects are part of the general population, can we use scientific evidence on constipated subjects to substantiate a claim intended for the general population?
Nestlé S.A.	3.4. Claims on gastro-intestinal discomfort	Nestlé recommends that the upcoming guidance is clear on the principles and criteria that are considered appropriate for making Claims on gastro-intestinal discomfort. Examples for appropriate study population, beneficial effects, and effect sizes, tools and markers considered validated will be welcomed, while ensuring lists are not exhaustive. Information about what is clinically relevant and meaningful can and should be addressed in the human intervention trial and data analysis plans, depending on the targeted claim.

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		Please find below some specific examples that Nestlé suggest to consider: Nestlé suggests that: -§ EFSA provides examples of validated questionnaires to measure gastro-intestinal discomfort, like Birmingham IBS symptom questionnaire (Roalfe Ak et al., 2008, Spiegel BM et al., 2010 - Likert scales or visual analogue scales (VAS) (used for example to measure pain severity) are considered as acceptable/relevant as validated questionnaires, provided that a significant (pre-defined) reduction of symptoms is reached (e.g. ≥30% decrease in abdominal pain); - EFSA to provide the criteria it applies to decide whether an effect size is relevant -§ a population that meets only a subset of official disease criteria (e.g. Rome III) is considered an appropriate study group provided that the improvements in symptoms are shown using validated evaluation methods; § in the last paragraph of the current guidance, the sentence is rephrased to "… higher frequency and/or greater severity …". Roalfe AK, Roberts LM, Wilson S (2008). Evaluation of the Birmingham IBS symptom questionnaire. BMC Gastroenterol; 8: 30. Spiegel BM, Bolus R, Agarwal N, Sayuk G, Harris LA, Lucak S, Esrailian E, Chey WD, Lembo A, Karsan H, Tillisch K, Talley J, Chang L (2010). Measuring symptoms in the irritable bowel syndrome: development of a framework for clinical trials. Aliment Pharmacol Ther. 32(10):1275-1291.
Yakult Europe BV	3.4. Claims on gastro-intestinal discomfort	Is EFSA planning to integrate symptoms in the upper GI tract as relevant markers to measure GI discomfort ?

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		Inclusion in the new guidance of the possibility, as indicated in recent opinions, to substantiate a claim on maintenance of normal defecation during antibiotic treatment with studies demonstrating an effect on AAD occurrence, duration or severity.
GAP/IPA/YLFA	3.4. Claims on gastro-intestinal discomfort	Is it possible to differentiate GI discomfort claims into different categories: • Weight or average symptoms • Other signs such as hard stool symptoms? Is EFSA planning to integrate symptoms in the upper GI tract as relevant markers to measure GI discomfort?
DuPont	3.5. Claims on defence against pathogens	• What does the 'magnitude' mean? Can EFSA provide examples which demonstrate the "relevant magnitude" in this context? • In the 2011 guidance it is said: 'For function claims related to defence against pathogens in the gastro-intestinal tract, appropriate outcome measures are gastro-intestinal infections (e.g. number of episodes and severity or duration of infection). The infectious nature of the disease should be established, e.g. by clinical diagnosis and/or the use of validated questionnaires for recording self-reported data and/or microbiological data depending on the type of the infection. For function claims related to defence against pathogens at other sites of the body, for example upper respiratory tract or urinary tract, a similar approach would be appropriate.' It would be crucial to define in the revised guidance: - Whether a self-reported data is sufficient or whether a microbiological data is required as well. Or, whether a diagnosis following general medical practice is sufficient . The expression like '…and/or…' is unclear for the applicant. • If clinical data provided indicate that one pathogen is the causative agent of the infections, the claim will be restricted to this pathogen (ex: rotavirus vs gastro-intestinal infections) ? • Clinical demonstration of infections prevention with food in EU general population is complex and expensive : low incidence of infections, wide range of pathogens, large number of subjects. How is EFSA considering such a situation while we are talking about food? • Can an experimental infection model/challenge model be sufficient to substantiate a claim on defences against natural infection and would immune parameters measured in this kind of model be suitable to sustain a

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		functional claim on immune system under 13.5 ? • Most of the foodborne pathogens mentioned in the EFSA guidance document in 2011 are not relevant and should be revised. Claims on immune defence against pathogens Is there new immune markers that can be used and be self-sufficient (not associated with clinical markers) to substantiate claims on immune defence against pathogens?
Food Supplements Europe	3.5. Claims on defence against pathogens	We would ask EFSA top address the practical difficulties of and need for identifying specific pathogenic organisms or their toxins. This is especially relevant as different pathogens exert different effects at different times and subjects may not be in a situation to allow the pathogen to be determined (e.g. traveller's diarrhoea). Also pathogens are transient, and monitoring pathogens and providing sufficient characterisation are very difficult, if not impossible! In addition, inducing or inoculation with pathogens is not possible or acceptable. Currently episodes of infection, severity of symptoms, duration of infection as indicated by diarrhoea are accepted as supporting evidence only, when the infectious nature has not been established. While these are of more relevance for the consumers than the type of pathogen they are infected with. This seems disproportionate and we would appreciate that clarification on this is included on the guidance. Also, the number of persons being colonized with pathogenic microorganisms after intervention against a placebo could be an outcome that could be acceptable to assess the protective effects of pre- and probiotics products., even in the context of disease risk factors. Guidance on acceptable cut off values for the presence or decrease in pathogens or pathogen metabolites would also be very welcome. Amongst the sites that are proposed to be covers, we note that the oral cavity is missing.
Nestlé S.A.	3.5. Claims on defence against pathogens	Nestlé recommends that the upcoming guidance is clear on the principles and criteria that are considered appropriate for making Claims on defence against pathogens. Examples for appropriate study population, beneficial effects, and effect sizes, tools and markers considered validated will be welcomed, while ensuring lists are not exhaustive.

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		Information about what is clinically relevant and meaningful can and should be addressed in the human intervention trial and data analysis plans, depending on the targeted claim. Please find below some specific examples that Nestlé suggest to consider: -§ population groups with a sub-optimal immune status such as for example stressed individuals or those doing heavy physical exercise are considered as appropriate study groups to substantiate claims on defence against pathogens in the generally healthy population; -§ human experimental infection models are considered acceptable to substantiate a claim on defence against pathogens. Such valid models could include experimental infection with rhinovirus (Peterson et al., 2009; Mallia et al., 2011) or Escherichia Coli (Ouwehand et al., 2014); EFSA to provide criteria used to evaluate extrapolation of results to a healthy population. -§ an effect demonstrated on rotavirus infection can be used to substantiate a generic claim on viral GI infections; -§ in the second paragraph of the current guidance, the sentence is rephrased to "… number of episodes and/or severity and/or duration of infection". This would clarify whether amelioration in any single item is recognized as a valid outcome measure for a beneficial effect; -§ cohort studies can be used to establish an association between the reduction of the presence of specific pathogens, toxins or virulence factors and reduction in clinical outcomes. -§ a reduction of specific pathogens, their toxins, or other virulence factors in the oral cavity (since these may include cariogenic or other species different from pathogens in the respiratory tract per s e) is also considered beneficial physiological effect; -§ both qualitative and quantitative reductions in the presence of specific pathogens, their toxins, or other virulence factors are considered physiologically relevant and acceptable.

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Yakult Europe BV	3.5. Claims on defence against pathogens	• What does the 'magnitude' mean? Can EFSA provide examples which demonstrate the "relevant magnitude" in this context? • In the 2011 guidance it is said: 'For function claims related to defence against pathogens in the gastro-intestinal tract, appropriate outcome measures are gastro-intestinal infections (e.g. number of episodes and severity or duration of infection). The infectious nature of the disease should be established, e.g. by clinical diagnosis and/or the use of validated questionnaires for recording self-reported data and/or microbiological data depending on the type of the infection. For function claims related to defence against pathogens at other sites of the body, for example upper respiratory tract or urinary tract, a similar approach would be appropriate.' It would be crucial to define in the revised guidance: - Whether a self-reported data is sufficient or whether a microbiological data is required as well. The expression like '…and/or…' is unclear for the applicant. - In addition, the feasibility of the requirement needs to be revisited, before the revision of the guidance document. For example, in case of URTI, it was earlier commented by EFSA that the symptom questionnaire was insufficient to distinguish the common cold from allergy however it was the most commonly used questionnaire for clinical practice and was hardly feasible to conduct a trial with microbiological data. Can EFSA make clear whether what is being used in the clinical practice is in principle acceptable as a validated methodology? • Clinical demonstration of infections prevention with food in EU general population is complex and expensive : low incidence of infections, wide range of pathogens, large number of subjects. How is EFSA considering such a situation while we are talking about food? • Can an experimental infection model/challenge model be sufficient to substantiate a claim on defences against natural infection and would immune parameters measured in this kind of model be suitable to sus tain a functional claim on immune system under 13.5 ?

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		• Most of the foodborne pathogens mentioned in the EFSA guidance document in 2011 are not relevant and should be revised.
GAP/IPA/YLFA	3.5. Claims on defence against pathogens	The current guidance defines the following, '*For function claims related to defence against pathogens in the gastro-intestinal tract, appropriate outcome measures are gastro-intestinal infections (e.g. number of episodes and severity or duration of infection). The infectious nature of the disease should be established, e.g. by clinical diagnosis and/or the use of validated questionnaires for recording self-reported data and/or microbiological data depending on the type of the infection.*
BENEO-Institute	3.5.1. Claims on defence against pathogens related to the gastrointestinal tract	Information on the suitability of a particular study population or a selected at-risk subpopulation (see e.g. Albers et al Br J Nutr 2013) for claims intended for the general population is largely missing. It would thus be helpful to include in the revised Guidance document non-exhaustive examples on what is sufficient or suitable. For instance, whether or not a) healthy people that are challenged (e.g. by travelling to high risk countries, by receiving attenuated pathogenic bacterial or viral strains, by experiencing physical stress (e.g. endurance exercise)), or b) non-healthy people receiving antibiotics (as in case of C. diff. associated diarrhea) are a suitable model system and study population to show a health benefit for the general population. In the clinical field, stool diaries filled by the volunteer/patient are accepted tools to assess outcome measures related to defence against pathogens (number of episodes, severity, and duration) and are used for clinical diagnosis. Although such instruments may not have been "formally validated", they are considered as "generally accepted" according to the methodological standards in scientific research. The revised Guidance should thus address whether it is considered appropriate (or not) to have a reduction of the incidence/ duration/ severity of symptoms diagnosed by a clinician based on stool diaries.
DANONE	3.5.1. Claims on defence against pathogens related to the gastrointestinal tract	In the current guidance, EFSA acknowledges that "the presence of pathogenic microorganisms may cause infections at various sites of the body, and defence against pathogens at a specific site of the body is considered a beneficial physiological effect". The NDA Panel listed a non-exhaustive list of pathogens which are considered pathogenic and do not need further characterization. In the last release of the 9 million gene human gut microbiome catalog by the European MetaHIt consortium (July 2014; Li et al., PMID: 24997786), some of the foodborne pathogens listed by the panel (i.e. Salmonella spp., Shigella spp., Campylobacter spp) are commonly found in the microbiota of the general population. Consequently, some of those should be requalified as "food borne, toxigenic and opportunistic pathogens (=pathobionts) organism" since they

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		normally inhabit human microbiota.
analyze&realize GmbH	3.5.2. Claims on defence against pathogens related to the respiratory tract	We would like to understand under which circumstances EFSA would accept the physician-diagnosed infection of the respiratory tract and what kind of diagnoses by a physician is required by EFSA? Does EFSA propose specific procedures/questionnaires for the assessment of common cold in children? Considering the various difficulties in interventional trials with naturally required common cold, would EFSA accept challenge type trial designs, where subjects would be inoculated with mild officially approved virus i.e. rhinovirus causing upper respiratory tract infection? If so, what kind of virus would EFSA accept? Additionally, we are wondering whether one should have to exclude influenza infections, which cause similar symptoms as a cold although it is not a upper respiratory tract infection?
BENEO-Institute	3.5.2. Claims on defence against pathogens related to the respiratory tract	Information on the suitability of a particular study population or a selected at-risk subpopulation for claims intended for the general population is largely missing. It would thus be helpful to include in the revised Guidance document non-exhaustive examples on what is sufficient or suitable. For instance, whether or not healthy people that are challenged (e.g. by receiving attenuated pathogenic bacterial or viral strains, by experiencing physical stress (e.g. endurance exercise)), are a suitable model system and study population to show a health benefit for the general population.
DANONE	3.5.2. Claims on defence against pathogens related to the respiratory tract	In the current guidance (EFSA Journal 2011;9(4):1984), for function claims related to defence against pathogens, appropriate outcome measures are infections (e.g. number of episodes and severity or duration of infection). The infectious nature of the disease should be established, e.g. by clinical diagnosis and/or the use of validated questionnaires for recording self-reported data and/or microbiological data depending on the type of the infection. In the case of use of clinical diagnosis or questionnaire and in the absence of pathogens identification, the new guidance should clarify whether a claim on defense against pathogens could be used with no restriction on the type of pathogens potentially responsible for the infections. If NDA panel anticipate some possible restriction, the guidance should indicate precisely in which situation this could be required and to which extend: restriction to microbes type (virus, bacteria..). Conversely, in case of pathogen identification, the new guidance should indicate whether a claim related to defence against pathogens should be restricted to the identified pathogens or whether this could be not

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		required, for instance in case of partial identification (in only a sub-group of subjects) or in absence of demonstration that the identified pathogen(s) is the causative agent of the infections. The last option might be more adapted to the actual possibility to identify pathogens which is quite reduced in case of most common gastro-intestinal or respiratory infections. In the current guidance the NDA panel provides a non-exhaustive informative list of intestinal microorganisms considered as pathogenic or toxicogenic. No list of pathogens is given for other body sites than the gut. In the new guidance, the panel should also provide a list of microorganisms considered as pathogenic or toxicogenic in respiratory, urinary and vaginal tracts. During the last EFSA consultation on the 2nd december 2010, the following question was addressed on the use of studies on experimental infection model in human: would an experimental infection model be sufficient to susbstantiate a claim on defences against natural infection and would immune parameters measured in this kind of model be suitable to sustain a functional claim on immune system under 13.5? The NDA panel said that this kind of model would be very helpful to support a claim but, to substantiate an immune related claim, information on immune system is however required. The new guidance must clearly specify the following: - Whether repeated studies performed only on an experimental infection model could substantiate a claim on defence against pathogen in the target site of infection (gastro-intestinal, respiratory…). - Whether a claim on defence against pathogen substantiated by studies on an experimental infection model would be restricted to pathogen of the same species beyond the experimental condition of challenge and applicable to natural infection. In the current guidance, an appropriate outcome measure for function claims related to defence against pathogens would be the reduction of the presence of specific pathogens, their toxins or other virulence factors, as measured in suitable samples (e.g. stools). The relevance of such reductions should be justified, for example by the magnitude of reduction or by evidence of a reduction in clinical outcomes related to infection accompanying the reduction in pathogens/toxins. The new guidance should clarify whether this include the possibility to show a reduction of pathogens intended as “commensal” pathogens in healthy carriers, potentially responsible for opportunistic infection such as C. difficile, in addition to reduction of pathogens in the course of related infection.

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Association of the Self-Medication Industry (AESGP)	3.6. Claims on immune defence against pathogens	Reference: 'EFSA Guidance on the scientific requirements for health claims related to gut and immune function', section 4.1, page 9: "The Panel considers that maintaining a normal immune function is a beneficial physiological effect. Given the multiple roles of the immune system, the specific aspect of immune function which is the subject of the claim should be indicated." Comment: It would be helpful to clarify whether a claim on 'normal function of the immune system' could be substantiated, e.g. with a study showing probiotics increased antibody titer to a vaccine or whether a claim should be more specific, e.g. 'maintains a healthy adaptive immune response'. It would be also helpful to clarify what would be an acceptable study population, e.g. a population with a higher level of immune markers or with high incidence of minor illnesses such as the common cold, diarrhoea or allergy episodes. Reference: 'EFSA Guidance on the scientific requirements for health claims related to gut and immune function', section 4.1, page 10: "These proposed markers include the numbers of various lymphoid subpopulations in the circulation, proliferative responses of lymphocytes, phagocytic activity of phagocytes, lytic activity of natural killer cells and cytolytic T cells, production of cellular mediators, serum and secretory immunoglobulin levels, delayed-type hypersensitivity responses, etc. The evidence available to the Panel does not establish that stimulation of any of these markers is in itself a beneficial physiological effect, but changes need to be accompanied by a beneficial physiological or clinical outcome, preferably shown in the same intervention studies."; "(…) studies on subjects with immunosuppression (confirmed by symptoms and/or immune markers) showing improvement of those symptoms and/or immune markers may be considered appropriate." Comment: EFSA is kindly asked to clarify why these markers are not accepted as outcomes of substantiation of claims on immune function and whether a biologically plausible justification of the relation and effect to the immune system function would be accepted as primary data. It would be also helpful to clarify whether the use of a (well accepted) biomarker should also include an effect on a specific symptom. If effect on specific symptoms can be correlated with a biomarker with a biological explanation, would a symptom effect be required in future studies? Reference: 'EFSA Guidance on the scientific requirements for health claims related to gut and immune function', section 4.1, page 10: "It is generally accepted that higher vaccination responses (as measured by increased numbers of individuals attaining protective levels, as well as by increments in titres in groups of individuals) are beneficial."

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		Comment: EFSA is kindly asked to clarify the following issues: If it is demonstrated that a probiotic strain significantly increases the antibody tier to an influenza vaccine would it be possible to claim increased protection against influenza without performing a study showing a reduction in influenza infections? Does the claim have to be specific to the immunising antigen (influenza) or can broader protection claims be made?
BENEO-Institute	3.6. Claims on immune defence against pathogens	The current Guidance document considers for claims on maintaining normal immune function in "population groups (…) at risk of immunosuppression" studies on subjects with immunosuppression as appropriate. Information on the suitability of a particular study population or a selected at-risk subpopulation for claims intended for the general population is missing. It would thus be helpful to include in the revised Guidance document further examples on what is sufficient or suitable. For instance, whether or not a) healthy people that are challenged (e.g. by travelling to high risk countries, by receiving attenuated pathogenic bacterial or viral strains, by experiencing physical stress (e.g. endurance exercise)), or b) non-healthy people receiving antibiotics (as in case of C. diff. associated diarrhea) are a suitable model system and study population to show a health benefit for the general population.
Biothera	3.6. Claims on immune defence against pathogens	The measurement and interpretation of immune system biomarker data is rapidly growing, but it is still a field of emerging science. There often is little or no consensus on use of immune system biomarkers as predictive markers of healthy immune function (Albers et al 2013). Selecting the appropriate immune biomarkers for use in a human clinical trial will depend upon the mechanism of action by which a given ingredient interacts with the immune system. This type of research often involves evaluating a large number of potential biomarkers. Some of these biomarkers are well-documented and accepted by EFSA as valid immune biomarkers (e.g. sIgA as discussed by Albers et al. 2013) ; other biomarkers are not well-accepted by EFSA, but offer industry the opportunity to demonstrate an efficacious effect on immune system support (e.g. circulating or ex vivo-produced cytokines, Albers et al. 2013). How can EFSA better work with industry to set guidelines for proper degree of scientific support of new biomarkers for substantiating beneficial immune support in human populations? A mechanism by which companies can select biomarkers based on the best available science and consult with EFSA prior to initiating a study to determine if those markers would be acceptable for claims support would be in the best interests of both the agency and the food industry.

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DANONE	3.6. Claims on immune defence against pathogens	Health relevance of specific immune markers have been recently discussed by a group of experts (Albers et al. 2013, BJN, August 2013) and were classified to be both clinically relevant and indicative of the involvement of immune function(s). In the case of defence against pathogens, these include: - immune responses to a natural or experimental infection (Pathogen-specific antibodies, pathogen-specific T-cell response) - Vaccine-specific immune response (seroprotection, seroconversion, specific antibodies and specific T cells) - mucosal IgA (in saliva, …) In addition to the challenge tests, other markers are placed in this group because they are clear indicators of the involvement of the immune system and their clinical relevance in the general population has been established, and modulation in the relevant direction would, therefore, be considered a beneficial health effect. For instance, mucosal IgA was clustered with the above markers because it is a marker of immune function and low (salivary) IgA is a risk factor for respiratory infections in children and athletes (van Riet et al., 2012 Vaccine, 30, 5893-5900). This list of markers is non-exhaustive and should not be regarded as final since markers may evolve if more data become available. New EFSA guidance should clearly indicates which immune markers will be regarded as clinically relevant and that could then be used alone, without measuring clinical outcomes, to substantiate a health claim related to immune defence against pathogens. Regarding vaccination models, current guidance indicates that it is generally accepted that higher vaccination responses are beneficial. Guidance also mentioned that stimulation of protective antibody titres, as measured by increased numbers of individuals attaining protective levels, could be used to substantiate a health claim on the function of the immune system related to defence against pathogens. However, during the last EFSA consultation, NDA panel also said that increase of the number of protected individu als might be the most beneficial but increase of protective antibody might be considered. Considering that increments in antibody titres has been clearly retained as beneficial, NDA panel should clarify the possibility of use of this parameter also for substantiation of a claim on the function of the immune system related to defence against pathogens and if the claim should be restricted to the pathogen(s) targeted by the vaccination. New guidance should clarify if the innate immune response specifically towards to infection can be considered a function for a 13.5 claim. In this case, guidance should also indicate whether immune marker(s) measured in the incubation period of infection or during infection (e.g. Natural Killer cell activity/cell count) could be considered appropriate to substantiate a claim on immune defence against pathogens. It must be also clarify if any effect on these parameters should be systematically supported by concomitant beneficial effects on clinical outcomes or if in specific cases to be detailed an improvement of innate immune response to pathogens might be

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		sufficient. Current guidance otherwise proposes that for a claim related to immune defence against pathogens, appropriate outcome measures are those which may be used to substantiate claims related to defence against pathogens together with concomitant changes in relevant immunological parameters, preferably shown in the same intervention studies. During the last EFSA consultation, NDA panel however indicated that providing evidence on body function and clinical outcome in same studies was not mandatory and that in case of separate demonstrations, the different studies should however present similar design and target populations.
DuPont	3.6. Claims on immune defence against pathogens	• Is there any other claim allowed than 'lactose intolerance' and 'iron absorption'? • Can the lactose-intolerance claim be extended to any product containing deliverable number of live lactobacilli/bifidobacteria which have sufficient activity of lactase rather than just yogurt?
Food Supplements Europe	3.6. Claims on immune defence against pathogens	Concerning claims on gut microflora and immune function, true endpoints looking at reduction in incidence, duration and severity of infections should be acceptable as indicative markers for immune function. Such true endpoint are far more relevant for the consumer than immunemarkers per se. We understand that for reduction of disease risk claims an effect on a risk factor should be demonstrated. However, also in this case, evidence of true end points of the disease should not be disregarded as this is the strongest evidence that can be provided and in case a significant effect is observed, not consuming the food or food component may in itself be considered as a risk factor. More guidance on the acceptable relevant immune markers would be welcome. We note that the area of immune function is only covered by the effect on immune defense against pathogens. Other immune-related effects are not considered, while this is a very important field where health benefits could mean much to consumers. We would like to ask EFSA to cover this area in detail, in particular since a number of recent publications have provided more insight in this complex area. We would appreciate if these articles could be considered for providing advice on which outcomes would be appropriate to support claims relating to the strengthening of the immune system (e.g. Albers et al. 2013 Brit J Nutr 110: S1-30; Calder et al. 2013 Brit J Nutr 109: S1-34).

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Nestlé S.A.	3.6. Claims on immune defence against pathogens	Nestlé recommends that the upcoming guidance is clear on the principles and criteria that are considered appropriate for making claims on immune defence against pathogens. Examples for appropriate study population, beneficial effects, and effect sizes, tools and markers considered validated will be welcomed, while ensuring lists are not exhaustive. Information about what is clinically relevant and meaningful can and should be addressed in the human intervention trial and data analysis plans, depending on the targeted claim. Please find below some specific examples that Nestlé suggest to consider: -§ guidance is provided to better define under which circumstances the restoration of a mildly challenged immune system would be considered per se beneficial. This could include elderly, and stressed people (medical care-givers, athletes, students during exam period); -§ human experimental infection models are considered acceptable to substantiate a claim on defence against pathogens. Such valid models could include experimental infection with rhinovirus (Peterson et al., 2009; Mallia et al., 2011) or Escherichia Coli (Ouwehand et al., 2014); -§ vaccination being considered as a challenge model, significant increases in the absolute titre of antibodies (irrespective of whether they relate to the protective levels) are considered as valid outcome measures; This would reflect an increase in the ability of the immune system to respond to a specific pathogen challenge, thus differing from showing increases in other non-specific immune markers such as NK cells, neutrophils and so on; -§ clarification is provided on what would be considered a “generally recognized point (age range)” where the immune system is considered mature, i.e. to be equally developed as the adult one; -§ benefits shown in subjects with 'sub-optimal immune status' are considered valid to substantiate claims in the general population. EFSA to provide criteria used to evaluate extrapolation of results to this population. Mallia P, Message SD, Gielen V, Contoli M, Gray K, Kebadze T, Aniscenko J, Laza-Stanca V, Edwards MR, Slater L, Papi A, Stanciu LA, Kon OM, Johnson M, Johnston SL (2011). Experimental rhinovirus infection as

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		a human model of chronic obstructive pulmonary disease exacerbation. Am J Respir Crit Care Med. 183(6):734-742. Ouwehand AC, ten Bruggencate SJ, Schonewille AJ, Alhoniemi E, Forssten SD, Bovee-Oudenhoven IM (2014). Lactobacillus acidophilus supplementation in human subjects and their resistance to enterotoxigenic Escherichia coli infection. Br J Nutr. 111(3):465-473. Peterson KM, O'Shea M, Stam W, Mohede IC, Patrie JT, Hayden FG (2009). Effects of dietary supplementation with conjugated linoleic acid on experimental human rhinovirus infection and illness. Antivir Ther. 14(1):33-43.
GAP/IPA/YLFA	3.6. Claims on immune defence against pathogens	Are there new immune markers that can be used and be self-sufficient (not associated with clinical markers) to substantiate claims on immune defence against pathogens? The current guidance also indicates that stimulation of many immune markers is not in itself a beneficial physiological effect, such as immune cell count, proliferative responses of lymphocytes, phagocytic activity of phagocytes, lytic activity of natural killer cells and cytolytic T cells, production of cellular mediators, serum and secretory immunoglobulin levels, delayed-type hypersensitivity responses, etc. The NDA panel did not address the case of parameters related to the innate immune response specifically towards infection as was done for adaptive counterparts through the position given on vaccination models. The parallel demonstration of an effect on immune markers and clinical outcomes in the same trial raises the following concerns that should be addressed in the new guidance. 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 with consequences for managing multiple comparisons with adjustment of alpha-risk. In case of combined investigation of disease outcomes and immune function parameters in the 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 a secondary parameter to substantiate a body function claim? This option will however be mandatory in most cases where the infectious disease endpoint must be defined as the primary parameter since it usually requires a higher sample size to allow a demonstration of effect than a body function, especially for natural common infections.

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DANONE	3.7. Claims on a beneficial change in the response to allergens	Characterisation of the study population and of the target population, and scientific requirements for substantiation. Title : Need for inclusion in the new guidance of self-sufficient immune parameters for claim substantiation on resistance against allergens. Health relevance of specific immune markers have been recently discussed by a group of experts from academia, government and the food industry (Albers et al. 2013, British Journal of Nutrition, Vol. 110 Supplement No. 2 August 2013). Several markers were classified to be both clinically relevant and indicative of the involvement of immune function(s). In the case of response to allergens, commonly used allergen provocation tests such as prick, intradermal and patch tests and labial, respiratory and oral challenges with specific allergens fall into this category. In addition to the challenge tests, several other markers are placed in this group because they are clear indicators of the involvement of the immune system and their clinical relevance in the general population has been established, and modulation in the relevant direction would, therefore, be considered a beneficial health effect. For instance, the basophil activation test (Kosnik M, Silar M, Bajrovic N, et al. (2005) High sensitivityof basophils predicts side-effects in venom immunotherapy.Allergy 60, 1401–1406; Lambert C, Guilloux L, Dzviga C, et al. (2003) Flow cytometry versus histamine release analysis of in vitro basophil degranulation in allergy to Hymenoptera venom. Cytometry B Clin Cytom 52, 13–19.) and tryptase (Rueff F, Przybilla B, Bilo MB, et al. (2009) Predictors of severe systemic anaphylactic reactions in patients with Hymenoptera venom allergy: importance of baseline serum tryptase – a study of the European Academy of Allergology and Clinical Immunology Interest Group on Insect Venom Hypersensitivity. J Allergy Clin Immunol 124, 1047–1054) in plasma reflect basophil reactivity in allergic patients and are considered risk factors correlated with the severity of the reacti on. This list of markers is non-exhaustive and should not be regarded as final since markers may evolve if more data become available. New EFSA guidance should clearly indicates which immune markers will be regarded as clinically relevant and that could then be used alone, without measuring clinical outcomes, to substantiate a health claim related to resistance against allergens.

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Nestlé S.A.	3.7. Claims on a beneficial change in the response to allergens	Nestlé recommends that the upcoming guidance is clear on the principles and criteria that are considered appropriate for making Claims on a beneficial change in response to allergens. Examples for appropriate study population, beneficial effects, and effect sizes, tools and markers considered validated will be welcomed, while ensuring lists are not exhaustive. Information about what is clinically relevant and meaningful can and should be addressed in the human intervention trial and data analysis plans, depending on the targeted claim. Please find below some specific examples that Nestlé suggest to consider: -§ EFSA provide the criteria used to evaluate what may be considered as beneficial change in response to allergens (e.g. certain % improvement in Rhinoconjunctivitis Quality of Life Questionnaire [RQLQ] or symptom scores); - similar to the acceptable outcome measures for infections, the duration of an allergic manifestation is considered a valid outcome measure; -§ a decrease in the use of anti-allergy medication or improvement over standard of care (i.e. over anti-histamines) is considered a beneficial change in the response to allergens; -§ in relation to respiratory allergy, a benefit demonstrated for pollen allergy can be used to substantiate a general claim on aero-allergens; -§ a reduction of response as measured by specific biomarkers is accepted (Singh et al,. 2014, Actis-Goretta et al., 2012) Singh A, Demont A, Actis-Goretta L, Holvoet S, Lévêques A, Lepage M, Nutten S and Mercenier A (2014). Identification of epicatechin as one of the key bioactive constituents of polyphenol-enriched extracts that demonstrate an anti-allergic effect in a murine model of food allergy. Br J Nutr 112 (3): 358-368. Actis-Goretta L, Lévèquesa A, Giuffrida F, Romanov-Michailidis F, Viton F, Barron D, Duenas-Paton M, Gonzalez-Manzano S, C Santos-Buelga, Williamson G, Fabiola Dionisi (2012): Elucidation of (−)-epicatechin

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		metabolites after ingestion of chocolate by healthy humans. Free Rad ic. Biol. Med.53 787–795.
BENEO-Institute	3.8. Claims on improvement in digestion and/or absorption of nutrients	The existing EFSA Guidance for claims on gut and immune function did only mention that "improving iron absorption is considered a beneficial physiological effect" (EFSA Journal; 9(4):1984). In line with previous opinions of the EFSA NDA Panel, the new Guidance document should also mention other nutrients such as calcium ("an increase in calcium absorption leading to an increase in calcium retention might be a beneficial physiological effect" (EFSA Journal 2011; 9(6):2234)).
DANONE	3.8. Claims on improvement in digestion and/or absorption of nutrients	No comment.
Nestlé S.A.	3.8. Claims on improvement in digestion and/or absorption of nutrients	Nestlé recommends that the upcoming guidance is clear on the principles and criteria that are considered appropriate for making Claims on improvement in digestion and/or absorption of nutrients. Examples for appropriate study population, beneficial effects, and effect sizes, tools and markers considered validated will be welcomed, while ensuring lists are not exhaustive. Information about what is clinically relevant and meaningful can and should be addressed in the human intervention trial and data analysis plans, depending on the targeted claim. Please find below some specific examples that Nestlé suggest to consider: -§ improvement in either tolerated and/or digested lactose amount is considered a beneficial effect (i.e. improved lactose tolerance/digestion);

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		-§ a decrease in severity of most frequently reported symptoms (diarrhea, abdominal cramping, vomiting, audible bowel sounds, flatulence or gas) experienced after lactose ingestion, evaluated by a visual analogue scale (VAS) score is considered a valid outcome measure (Casellas et al., 2009). Casellas F1, Varela E, Aparici A, Casaus M, Rodríguez P (2009). Development, validation, and applicability of a symptoms questionnaire for lactose malabsorption screening. Dig Dis Sci. 54(5):1059-1065.
Yakult Europe BV	3.8. Claims on improvement in digestion and/or absorption of nutrients	• Are there anything allowed as a claim other than 'lactose intolerance' and 'iron absorption'? • Can the lactose-intolerance claim be extended to any product containing deliverable number of live lactobacilli which have sufficient activity of lactase rather than just yogurt?
SENSUS	4. Disease risk reduction claims	In the Guidance document it should be clearly indicated what EFSA considers as risk factors for infections. Is it a high number of infectious agents in the gut, which is mostly of a transient nature and thus difficult to influence with food ingredients and often difficult to measure? Moreover, in many cases the number of infectious agents in a person with manifest disease symptoms is often low as these lag behind the start of the infection. Is it a less well functioning immune system, e.g. due to stress or medication, and how can this then be measured and affected by food consumption?
Association of the Self-Medication Industry (AESGP)	4.1. Beneficial change in a risk factor for infections	Reference: 'EFSA Guidance on the scientific requirements for health claims related to gut and immune function', section 4.1, page 10: "These proposed markers include the numbers of various lymphoid subpopulations in the circulation, proliferative responses of lymphocytes, phagocytic activity of phagocytes, lytic activity of natural killer cells and cytolytic T cells, production of cellular mediators, serum and secretory immunoglobulin levels, delayed-type hypersensitivity responses, etc. The evidence available to the Panel does not establish that stimulation of any of these markers is in itself a beneficial physiological effect, but changes need to be accompanied by a beneficial physiological or clinical outcome, preferably shown in the same intervention studies." and "(…) studies on subjects with immunosuppression (confirmed by symptoms and/or immune markers) showing improvement of those symptoms and/or immune markers may be considered appropriate."

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		Comment: EFSA is kindly asked to clarify why these markers are not accepted as outcomes of substantiation of claims on immune function and whether a biologically plausible justification of the relation and effect to the immune system function would be accepted as primary data. In this context, a high cost of studies in immune-compromised patients should be noted. Reference: 'EFSA Guidance on the scientific requirements for health claims related to gut and immune function', section 2.1, page 10: "For studies carried out in children to substantiate a claim on the function of the immune system, the Panel notes that, in general, data from infants and young children cannot be extrapolated to the adult population, as the immune system in early childhood is still developing; hence the immune system in early childhood is different from adults." Comment: It would be useful to clarify whether extrapolation of adult data to children is considered acceptable. Reference: 'EFSA Guidance on the scientific requirements for health claims related to gut and immune function ', section 2.1, page 5: "The NDA Panel considers that the population group for which health claims are intended is the general (healthy) population or specific subgroups thereof, for example, elderly people, physically active subjects, or pregnant women." Comment: EFSA is kindly requested to clarify whether the following subgroups are also considered appropriate in this context: symptomatic uncomplicated diverticular disease (SUDD), self-claimed constipation, obese subjects (e.g. BMI >30), populations at higher risk e.g. with poor diets or food intolerances, claimed occasional diarrhoea and claimed occasional traveller's diarrhoea. It would be useful to include more clarification on the following aspects, ideally illustrated with some examples: - What study duration would be required for a variety of endpoints e.g. constipation relief? - What minimum size of the study group would be acceptable?

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DANONE	4.1. Beneficial change in a risk factor for infections	The scientific requirements for substantiation in relation to study duration, appropriate/non-appropriate outcome measures, study population vs. target population, and differences depending on the target organ system will be addressed. Title : Inclusion in the new guidance of a statement on the qualification of dysbalance of gut microbiota as a risk factor for infection In the current guidance (EFSA Journal 2011;9(4):1984), NDA panel states that a risk factor is an independent predictor of disease risk (such a predictor may be established from intervention and/or observational studies) and that the relationship of the risk factor to the development of the disease is biologically plausible. The panel also introduced the concept of "well established risk factors" but does not provide any example apart from presence of pathogens presented as a risk factor for infections. The new guidance should include other examples of risk factors for infections possibly based on experiences gained in the evaluation of health claims. New guidance should include a statement on the qualification of dysbalance of gut microbiota as a risk factor for infection. This might be consistent with a former opinion by NDA panel who considered that contribution to maintaining individual intestinal microbiota in subjects receiving antibiotic treatment might be a beneficial physiological effect and that disturbance of intestinal microbiota may be associated with adverse effects, for example gastro-intestinal infections (EFSA Journal 2011;9(4):2029).
DuPont	4.1. Beneficial change in a risk factor for infections	• Some diseases/discomforts do not have established risk factors, but when studies clearly show a reduction in occurrence of a disease or health problem, can the clinical outcome itself (eg reduction of incidence) and/or the alleviation of a symptom/discomfort itself be a health claim? For example common cold/upper respiratory tract infection (URTI), antibiotics-associated diarrhoea (AAD), allergy etc. • The panel introduced the concept of "well established risk factors" but does not provide any example apart from presence of pathogens presented as a risk factor for infections. Is the NDA Panel planning to include other examples of risk factors for infections based on experiences gained in the evaluation of health claims? • Considering opinion from the NDA panel that contribution to maintaining individual intestinal microbiota in subjects receiving antibiotic treatment might be a beneficial physiological effect and that disturbance of intestinal microbiota may be associated with adverse effects, for example gastro-intestinal infections, is the NDA panel considering the possibility that imbalance of gut microbiota be considered as a risk factor for infection?

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Nestlé S.A.	4.1. Beneficial change in a risk factor for infections	Nestlé suggests that, for example: § specific changes in relevant immunological parameters, in groups/communities of intestinal bacteria (for which a relationship with disease occurrence has been shown in association studies), or in host immune competence (for which a relationship with disease occurrence would have been shown in association studies) are considered valid 'risk factors' for infections, provided that the amelioration is accompanied by a concomitant improvement in a clinical outcome.
Valio Ltd	4.1. Beneficial change in a risk factor for infections	4. Disease risk reduction claims Identification of the risk factor With probiotics, it is possible to show prevention or reduction in the incidence of several infections. For a health claim in this area, e.g. "…reduces the risk factor of X infections", EFSA requires that the pathogen (virus or bacteria) causing the infection has to be identified and its elimination/reduction/prevention or some kind of "negation" shown. However, the exact agent of the infection is rarely determinable. In addition, both viruses and bacteria are often present in infections and the principal cause cannot be isolated. The majority of bacterial upper respiratory tract infections, for example, are secondary superinfections of initial viral infections (Heikkinen and Järvinen 2003). As it is generally known that infections are caused by pathogens, and reduction in the occurrence/length/severity of any infection is a result of preventing or reducing the action of the pathogens causing that infection, there should be no need to demonstrate this obvious reduction of pathogens, but the clinical evidence should be enough for a claim on "reduces the risk factor for an X infection". Ref. Heikkinen T, Järvinen A. The common cold. Lancet 2003;361: 51–9.
Yakult Europe BV	4.1. Beneficial change in a risk factor for infections	• Some diseases/discomforts do not have established risk factors, but when studies clearly show a clear reduction in occurrence of a disease or health problem, can the clinical outcome itself (eg reduction of incidence) and/or the alleviation of a symptom/discomfort itself be a health claim? For example common cold/upper respiratory tract infection (URTI), antibiotics-associated diarrhoea (AAD), allergy etc. • The panel introduced the concept of "well established risk factors" but does not provide any example apart from presence of pathogens presented as a risk factor for infections. Is the NDA Panel planning to include other examples of risk factors for infections based on experiences gained in the evaluation of health claims?

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		• Considering opinion from the NDA panel that contribution to maintaining individual intestinal microbiota in subjects receiving antibiotic treatment might be a beneficial physiological effect and that disturbance of intestinal microbiota may be associated with adverse effects, for example gastro-intestinal infections, is the NDA panel considering the possibility that imbalance of gut microbiota be considered as a risk factor for infection?
GAP/IPA/YLFA	4.1. Beneficial change in a risk factor for infections	Some diseases/discomforts do not have established risk factors, but when studies clearly show a clear reduction in the occurrence of a disease or health problem, can the clinical outcome itself (e.g. reduction of incidence) and/or the alleviation of a symptom/discomfort itself be a health claim? For example, common cold/upper respiratory tract infection (URTI), antibiotics-associated diarrhoea (AAD), allergy, etc. The panel introduced the concept of "well established risk factors" but does not provide any example apart from presence of pathogens presented as a risk factor for infections. Is the NDA Panel planning to include other examples of risk factors for infections based on experiences gained in the evaluation of health claims? Considering opinions from the NDA panel that contribution to maintaining individual intestinal microbiota in subjects receiving antibiotic treatment might be a beneficial physiological effect and that disturbance of intestinal microbiota may be associated with adverse effects, for example gastro-intestinal infections, is the NDA panel considering the possibility that imbalance of gut microbiota can be considered as a risk factor for infection?
Association of the Self-Medication Industry (AESGP)	4.2. Beneficial change in a risk factor for allergy	Reference: 'EFSA Guidance on the scientific requirements for health claims related to gut and immune function', section 4.4, page 11: "For function claims referring to reduction of inflammation, a change in markers of inflammation such as various interleukins does not indicate a beneficial physiological effect per se, but should be accompanied by a beneficial physiological or clinical outcome." Comment: EFSA is kindly asked to clarify the following issues: - What are acceptable models for injury and inflammatory response? - Can a general anti-inflammatory claim be made with substantiation in a clinical study in a disease state, i.e. arthritis or inflammatory bowel disease? - What diseases would be considered as acceptable, what would be acceptable study populations and what form of extrapolation would be acceptable? For example, are tests in ill subjects needed or can testing be done among subjects with a high level of the relevant immune markers? Can both scenarios be accepted for

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		extrapolation to the general healthy population?
DANONE	4.2. Beneficial change in a risk factor for allergy	No comment
Nestlé S.A.	4.2. Beneficial change in a risk factor for allergy	Nestlé suggests that, for example: - functional readouts related to circulating IgE levels such as skin prick test, degranulation responses (mast cells, basophil reactivity), as well as the level of sensitization to a number of allergens are considered valid 'risk factors' (if accompanied by an improvement in a clinical outcome).
Yakult Europe BV	4.2. Beneficial change in a risk factor for allergy	Why does EFSA only plan to address risk factors for infection and allergy?
GAP/IPA/YLFA	4.2. Beneficial change in a risk factor for allergy	Why does EFSA only plan to address risk factors for infection and allergy? Clarity is needed on how studies should be designed in order to address quality of life and symptom improvement in people with allergy. Can claims be addressed specifically to people with allergy symptoms and what type of claims would be possible?

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DANONE	5. Other comments	The technical report provided by EFSA in view of the consultation indicates that the revision of the guidance will be based on experiences gained in the evaluation of health claims in the context of specific applications. In former evaluations NDA panel adopted new positions on acceptable claims that were not addressed in the guidance published in 2011 (EFSA Journal 2011;9(4):1984) where claim accessibility was however discussed. The new guidance could thus mentioned these claims newly considered as accessible in order to clearly endorse the past NDA positions. In particular, in a scientific opinion (EFSA Journal 2011;9(4):2029), NDA panel considered that contribution to maintaining individual intestinal microbiota in subjects receiving antibiotic treatment might be a beneficial physiological effect. NDA panel justified its position by indicating that disturbance of intestinal microbiota may be associated with adverse effects, for example gastro-intestinal infections. This position should be part of the possible claims related to function claims on gastro-intestinal microbiota in the new guidance. In addition, guidance should clearly indicates whether a demonstrated effect on maintaining individual intestinal microbiota in subjects receiving antibiotics is sufficient per se to substantiate the claim or this should be accompanied by a beneficial physiological or clinical outcome. There is no mention of intestinal oxidative stress in the current guidance (EFSA Journal 2011;9(4):1984), while it is admitted that it occurs in the intestine and has an important role in the onset or perpetration of intestinal diseases or disorders (PMID: 24692350 ; Bhattacharyya A et al 2014). In the scientific opinion EFSA Journal 2010;8(10):1816, the Panel considers that "protection of DNA, protein and lipids from oxidative damage may be a beneficial physiological effect". This scientific opinion is not specific to any part of the human body and does not refer to human intestine. Since accessibility to human colon is technically challenging definition of fecal markers of fecal oxidative stress in a new guidance would help in assessing the effect of dietary intervention on the intestinal oxidative stress. Beyond the impact on the host tissue (e.g. DNA, protein and lipids modification), it is today admitted by the scientific community that intestinal oxidative stress is also involved in the development of gut microbiota dysbiosis by making available reactive oxygen or nitrogen species that might directly or indirectly contribute to inhibits strict anerobes, unarmed to deal with oxidative stress, and/or stimulates opportunistic pathogens from the Proteobacteria phylum (ie. aerobes) which can use ROS/RNS derived metabolites (i.e. tetrathionate or nitrate) (Winter & Baumler; 2014; Cell Host and Microbes: PMID: 24286560). In light with this new data, oxidative stress might be eligible to be qualified as a risk factor (for IBD) and/or beneficial effect per se given that its decrease might be seen as a way to protect the strict anaerobes o f the gut microbiota or restraint growth of aerobic pathobionts.

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DuPont	5. Other comments	Why does EFSA only plan to address risk factors for infection and allergy?
Food Supplements Europe	5. Other comments	Background as provided by EFSA Food Supplements Europe would like to ask EFSA to take the opportunity of this revision to address the practicability of some of the criteria of the current guidance (e.g. relating to pathogens and infection) and to include in the accepted approach clarification on the value of non-clinical data in support of overall health benefits. Since this is of a general nature we think it is highly appropriate and would strongly support the development of new guidance documents on the scientific requirements for the substantiation of health claims. Problem statement We note that in the previous consultation, comments that were considered to be too detailed and technical were left out. These covered for example comments on experimental design and methods, statistical analysis or exhaustive lists of appropriate outcome measures for claimed effects. These elements are nevertheless important and in reality constitute points of uncertainty that influence investments in specific studies. Although we understand that it is not possible for EFSA to predict all potential claims and outcome measures and we should urge EFSA to consider an as broad as possible scope of topics in its guidance document to help applicants understand the requirements and increase chances of success. Scope and plan for the revision EFSA already states in this discussion document that the revision is not aimed at addressing and proposing new possible beneficial effects and/or studies/outcome measures which may be acceptable beyond those evaluated so far. One of the major concerns of applicants is the lack of certainty that a certain claimed benefit will be accepted or not. Industry groups have called therefore for pre-submission guidance meetings, which EFSA has declined. In order to provide certainty, we would ask EFSA to include in this guidance its views, based on the latest advances in science on what would or would not be accepted as beneficial effects, outcome measures and methodologies. Elements of relevance submitted by interested parties should be addressed by EFSA in the

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		guidance document. Some of these elements have already been submitted in the context of the previous consultation and technical meeting.
Mondelez International	5. Other comments	• Page 4 : "The revision is not aimed at addressing and proposing new possible beneficial effects and/or studies/outcome measures which may be acceptable beyond those evaluated so far." Does it mean that the list of acceptable beneficial effects and studies/ outcomes measures could not be updated in order to take into account the evolution of science? • Will the EFSA plan a meeting with experts/ stakeholders to discuss and finalized the updated guidance on the scientific requirements for health claims related to gut and immune function (like the meeting organized in December 2010 in Amsterdam to discuss the first draft of this document)?
Nestlé S.A.	5. Other comments	Claims based on reduction of inflammation Nestlé suggests that, for example: § older adults with low grade inflammation or obese people are considered as appropriate study groups for inflammation-related outcomes; Schiffrin EJ1, Morley JE, Donnet-Hughes A, Guigoz Y. The inflammatory status of the elderly: the intestinal contribution. Mutat Res. 2010 Aug 7;690(1-2):50-6. doi: 10.1016/j.mrfmmm.2009.07.011. Epub 2009 Aug 8. Phillips CM1, Perry IJ, Does inflammation determine metabolic health status in obese and nonobese adults? J Clin Endocrinol Metab. 2013 Oct;98(10):E1610-9. doi: 10.1210/jc.2013-2038. Epub 2013 Aug 26. .J. Lim, A. Iyer, L. Liu, J. Y. Suen, R.-J. Lohman, V. Seow, M.-K. Yau, L. Brown, D. P. Fairlie. Diet-induced obesity, adipose inflammation, and metabolic dysfunction correlating with PAR2 expression are attenuated by PAR2 antagonism. The FASEB Journal, 2013; 27 (12): 4757 DOI: 10.1096/fj.13-232702 § a decrease in incidence not only of diseases, but also of associated co-morbidities (e.g. insulin resistance) is

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		considered as valid and sufficient outcome measure to show a reduction of inflammation.
Valio Ltd	5. Other comments	Most negative opinions made by EFSA evaluating the probiotic claim applications are due to short-comings in the protocol, methodology or in statistical planning and analysis – not in the strength of clinical outcomes. Case by case assessment creates uncertainty of requirements applied for the studies, and so for the company planning a novel clinical trial, the risk is too high for investments in clinical trials with uncertainty in both requirements and clinical outcome. Dialogue between the applicant and EFSA before initiating clinical trials would result in better trials as well as in fewer and better applications.

ABBREVIATIONS

IBS	Irritable Bowel Syndrome
sIgA	Secretory IgA
WURSS	The Wisconsin Upper Respiratory Symptom Survey.