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Draft Scientific and technical guidance for the preparation and presentation of a health claim application

(Revision 2)

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

Abstract

The European Food Safety Authority (EFSA) asked the Panel on Dietetic Products Nutrition and Allergies (NDA) to update the scientific and technical guidance for the preparation and presentation of an application for authorisation of a health claim published in 2011. Since then, the NDA Panel has gained considerable experience in the evaluation of health claims, and has also increased interactions and exchange of views with stakeholders. Lessons learnt from these experiences have been translated into a new General scientific guidance for stakeholders on health claim applications (published in January 2016). In this context, it is noted the need to adapt the existing scientific and technical guidance for stakeholders to the new scientific and technical developments in this area. This guidance document presents a common format for the organisation of information for the preparation of a well-structured application for authorisation of health claims which fall under Articles 13(5), 14, and 19 of Regulation (EC) No 1924/2006. This guidance outlines: the information and scientific data which must be included in the application, the hierarchy of different types of data and study designs (reflecting the relative strength of evidence which may be obtained from different types of studies) and the key issues which should be addressed in the application to substantiate the health claim.

Keywords: health claims, food/constituent, substantiation, human pertinent data, comprehensive review, application, guidance

Requestor: European Commission

Question number: EFSA-Q-2016-00285

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Summary

The European Food Safety Authority (EFSA) asked the Panel on Dietetic Products, Nutrition and Allergies (NDA) to update the scientific and technical guidance for the preparation and presentation of an application for authorisation of a health claim, which was published in 2007 and subsequently revised in 2011 to include purely administrative nature modifications.

Since then, the NDA Panel has gained considerable experience in the evaluation of health claims, and has also increased interactions and exchange of views with stakeholders, both through a technical meeting and through public consultations on guidance documents. Lessons learnt from these experiences have been translated into a new General scientific guidance for stakeholders on health claim applications (published in January 2016), which represents a step forward in assisting applicants to compile their applications for health claims authorisation. In this context, it is noted the need to adapt the existing scientific and technical guidance for stakeholders to the new scientific and technical developments in this area.

The revision of the guidance, endorsed by the NDA Panel on 29 June 2016 for release for public consultation, has been aligned with the General scientific guidance for stakeholders on health claim applications and adapted to include claims that are based on the essentiality of nutrients. It has also been re-structured concerning Parts 1 to 6 including the Appendices to clearly outline the information to be provided.

The purpose of this guidance is to assist applicants in preparing and presenting their applications for authorisation of health claims which fall under Article 14 (referring to children's development and health, and to disease risk reduction claims) or 13(5) (which are based on newly developed scientific evidence and/or which include a request for the protection of proprietary data), or for modification of an existing authorisation in accordance with Article 19 of the Regulation (EC) No 1924/2006.

This guidance applies to health claims related to the consumption of a food category, a food, or its constituents (including a nutrient or other substance, or a fixed combination of constituents); hereafter referred to as food/constituent.

The guidance presents a common format to assist the applicant in the preparation of a well-structured application. This format will also help the NDA Panel to deliver its scientific opinion in an effective and consistent way.

It is important to consider whether or not the health claim proposed is based on the essentiality of nutrients. Data requirements for claims based on the essentiality of nutrients differ compared to other claims, e.g. for the characterisation of the food/constituent, for the characterisation of the claimed effect, for the scientific substantiation of the claim, and for establishing conditions of use.

The application must contain: a proposal for the wording of the health claim and the specific conditions of use. The following should be specified: the target population for the health claim; the quantity of the food/constituent and pattern of consumption required to obtain the claimed effect, and whether this quantity could reasonably be consumed as part of a balanced diet. Where appropriate, the following should also be provided, with a rationale: a statement addressed to persons who should avoid using the food/constituent for which the health claim is made; a warning for any food/constituent that is likely to present a health risk if consumed in excess; any other restrictions of use; directions for preparation and/or use.

The application must also contain:

- information on the characteristics of the food/constituent for which the claim is made. Such characteristics may depend on the nature of the food/ constituent, but also on the claimed effect. Where applicable, this information should contain aspects: such as the composition, physical and chemical characteristics, manufacturing process, and stability, in order to show consistency in the final product for those characteristics considered to influence the claimed effect;
- information to allow characterisation of the claimed effect. For function claims, the (specific) function of the body that is the target of the claim should be specified; for reduction of disease risk claims, both the risk factor and the disease should be identified. A rationale that the proposed changes in the function or the risk factor for disease are beneficial physiological effects for the

target population for which the claim is intended should be provided, together with the outcome measures and methods of measurement which could be used to assess such changes in *in vivo* in humans;

- all pertinent scientific data (published and unpublished, data in favour and not in favour) which form the basis for substantiation of the health claim. For claims other than those based on the essentiality of nutrients, data from studies in humans addressing the relationship between the consumption of the food/constituent and the claimed effect are required for substantiation. Because of the scientific uncertainties in extrapolating non-human data to humans, data from studies in animals or other model systems alone cannot substitute for human data, but may be included only as supporting evidence, for example to provide evidence on the biological plausibility of the specific claim, including evidence on the mechanisms by which the food/constituent could exert the claimed effect.
- for claims other than those based on the essentiality of nutrients, a comprehensive review of **published** human studies addressing the specific relationship between the food/constituent and the claimed effect is required. This review, and the identification of studies considered pertinent to the health claim, should be performed in a systematic and transparent manner in order to demonstrate that the application adequately reflects the balance of all the evidence available. The procedure followed to identify **unpublished human studies** that are considered as pertinent to the health claim should be depicted. For claims based on the essentiality of nutrients, the procedure followed to identify the evidence on the essentiality of the nutrients should also be depicted.

In cases where any of the required data are not relevant for a particular application, reasons/justification must be given for the absence of such data in the application.

As specified in the Regulation, health claims should be substantiated by taking into account the totality of the available scientific data and by weighing the evidence, subject to the specific conditions of use. In particular, the evidence should demonstrate the extent to which:

i. the food/constituent is defined and characterised;

ii. the claimed effect is based on the essentiality of a nutrient, OR

the claimed effect is defined and is a beneficial physiological effect for the target population, and can be measured *in vivo* in humans;

iii. a cause and effect relationship is established between the consumption of the food/constituent and the claimed effect in humans (for the target group under the proposed conditions of use), by considering the strength, consistency, specificity, dose–response, and biological plausibility of the relationship;

iv. the quantity of the food/constituent and pattern of consumption required to obtain the claimed effect could reasonably be achieved as part of a balanced diet.

It is intended that the guidance will be kept under review and will be further updated as appropriate in the light of experience gained from the evaluation of health claim applications. Once adopted, this guidance supersedes the scientific and technical guidance for the preparation and presentation of an application for authorisation of a health claim published in 2011.

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Background and Terms of reference as provided by EFSA

Background

Regulation (EC) No 1924/2006[1] harmonises the provisions related to nutrition and health claims and establishes rules governing the Community authorisation of health claims made on foods. According to the Regulation, health claims should be only authorised for use in the Community after a scientific assessment of the highest possible standard to be carried out by 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 efforts on developing scientific criteria for the substantiation of health claims, and has published guidance on the scientific substantiation of health claims since 2007[2].

In the last years, the NDA Panel has gained considerable experience in the evaluation of health claim applications. Interactions and exchange of views with stakeholders have also increased considerably, both through a technical meeting[3] and through public consultations on guidance documents[4]. The NDA Panel has translated the lessons learnt from these experiences into a revised General scientific guidance for stakeholders on health claim applications[5], which was recently published and represents a step forward in assisting applicants to compile their applications for health claims authorisation. In this context, it is noted the need to adapt the existing scientific and technical guidance for stakeholders[6] to the new scientific and technical developments in this area.

To this end, the NDA Panel is asked to update the scientific and technical guidance for the preparation and presentation of an application for authorisation of a health claim[7].

Terms of reference

The NDA Panel is requested by EFSA to update the scientific and technical guidance for the preparation and presentation of an application for authorisation of a health claim.

The guidance document shall clarify and address the scientific and technical developments in this area, taking into account the experience gained by the NDA Panel with the evaluation of health claims and the comments received from stakeholders in technical meetings and public consultations.

The draft guidance shall be released for public consultation prior to finalisation.

The draft guidance shall be revised taking into account the comments received during the public consultation before the adoption by the NDA Panel. A technical report on the outcome of the public consultation shall be published.

Introduction

1. Scope

The guidance presented in this document is for preparing and presenting applications for authorisation of health claims which fall under Article 14 of the Regulation, i.e. reduction of disease risk claims and claims referring to children's development and health.

- "Reduction of disease risk claim" means any health claim that states, suggests or implies that the consumption of a food category, a food or its constituents significantly reduces a risk factor in the development of a human disease (as defined in the Regulation).

[1] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.
[2] http://www.efsa.europa.eu/en/nda/ndaclaims.htm
[3] http://www.efsa.europa.eu/it/supporting/pub/569e
[4] http://www.efsa.europa.eu/it/supporting/pub/569e
[5] http://www.efsa.europa.eu/it/efsajournal/pub/4367
[6] Scientific and technical guidance for the preparation and presentation of an application for authorisation of a health claim http://www.efsa.europa.eu/en/efsajournal/pub/2170
[7] http://www.efsa.europa.eu/en/efsajournal/pub/2170

- "For children's claims", there is no definition given in the Regulation. Therefore the proposed health claims referring to children's development and health will be considered on a case by case basis (see also Commission guidance on the implementation of Regulation (EC) No 1924/2006).

The guidance is also applicable to applications for authorisation of health claims which fall under Article 13(5) of the Regulation, i.e. which are based on newly developed scientific evidence and/or which include a request for the protection of proprietary data.

Applications for the modification of existing authorisations of health claims in accordance with Article 19 of the Regulation shall also be presented, as appropriate, in the format outlined in this document.

2. Objectives

Without prejudice to Commission Regulation (EC) No 353/2008, the guidance presented in this document is intended to assist applicants in the preparation and presentation of well-structured applications for authorisation of health claims.

It presents a common format for the organisation of the information to be provided and outlines:

- the information and scientific data which must be included in the application, i.e. for health claims which are based on the essentiality of nutrients and for other health claims,
- the hierarchy of different types of data and study designs, reflecting the relative strength of evidence which may be obtained from different types of studies,
- the key issues which should be addressed in the application to substantiate the health claim.

It is intended that the guidance will be kept under review, and will be further updated as appropriate in the light of experience gained from the evaluation of health claim applications.

This guidance supersedes the scientific and technical guidance for the preparation and presentation of an application for authorisation of a health claim published in 2011.

General principles

This document should be read in conjunction with the General scientific guidance for stakeholders on health claim applications (EFSA NDA Panel, 2016), Regulation on Nutrition and Health Claims made on foods,[8] the Guidance on the implementation of Regulation (EC) No 1924/2006 (Standing Committee on the Food Chain and Animal Health, 2007), Commission Regulation (EC) No 353/2008,[9] the Commission Implementing Decision (2013/63/EU) of 24 January 2013,[10] and future guidelines and regulations, as applicable.

1) This guidance applies to health claims related to the consumption of a food category, a food, or its constituents (including a nutrient or other substance, or a fixed combination of constituents); hereafter referred to as **food/constituent**. A **fixed combination of constituents** means two or more nutrients and/or other substances which are all required in order to obtain the claimed effect, ideally in specified amounts.

2) In the context of this guidance document:

   - The term **application** means a stand-alone dossier containing the information and the scientific data submitted for the authorisation of a health claim.
   - A **disease/disorder** means a pathological process, acute or chronic, inherited or acquired, of known or unknown origin, having a characteristic set of signs and symptoms which are used for its diagnosis. The diagnosis of diseases/disorders relies on widely accepted, well-defined criteria (i.e. the criteria used for diagnosis are widely accepted by the medical community and can be verified by a physician). In this guidance document, the term **disease** is used to include diseases and disorders, which for the purpose of this guidance are considered as synonymous and have the same meaning.
   - The **totality of the evidence** describes all the studies (e.g. in humans, in animals, *in vitro*) which are taken into consideration to conclude on the substantiation of a claim (including studies in favour and not in favour of the claim).
   - **Efficacy study** refers to an intervention study (in humans, in animals) which investigates the relationship between the food/constituent and the claimed effect.
   - **Pertinent study** means a study from which scientific conclusions that are relevant to the substantiation of a claim (e.g. efficacy studies, bioavailability studies, studies on the mechanism(s) by which a food could exert the claimed effect) can be drawn.
   - **Supportive evidence** refers to studies/data which, on their own, are not sufficient for the scientific substantiation of a claim and that may be part of the totality of the evidence only if pertinent human studies showing an effect of the food/constituent are available.
   - The **target population** is the population group(s) for which health claims are intended (e.g. the general healthy population or specific subgroup(s) thereof).
   - The **study group** denotes individuals recruited for human studies which are submitted for the scientific substantiation of a claim.
   - A **suitable study group** means a study group which is representative of the target population for the claim or a study group from which extrapolation of the results to the target population is biologically appropriate.

[8] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25. Available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2006R1924:20100302:EN:PDF

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

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

3) It is the duty of the applicant to provide all the available scientific data (including data in favour and not in favour) which are pertinent to the health claim in order to demonstrate that the health claim is substantiated by the totality of the scientific data and by weighing the evidence. The NDA Panel should not be required to consider other data that are not part of the application, to undertake any additional literature reviews, or to assemble, or process data in order to evaluate the application. As such, the application should be comprehensive and complete. Each application will be considered on a case by case basis.

4) This guidance presents a common format for the organisation of the information in order to assist applicants in the preparation of well-structured applications. Adherence to this format will facilitate easy access to information and scientific data in applications to help the NDA Panel to carry out its evaluation and to deliver its scientific opinion in an effective and consistent way.

5) One application should be prepared for each individual health claim; this means that only one relationship between a food/constituent and a single claimed effect can be the object of each application. However, multiple formulations of a food/constituent can be proposed by the applicant in the same application as candidates to bear the health claim, provided that the scientific evidence is valid for all proposed formulations of a food/constituent bearing the health claim.

6) Not all the information and data specified in this guidance will be required for each application. In cases where some of the data mentioned in this guidance do not apply to a particular application, reasons/justification must be given for the absence of such data in the application.

7) It is important to consider whether or not the health claim proposed is based on the essentiality of nutrients. Data requirements for claims based on the essentiality of nutrients differ compared to other claims, e.g. for the characterisation of the food/constituent, for the characterisation of the claimed effect, for the scientific substantiation of the claim, and for establishing conditions of use (EFSA NDA Panel, 2016).

8) The application must include a proposal for the wording of the health claim and the specific conditions of use. The following should be specified: the target population for the health claim; the quantity of the food/constituent and pattern of consumption required to obtain the claimed effect, and whether this quantity could reasonably be consumed as part of a balanced diet. Where appropriate, the following should also be provided, with a rationale: a statement addressed to persons who should avoid using the food/constituent for which the health claim is made; a warning for any food/constituent that is likely to present a health risk if consumed in excess; any other restrictions of use; directions for preparation and/or use.

9) The application must contain information on the characteristics of the food/constituent for which the claim is made. Such characteristics may depend on the nature of the food/ constituent, but also on the claimed effect. Where applicable, this information should contain aspects such as the composition, physical and chemical characteristics, manufacturing process, and stability, in order to show consistency in the final product for those characteristics considered to influence the claimed effect. Measurements should be performed in a competent laboratory which can certify the data. Whenever a quality control system is in place for performance/control/documentation (e.g. good manufacturing practice (GMP), good laboratory practice (GLP), applicable ISO standard), the particular system should be indicated.

10) The application must also contain information to allow characterisation of the claimed effect. Such information may depend on the type of claim. For function claims, the (specific) function of the body that is the target of the claim should be specified; for reduction of disease risk claims, both the risk factor and the disease should be identified. A rationale that the proposed changes in the function or the risk factor for disease are beneficial physiological effects for the target population for which the claim is intended should be provided, together with the outcome measures and methods of measurement which could be used to assess such changes in *in vivo* in humans.

11) The application must contain all pertinent scientific data (published and unpublished, data in favour and not in favour) which form the basis for substantiation of the health claim. For

claims other than those based on the essentiality of nutrients, data from studies in humans addressing the relationship between the consumption of the food/constituent and the claimed effect are required for substantiation. Because of the scientific uncertainties in extrapolating non-human data to humans, data from studies in animals or other model systems alone cannot substitute for human data, but may be included only as supporting evidence, for example to provide evidence on the biological plausibility of the specific claim, including evidence on the mechanisms by which the food/constituent could exert the claimed effect.

12) For claims based on the essentiality of nutrients, the procedure followed to identify the evidence on the essentiality of the nutrients should be depicted.

For claims other than those based on the essentiality of nutrients, a comprehensive review of published human studies addressing the specific relationship between the food/constituent and the claimed effect is required. This review, and the identification of studies considered pertinent to the health claim, should be performed in a systematic and transparent manner in order to demonstrate that the application adequately reflects the balance of all the evidence available. The procedure followed to identify **unpublished human studies** that are considered as pertinent to the health claim should be depicted.

13) Data from intervention and observational studies in humans should be organised according to a hierarchy of study designs, and should reflect the relative strength of evidence which may be obtained from different types of studies. For claims other than those based on the essentiality of nutrients, well-designed and conducted randomised controlled trials (i.e. at low risk of bias) investigating the effect of a food/constituent which complies with the specifications of the food/constituent for which the claim is proposed on appropriate outcome variables for the claimed effect, in a suitable study group, and under the conditions of use proposed for the claim are at the top of the hierarchy which informs decisions on substantiation.

14) Data provided to substantiate a health claim should be of high quality with respect to the methodology and reporting. Whenever a quality control system has been used/reported in the conduct of the studies (e.g. GLP, good clinical practice (GCP), as relevant), the particular system should be indicated. Journal abstracts and articles published in newspapers, magazines, newsletters or hand-outs, books or chapters of books for consumers or the general public should not be cited.

15) As specified in the Regulation, health claims should be substantiated by taking into account the totality of the available scientific data and by weighing the evidence, subject to the specific conditions of use. In particular, the evidence should demonstrate the extent to which:

v. the food/constituent is defined and characterised;

vi. the claimed effect is based on the essentiality of a nutrient, OR

the claimed effect is defined and is a beneficial physiological effect for the target population, and can be measured *in vivo* in humans;

vii. a cause and effect relationship is established between the consumption of the food/constituent and the claimed effect in humans (for the target group under the proposed conditions of use), by considering the strength, consistency, specificity, dose–response, and biological plausibility of the relationship;

viii. the quantity of the food/constituent and pattern of consumption required to obtain the claimed effect could reasonably be achieved as part of a balanced diet.

16) The entire application in itself cannot be claimed as confidential. Specific parts, sections, words, graphs or datasets considered as confidential by the applicant should be kept to a minimum and clearly identified. The applicant is required to provide detailed and verifiable justification for every part of the dossier claimed as confidential.

17) As defined in the Regulation, EFSA will make public the summary of the application when received and as provided by the applicant. EFSA will also make public, once adopted, its

scientific opinion on the data and information included in the application, excluding the information considered as confidential[11].

Organisation and content of the application

The following information should be provided in the application, and the structure should follow a common format, i.e. order and numbering system (particularly for the Parts, their main heading and first and second sub-headings). Data provided in the application should be organised into six Parts.

- **Part 1** contains the specific requirements for the administrative and technical data, such as information related to the applicant and the nature of the application (including regulatory status of the health claim), health claim particulars, the application form and the summary of the application.
- **Part 2** contains information specific to the food/constituent that is the target for the claim and its characteristics.
- **Part 3** contains information regarding the characterisation of the claimed effect.
- **Part 4** contains all pertinent scientific data (published and unpublished, data in favour and not in favour) which form the basis for substantiation of the health claim.
- **Part 5** comprises an overall summary of the pertinent scientific data.
- **Part 6** comprises the glossary or abbreviation of terms quoted throughout the different Parts, full reprints of pertinent publications, full study protocols and study reports of unpublished pertinent data, and scientific opinions of regulatory bodies outside the European Union (EU).

Where some of the data described in this guidance do not apply to a particular application, reasons/justification must be given for the absence of such data in the application.

If a study appears under different Parts, cross-references should be given.

[11] More information about how EFSA handles confidential data can be found in Annex A, section A.4. of the General scientific guidance for stakeholders on health claim applications, available at: http://www.efsa.europa.eu/it/efsajournal/pub/4367.

1. Part 1: Administrative and technical data

1.1. Comprehensive table of contents of the application

1.2. Applicant

1.2.1. Company/organisation

Provide the name and address of the company or organisation.[12]

1.2.2. Contact person

Indicate the contact person authorised to communicate with EFSA on behalf of the applicant.[13]

1.3. Specifications

Please select one of the options below:

☐ Application for a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006

Please specify:

☐ Based on newly developed scientific evidence and/or

☐ Includes a request for the protection of proprietary data

☐ Application for a health claim pursuant to Article 14 of Regulation (EC) No 1924/2006

Please specify:

☐ Disease risk reduction claim

☐ Claim referring to children's development and health

☐ Application for a modification of an existing health claim authorisation in accordance with Article 19 of Regulation (EC) No 1924/2006

Please specify:

The health claim that has been authorised and for which the modification is requested

The Commission Regulation under which the claim has been authorised

The part of the authorisation which should be modified

1.4. Proprietary data

State whether the application includes a request for the protection of proprietary data:

☐ yes

☐ no

[12] In case more than one company or organisation submits an application, provide their names and addresses. EFSA requires that only one contact person be authorised to communicate with EFSA.

[13] To facilitate communication, EFSA requires that there be only one contact person per application.

If yes, please specify the Part(s) of the application which include proprietary data for which protection is requested, clearly stating section(s) and page number(s):

Provide verifiable justification[14]/declaration for the proprietary claim:

1.5. Confidential data

State whether the application includes confidential data

☐ yes

☐ no

If yes, please specify the Part(s) in the application (including unpublished studies) which contain confidential data, clearly stating section(s) or data sets, and page number(s) (see also Annex A, section A.4. of the General scientific guidance for stakeholders on health claim application (EFSA NDA Panel, 2016)), and verifiable justification(s)[14]/reasons(s) why the afore-mentioned information needs to be kept confidential should be provided:

Elements of the application dossier for which a request for confidentiality treatment was filed by the applicant	Section(s) or data sets, and page number(s)	Verifiable justification(s)/reasons(s)

1.6. Regulatory status outside the European Union

If this health claim or a similar one has been submitted by the applicant to any regulatory body for a health claim authorisation outside the European Union (EU), please indicate the status of the evaluation of such health claim by each regulatory body (if more than one), as appropriate:

☐ Under consideration

Specify the claimed effect, the wording of the claim, the food/constituent for which the claim has been submitted, and the date of submission. Indicate the regulatory body which is dealing with the application for authorisation of the health claim.

☐ Withdrawn

Provide the claimed effect and the wording of the claim which were withdrawn, the date of submission, the date of withdrawal, and the reason for withdrawal. Indicate the regulatory body at the time of withdrawal.

☐ Approved

Specify the approved claimed effect and the wording of the claim, the food/constituent for which the claim has been approved, the date of approval. Indicate the regulatory body which approved the health claim, and if available, provide a copy of the scientific opinion of the regulatory body which authorised the health claim (in Part 6, section 6.5).

[14] Precise and factual information, ideally documents, proving that the disclosure of the information requested by the applicant to be treated as confidential would result in concrete harm to the commercial or economic interest of the applicant/requestor, or would undermine the protection of privacy and/or integrity of concerned individual(s).

☐ Rejected

Specify the rejected claimed effect and the wording of the claim, the date of rejection and the reasons for rejection. Indicate the regulatory body which rejected the health claim, and if available, provide a copy of the scientific opinion of the regulatory body which rejected the health claim (in Part 6, section 6.5).

1.7. Health claim particulars

1.7.1. Specify the food/constituent for which the health claim is made

1.7.2. Describe the relationship between the food/constituent and the claimed effect, including the outcome variable(s) used to assess the claimed effect *in vivo* in humans and the methods of measurement

1.7.3. Provide a proposal for the wording of the health claim

The proposed wording should be in English.

1.7.4. Conditions of use

Specify the target population for the health claim.

Indicate the quantity of the food/constituent and pattern of consumption required to obtain the claimed effect, and whether this quantity could reasonably be consumed as part of a balanced diet.

Provide, where appropriate, a statement addressed to the category(ies) of the population who should avoid using the food/constituent for which the health claim is made, and include a rationale.

Specify, where applicable, a warning for any food/constituent that is likely to present a health risk if consumed in excess, and provide a rationale.

Specify, where applicable, other restrictions of use, and provide a rationale.

Specify, where applicable, directions for preparation and/or use.

1.8. Application form and summary of the application

Please use the application form provided in Appendix A.

For summary of the application, please use the form provided in Appendix B.

Information requested in Appendices A and B are mandatory.

Supporting documents cited (e.g. the scientific opinion of other regulatory bodies outside the EU) in Part 1 should be provided in Part 6 (section 6.5).

2. Part 2: Characterisation of the food/constituent

Indicate if the food/constituent that is the subject of the health claim is:

☐ a single constituent or a fixed combination of constituents. If yes, please go to section 2.1.

☐ a food or a food category. If yes, please go to section 2.2.

2.1. Single constituent or fixed combination of constituents

For single constituents or fixed combinations of constituents, which are exclusively vitamins and/or minerals, please go to section 2.1.1.

For single constituents which are not vitamins or minerals, and for fixed combinations of constituents in which at least one constituent is NOT a vitamin or a mineral (e.g. *a combination of EPA+DHA+GLA at a weight ratio of 9:3:1*), please go to section 2.1.2.

2.1.1. Vitamins and minerals

If the food constituent for which the claim is made is a vitamin or a mineral, or a fixed combination of vitamins and/or minerals, and its characterisation relates to the chemical form of the nutrient(s) naturally present in foods and forms that are approved for addition to foods[15], please specify:

The name of the food/constituent:

The chemical forms to which the health claim applies (one or more among those included in Commission Regulation (EC) No 1170/2009[15]):

2.1.2. Food/constituents other than vitamins and minerals

Name and characteristics

The source and specifications (e.g. physical and chemical properties, composition, and where applicable, microbiological constituents) of the constituent(s), or fixed combination of constituents, for which the health claim is made should be provided.

The variability from batch to batch should be addressed.

Analytical methods applied should be scientifically sound and standardised to ensure quality and consistency of the data.

Measurements should be performed in a competent laboratory that can certify the data. Whenever a quality control system is in place for performance/control/documentation (e.g. GLP and applicable ISO standard) the particular system should be indicated.

Manufacturing process

Where applicable, a brief overview should be provided. If the production process follows a quality system (e.g. GMP), the particular system should be indicated.

[15] Commission Regulation (EC) No 1170/2009 of 30 November 2009 amending Directive 2002/46/EC of the European Parliament and of Council and Regulation (EC) No 1925/2006 of the European Parliament and of the Council as regards the lists of vitamin and minerals and their forms that can be added to foods, including food supplements. OJ L 314, 1.12.2009, p.36–42.

Stability information

Where applicable, a brief summary of the studies undertaken (e.g. conditions, batches and analytical procedures), and of the results and conclusions of the stability studies, should be provided. Conclusions with respect to storage conditions and shelf-life should be given.

2.2. Food or category of food

2.2.1. Name and composition

A brief description of the food or food category, including characterisation of the food matrix and the overall composition (including the nutrient content of the food), should be provided.

The source and specifications of the food or food category for which the health claim is made should be provided, and in particular the content of the food/constituent(s) which may contribute to exert the claimed effect, if known.

The variability from batch to batch should be addressed.

Analytical methods applied should be scientifically sound and standardised to ensure quality and consistency of the data.

Measurements should be performed in a competent laboratory that can certify the data. Whenever a quality system is in place for performance/control/documentation (e.g. GLP and applicable ISO standard) the particular system should be indicated.

2.2.2. Manufacturing process

Where applicable, a brief overview should be provided. If the production follows a quality system (e.g. GMP), the particular system should be indicated.

2.2.3. Stability information

Where applicable, a brief summary of the studies undertaken (e.g. conditions, batches and analytical procedures), and of the results and conclusions of the stability studies, should be provided. Conclusions with respect to storage conditions and shelf-life should be given.

2.3. References

Provide a complete list of the references quoted in Part 2 (alphabetical order of first authors).

Supporting documents should be provided in Part 6 (section 6.5).

3. Part 3: Characterisation of the claimed effect

3.1. Function claims

The proposed health claim is based on the essentiality of a nutrient

☐ yes ☐ no

If yes, please specify:

a) the function of the body that is the subject of the claimed effect.

b) the rationale/reasons why the body function is a beneficial physiological effect for the target population for which the claim is intended.

If not, please specify:

a) the specific body function that is the subject of the claimed effect.

b) the rationale/reasons why the specific body function is a beneficial physiological effect for the target population for which the claim is intended.

c) how the specific body function can be assessed *in vivo*[16] in humans by generally accepted methods. Please indicate the outcome variable(s) and the methods of measurement proposed to assess the claimed effect in human studies.

3.2. Disease risk reduction claims

3.2.1. Definition of the claimed effect

Please specify:

a) the disease that is the subject of the health claim:

b) the criteria used for the diagnosis of the disease (i.e. the criteria used for diagnosis are widely accepted by the medical community and can be verified by a physician):

c) the risk factor for the development of the human disease:

d) how the specific risk factor can be assessed *in vivo*[13] in humans. Please indicate the outcome variable(s) and the methods of measurement proposed to assess the risk factor in human studies:

3.2.2. Characterisation of the relationship between the factor and the risk of disease

If available, provide evidence from observational studies for an independent association between the proposed risk factor and the incidence of the disease:

[16] 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*.

Provide evidence that the relationship between the risk factor and the development of the disease is biologically plausible:

If available, provide evidence from intervention (drug or dietary) studies that a reduction of the risk factor generally reduces the incidence of the disease:

3.3. References

Provide a complete list of the references quoted in Part 3 (alphabetical order of first authors):

Full reprints of the references quoted should be provided in Part 6 (section 6.2).

4. Part 4: Identification of pertinent scientific data

4.1. Claims based on the essentiality of nutrients

The procedure followed to identify the evidence on the essentiality of the nutrients should be depicted.

Provide case reports of clinical signs and symptoms of deficiency, depletion–repletion studies in humans, animal studies, *in vitro* studies, and/or any other evidence (in favour and not in favour) to establish that:

i. the food/constituent is required for normal human body function(s) i.e. it has an essential mechanistic role in a metabolic function and/or it has the ability to reverse clinical signs and symptoms of its deficiency;

ii. the food/constituent cannot be synthesised by the body, or cannot be synthesised in amounts which are adequate to maintain normal human body function(s);

iii. the food/constituent must be obtained from a dietary source (i.e. a source which is appropriate for human oral consumption).

A complete list of the references (alphabetical order of first authors) should be provided and organised as follows:

a) depletion–repletion studies in humans

b) case reports of clinical signs and symptoms of deficiency in humans

c) animal studies

d) *in vitro* studies

e) review publications (e.g. narrative reviews, text-book chapters, etc.)

Full reprints of references quoted should be provided in Part 6 (section 6.3).

4.2. Claims other than those based on the essentiality of nutrients

4.2.1. Identification of published human studies on the relationship between the consumption of the food/constituent and the claimed effect

Published human studies on the relationship between the consumption of the food/constituent and the claimed effect should be identified in a systematic and transparent manner through a comprehensive review of the scientific literature.

The following information on the comprehensive review should be provided, as appropriate:

Authorship

Name, affiliation, declaration of interests and signature of the reviewer(s) responsible for the comprehensive review should be indicated.

Objectives

The questions that the comprehensive review aims to address should be clearly specified in relation to the study participants, the food/constituent, the comparator (if applicable), the outcome variable(s) used to assess the claimed effect, the methods of measurement which are considered valid with respect to their analytical characteristics, and the study design(s).

Eligibility criteria

Specify the inclusion (and exclusion) criteria applied in order to select publications that are considered pertinent to the health claim with respect to the study participants, the food/constituent, the comparator (if applicable), the outcome variable(s) used to assess the claimed effect, the methods of measurement, the study design(s), and other characteristics, where appropriate.

Literature search and other data sources

The databases that have been searched should be listed.

Please provide the full search strategy, including the terms used, limits used (e.g. publication dates, publication types, languages, population subgroups or default tags), in order to allow replication. Other sources of data used to retrieve pertinent published human studies should be acknowledged (e.g. web sites, hand searching, expert knowledge, etc.).

Published human studies on the relationship between the consumption of the food/constituent and the claimed effect identified as pertinent to the health claim

a) Provide a reference list of the publications that have been identified through the literature search (and/or other data sources) and which have been considered as pertinent to the health claim (i.e. which meet the eligibility criteria specified above). The reference list should be organised in accordance with the hierarchy of study design and publication type as follows:

   a.1) Publications reporting on human intervention (efficacy) studies (e.g. randomised controlled studies, randomised uncontrolled studies, non-randomised controlled studies, other intervention studies)

a.2) Publications reporting on human observational studies (e.g. cohort studies, case-control studies, cross-sectional studies, other observational studies)

a.3) Summary publications reporting on human intervention and/or human observational studies (e.g. systematic reviews, pooled analyses, meta-analyses, other review publications)

Full reprints of the above-mentioned publications should also be provided in Part 6 (section 6.3).

b) Please provide a reference list of the publications that have been identified through the literature search (and/or other data sources) on the relationship between the consumption of the food/constituent and the claimed effect, which have NOT been considered as pertinent to the health claim (i.e. which do NOT meet the eligibility criteria specified above). **For each publication, the reason(s) for exclusion** of the publication from the application should be clearly specified. The full text of these publications should NOT be provided in the application.

4.2.2. Unpublished human studies on the relationship between the consumption of the food/constituent and the claimed effect

The procedure followed to identify unpublished human studies that are considered as pertinent to the health claim should be depicted.

Reference list of unpublished human studies

Provide a reference list of any unpublished human (intervention or observational) studies and of any summary publication (systematic reviews/meta-analyses/pooled analyses) reporting on human (intervention or observational) studies which the applicant considers as being pertinent to the health claim. The reference list should be organised in accordance with the hierarchy of study design and publication type, as follows:

a.1) Human intervention (efficacy) studies (e.g. randomised controlled studies, randomised uncontrolled studies, non-randomised controlled studies, other intervention studies)

a.2) Human observational studies (e.g. cohort studies, case-control studies, cross-sectional studies, other observational studies)

a.3) Summary reports of human intervention and/or human observational studies (e.g. systematic reviews, pooled analyses, meta-analyses, other reviews)

The full protocol and the full study report of the above-mentioned studies **SHOULD** be provided in **Part 6** (section 6.4). For study reports, please see **Appendix C** for the content requirements. EFSA will not evaluate study reports not complying with requirements outlined in Appendix C.

The quality of reporting should be sufficient to allow a full scientific assessment of the studies by the NDA Panel. To this end, applicants should follow international reporting guidelines[17] (e.g. the CONSORT guidelines for randomised controlled trials, the STROBE guidelines for observational studies,

[17] http://www.equator-network.org/

the PRISMA guidelines for systematic reviews, etc.) and the EFSA guidance on statistical reporting[18] (EFSA, 2014).

4.2.3. Published and unpublished supportive evidence

The procedure(s) followed to identify published and unpublished studies other than human studies on the relationship between the consumption of the food/constituent and the claimed effect (e.g. bioavailability studies, studies on the mechanism(s) by which a food could exert the claimed effect) should be depicted.

Reference list of published/unpublished studies

Provide a reference list of the publications/unpublished studies other than human studies on the relationship between the consumption of the food/constituent and the claimed effect which have been considered as pertinent to the health claim. The reference list should be organised in accordance with the hierarchy of study design and publication type, as follows:

a) human studies

b) animal efficacy studies

c) other animal studies

d) *in vitro* studies

Full reprints of the above-mentioned publications, and the full protocol and study report for unpublished studies, should also be provided in Part 6 (sections 6.3 for published studies and 6.4 for unpublished studies).

5. Part 5: Overall summary of pertinent scientific data

The scope of this section is to critically and concisely summarise the extent to which the relationship between the consumption of the food/constituent and the claimed effect is supported by the totality of the evidence identified as pertinent to the health claim in **Part 4** of the application.

Note: No new/additional references should be cited in Part 5, except those identified in Part 4.

5.1. Claims based on the essentiality of nutrients

Provide a reasoned and concise summary on the extent to which:

i. the food/constituent is required for normal human body function(s) i.e. it has an essential mechanistic role in a metabolic function and/or it has the ability to reverse clinical signs and symptoms of its deficiency. Please provide a rationale for the relationship between the metabolic function and/or the specific clinical signs and symptoms of deficiency and the human body function that is the subject of the health claim.

ii. the food/constituent cannot be synthesised by the body, or cannot be synthesised in amounts which are adequate to maintain the normal body function that is the subject of the health claim.

[18] http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/3908.pdf

iii. the food/constituent must be obtained from a dietary source (i.e. a source which is appropriate for human oral consumption).

Cross-references to the pertinent scientific data identified in Part 4 (section 4.1) should be given, where appropriate.

5.2. Claims other than those based on the essentiality of nutrients

The scope of sections 5.2.1 and 5.2.2 is to critically and concisely summarise the extent to which the relationship between the consumption of food/constituent and the claimed effect is supported by the totality of (published and unpublished) human studies identified as pertinent to the health claim in Part 4 (sections 4.2.1 and 4.2.2) of the application. Cross-references to pertinent human studies (intervention or observational) should be given, as appropriate.

5.2.1. Substantiation of a causal relationship between the consumption of the food/constituent and the claimed effect

The extent to which the data substantiate a causal relationship between the consumption of the food/constituent and the claimed effect should be addressed by considering:

i. the specificity of the effect

ii. the dose-response relationship

iii. the magnitude of the effect and its physiological relevance,

iv. the consistency of the effect across studies

5.2.2. Characterisation of the relationship between the consumption of the food/constituent and the claimed effect

The relationship between the consumption of the food/constituent and the claimed effect should be characterised by considering:

i. the study population in which the effect has been demonstrated and whether study participants are representative of the target population,

ii. the conditions under which the effect has been achieved (metabolic room, clinical setting, free-living subjects, etc.),

iii. the sustainability of the effect over time with continuous consumption of the food/constituent, where applicable

v. the lowest effective dose, when available.

vi. the amount of the food/constituent used to achieve the effect, the usual intakes of the food/constituent in the target population, and whether these amounts could be reasonably consumed as part of a balanced diet.

5.2.3. Supportive evidence

Bioavailability

Where applicable, concisely summarise the relevant data and rationale to support that the food/constituent for which the health claim is made is in a form that is available to be used by the human body (e.g. absorption studies).

If available, describe any factors (e.g. formulation and processing) that could affect the absorption or utilisation in the body of the food/constituent for which the health claim is made.

Note: If absorption is not necessary to produce the claimed effect (e.g. plant sterols, fibres and lactic acid bacteria), concisely summarise the relevant data and rationale to support that the food/constituent reaches the target site.

Mechanism(s) of action

If known, concisely describe the mechanism(s) by which the food/constituent could exert the claimed effect. If the food/constituent is a fixed combination of constituents, please indicate how each constituent could contribute to the claimed effect.

Cross-references to published and unpublished supportive studies identified in Part 4 (section 4.2.3) should be given, as appropriate.

Summary of supportive evidence

This section should critically and concisely summarise how, and the extent to which, the published and unpublished studies other than human studies on the relationship between the consumption of the food/constituent and the claimed effect identified in Part 4 (section 4.2.3) may help to support the relationship between the food/constituent and the claimed effect in humans (e.g. by providing evidence on the biological plausibility of the specific claim, including bioavailability of the food/constituent, and the mechanisms by which the food/constituent could exert the claimed effect).

6. Annexes to the application

6.1. Glossary and abbreviations

Used throughout the different Parts. To be presented alphabetically.

6.2. Copies/reprints of references related to characterisation of the claimed effect cited in Part 3

Copies/reprints should be provided by alphabetical order of first authors.

6.3. Copies/reprints of pertinent published data identified in Part 4

Copies/reprints of pertinent published data identified in Part 4 (sections 4.1, 4.2.1 and 4.2.3)

6.4. Full study protocols and reports of pertinent unpublished data identified in Part 4

Copies/reprints of pertinent published data identified in Part 4 (sections 4.2.2 and 4.2.3)

6.5. Other

If available, include here, e.g.:

907 Scientific opinions of regulatory bodies outside the EU for health claim authorisation if available, as
908 referred to in **Part 1**

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910 Supporting documents related to **Part 2** (sections 2.1 and 2.2)

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913 # References

914 EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2016. General scientific
915 guidance for stakeholders on health claim applications. EFSA Journal 2016;14(1):4367, 36 pp.
916 doi:10.2903/j.efsa.2016.4367

917 SCF (Scientific Committee on Food), 2000. Guidelines of the Scientific Committee on Food for the
918 development of tolerable upper intake levels for vitamins and minerals.

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Glossary

Notes: The definitions given in this glossary are valid only for the purpose of this guidance document

Applicant	Refers to the natural or legal person responsible for the submission and content of the application and for the interaction with regulatory authorities in the course of the evaluation until such time as the claim is included in the lists of permitted or rejected health claims by Commission Decision
Application	Means a stand-alone dossier containing the information and scientific data submitted for authorisation of the health claim in question
Bioavailability	Bioavailability of a nutrient relates to its absorption and may be defined as its accessibility to metabolic and physiological processes (SCF, 2000).
Central laboratory	In a multi-centre study, a laboratory is termed to be a central laboratory, if all samples for a certain analysis are sent to a single (central) laboratory for analysis
Clinical study with adaptive design	A study with a prospectively planned opportunity for modification of one or more specified aspects of the study design (e.g. sample-size, randomisation ratio, number of treatment arms) based on an interim analysis with full control of the type I error (FDA, EMA)
Disease/disorder	A pathological process, acute or chronic, inherited or acquired, of known or unknown origin, having a characteristic set of signs and symptoms which are used for its diagnosis
Efficacy study	An intervention study (in humans, in animals) which investigates the relationship between the food/constituent and the claimed effect
Health claim	Any claim which states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health (as defined in Regulation (EC) No 1924/2006)
Fixed combination of constituents	Two or more nutrients and/or other substances which are all required in order to obtain the claimed effect, ideally in specified amounts
Food/constituent	A food category, a food, or its constituents (including a nutrient or other substance, or a fixed combination of constituents)
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
Nutrient	Means protein, carbohydrate, fat, fibre, sodium, vitamins and minerals listed in point 1 of Part A of Annex XIII to Regulation (EU) No 1169/2011[19], and substances which belong to or are components of one of those categories
Other substance	Without prejudice to Regulation (EC) No 178/2002[20], it means a substance other than a nutrient that has a nutritional or physiological effect (as defined in Regulation (EC) No 1924/2006)
Pertinent study	A study from which scientific conclusions that are relevant to the substantiation of a claim (e.g. efficacy studies, bioavailability studies, studies on the mechanism(s) by which a food could exert the claimed effect) can be

[19] Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004. J L 304, 22.11.2011, p. 18–63. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011R1169&from=EN.

[20] 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. Official Journal of the European Union OJ L 31, 1.2.2002, p. 1–24.

	drawn
Study group	Individuals recruited for human studies which are submitted for the scientific substantiation of a claim
Suitable study group	A study group which is representative of the target population for the claim or a study group from which extrapolation of the results to the target population is biologically appropriate
Supportive evidence	Studies/data which, on their own, are not sufficient for the scientific substantiation of a claim and that may be part of the totality of the evidence only if pertinent human studies showing an effect of the food/constituent are available
Target population	The population group(s) for which health claims are intended (e.g. the general healthy population or specific subgroup(s) thereof)
Totality of the evidence	The population group(s) for which health claims are intended (e.g. the general healthy population or specific subgroup(s) thereof)

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Appendices

Appendix A – Application form [Mandatory]

Application form

The application form should be used for an application for a health claim pursuant to Article 13(5) or 14, or for a modification of an existing authorisation in accordance with Article 19 of Regulation (EC) No 1924/2006[21] submitted to a Member State of the European Union for the scientific evaluation by the European Food Safety Authority (EFSA).

A separate application form for each health claim is required.

Food/constituent[22] (specify as appropriate):

Proposed wording of the health claim:

Application for a health claim pursuant to:

- ☐ Article 13(5) of the Regulation 1924/2006
- ☐ Article 14 of Regulation 1924/2006 - Claim referring to children's development and health
- ☐ Article 14 of Regulation 1924/2006 - Reduction of disease risk claim
- ☐ Article 19 of Regulation (EC) No 1924/2006 - for a modification of an existing authorisation

Specify the recipient Member State's Competent Authority:

Applicant[23]**:**

(Company) Name:

Address:

Country:

Contact person[24]:

Name:

Company name:

Address:

Country:

Telephone/mobile number:

E-Mail:

It is hereby confirmed to our best knowledge that all existing data which are relevant to the health claim authorisation have been supplied in the application, as appropriate.

On behalf of the applicant:

Signature

[21] 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.
[22] "Food/constituent" refers to a food category, a food, or its constituents (including a nutrient or other substance, or a fixed combination of constituents).
[23] In case more than one company or organisation submit an application, provide their names and addresses.
[24] To facilitate communication, EFSA requires that there be only **one contact person per application**.

Name
Function
Place and date (dd-mm-yyyy)

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Appendix B – Summary of the application [Mandatory]

Summary of the application

The template provided should be used for the summary of the application for a health claim pursuant to Article 13(5) or 14, or for a modification of an existing authorisation in accordance with Article 19 of Regulation (EC) No 1924/2006[25] submitted to a Member State of the European Union for the scientific evaluation by the European Food Safety Authority (EFSA).

General information

Applicant[26]:
(Company) Name:
Address:
Country:

Recipient Member State of Application:

This application concerns:

☐ a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006

☐ a health claim referring to disease risk reduction pursuant to Article 14 of Regulation (EC) No 1924/2006

☐ a health claim referring to children's development and health pursuant to Article 14 of Regulation (EC) No 1924/2006

☐ a modification of an existing health claim authorisation in accordance with Article 19 of Regulation (EC) No 1924/2006

Please specify:

☐ Modification of an authorised Article 14 health claim

☐ Modification of an authorised Article 13(5) health claim

[25] 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.

[26] In case more than one company or organisation submit an application, provide their names and addresses.

Health claim particulars

Specify the food/constituent:

Describe the relationship between the food/constituent and the claimed effect, including the outcome measure(s) used to assess the claimed effect in humans:

Proposal of the wording of the health claim:

Specify the conditions of use:

Appendix C – Information to be presented in a full study report for unpublished studies or for proprietary studies

EFSA will not evaluate study reports not complying with requirements outlined below.

A study report can be considered complete when it contains at least the information as outlined in this Appendix. This Appendix has been adapted from the International Conference on Harmonization (ICH) guideline E3 on the structure and content of clinical study reports[27] for the purpose of health claim substantiation. Study reports which follow the full structure of ICH E3 are also acceptable.

1. Title page

The title page should include information on the food/constituent under investigation, the primary outcome variable studied, the method of measurement used to assess the outcome variable(s) *in vivo* in human, the study design (e.g. double or single-blind, two or more arms/periods, parallel or cross-over, single or multi-centre), the study population, the study initiation date, the study completion date, the place in which the study was conducted, the name of the funding source, the name of the principal investigator, the name of the author of the report and the date when the report has been signed off.

2. Summary

3. Table of contents

4. List of abbreviations and definition of terms

5. Ethical considerations

This section should include information about the review and approval of the study by an ethics committee. In case a review or approval by an ethics committee was not necessary under local requirements, this should be specified and a detailed justification should be given why this is the case. The section should also contain information about the ethical conduct of the study as well information pertaining to subject information and consent.

6. Trial registration

In this section it should be specified whether the study has been registered in a trial registry. If so, the trial registration number should be given. In case the study has not been registered, explanation should be given.

7. General information about the study

This section should include the name/affiliation of the investigators involved in the study as well as of other people with a major role in the study (e.g. staff carrying out observations related to the outcome variable(s) under investigation), the statisticians and the authors of the report. The section should also provide information about the facilities which were used (e.g. for multicentre studies: information about the study sites and about the use of a central laboratory vs. non-central sample analyses) and whether a contract research organisation has been tasked to carry out the work.

8. Study objectives

The study objectives (i.e. the aim of the study) should be specified in this section

9. Study design

This section should outline whether the study was planned as parallel or cross-over study, as open-label, single-blind (specifying who was unblinded) or double-blind study, as a single- or multi-centre study (with a specification about the number of study sites). This information should also contain information about the country setting, the type of control used, the study duration (including

[27] http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

information about the length of the different study periods) and a discussion on the choice of the study design for investigating the selected outcome. This should also include a discussion on why the chosen control was considered appropriate for the study context. In case the study was planned with an adaptive design, it should be specified which kind of adaptations at which time points were planned in the protocol and whether a Data Monitoring Committee has been used for the implementation of the plan.

10. Study population

In this section the inclusion and exclusion criteria should be described, including the diagnostic criteria (and their validation) used to select subjects, if applicable. This section should also contain a discussion about the appropriateness of the study population for the particular purpose of the study. Any pre-defined criteria for excluding subjects from the study after randomisation should also be given together with information on how these subjects are intended to be followed-up.

11. Study products

A detailed description of the food/constituent under investigation and the control used (if any), including information on the mode of administration, and the amounts used, should be given in this section.

12. Method of assigning subjects to groups

In this section details on the method of assigning subjects to groups (randomisation or minimisation) should be given. It should be given whether this allocation was done in a centralised or decentralised way, whether it was stratified (and if so by which factors) or whether the allocation was done in blocks. Information on the measures taken to conceal the allocation should also be given here.

13. Blinding

Information on the strategy used to ensure blinding should be provided in this section. It should be described how it was achieved that products were not distinguishable by smell, taste or packaging and how products were labelled (e.g. by subject individual codes or other). Information should be given on who had access to the product codes, whether there were any pre-defined circumstances in which the blind would be broken and who from the investigational team would be unblinded in case of such a need. For studies for which proper blinding could not be achieved, it should be discussed and justified why it was considered that this was not possible. In case of studies with an adaptive design, it should be reported how it was ensured that the study personnel remained blinded to the interventions, especially if the pre-planned adaptation required unblinding of the data. In such a case, it should be justified why the particular adaptation made it necessary to unblind the data and why the same aim could not have been achieved with statistical methods not requiring such unblinding.

14. Concomitant medication or interventions

Any concomitant medication or non-pharmacological interventions allowed by the study protocol should be described here.

15. Compliance with the intervention and the protocol

This section should include a detailed description about the measures taken to ensure and assess compliance with the intervention and the protocol.

16. Outcome variable(s) measured

Information about the pre-defined primary outcome variable(s), secondary outcome variable(s) and all other outcomes planned to be measured should be presented in this section.

The methods of measurement used to assess the outcome variable(s) *in vivo* in human should be specified.

This section should also include information about the timing of the measurements, ideally including a flow-chart and a justification of the appropriateness of the endpoints chosen for the aim and objectives of the study.

17. Data quality assurance

Any measures taken with respect to the quality assurance of collected data should be addressed here.

18. Pre-planned statistical analyses

This section should include information about what was planned with respect to the statistical analysis (and not what has actually been done). The choice of each statistical technique to be used should be appropriately justified. In this section, it should also be stated whether there were any pre-planned sub-group analyses. Also, the data analysis sets (e.g. ITT vs. PP) should be defined. It should be specified which of the analyses presented have been pre-specified as the main analysis in case several alternative analyses for one outcome are planned (e.g. ITT vs. PP or different models used). The reasons for the choice of the analysis should be given. In case it is planned to impute data, information should be given on how it is planned to assess the robustness of the assumptions made with respect to the imputation of data. For studies for which an adjustment for multiple comparisons is needed in order to preserve the family-wise type I error rate, the pre-planned approach towards adjusting for multiplicity should be specified. In case of studies with an adaptive design, the number and time-points of pre-specified interim analyses as well as the statistical methods used to conserve the type I error rate should be given. The appropriateness of the statistical method used for the design of the study should be discussed. Finally, it should be stated which analyses were planned to be confirmatory and which ones exploratory.

19. Determination of sample size

Detailed information on how the planned sample size of the study was calculated should be given here. This should include information about the expected size of the effect, the assumed standard deviation of the population, the significance level chosen, the anticipated power of the study, and the statistical tests (to be performed) to which the sample size calculation related. In addition, information should be given on whether equal or unequal allocation to groups has been accounted for in the sample size calculation (if unequal allocation is foreseen) and whether any allowance for drop-out has been made. Finally, the programme used to calculate the sample size should be stated. In case of studies with adaptive design allowing for sample size re-estimation, the planned method for re-estimating sample size should be described.

20. Protocol amendments, deviations and violations/deviations from the planned approaches and analyses

This section should address in detail any non-adherence or changes made during or after the study with respect to the pre-planned approaches or pre-planned analyses.

Any protocol amendments (i.e. a systematic change in the protocol after approval of the protocol), protocol deviations and violations (i.e. unplanned unsystematic deviations from the protocol either with minor effects (deviations) or affecting the scientific integrity (violations)) should be outlined in this section. A protocol amendment may for example relate to a systematic change of the pre-established inclusion and exclusion criteria, the planned study design, addition or deletion of endpoints, sample size or the planned statistical approaches and the definition of data analysis sets (e.g. ITT vs. PP).

If no protocol amendments have been made, it should be confirmed that the study was carried out according to the protocol and that all pre-established definitions were adhered to.

Protocol deviations and violations may relate to, for example, inadequate or not-timely collected informed consent, inclusion of subjects not meeting the eligibility criteria, improper breaking of the blind, improper assessment of an outcome, incorrect or missing tests, rescheduled or missed study visits, visits outside the permitted window, inadequate record keeping, use of not permitted medication or a non-pharmacological intervention.

In case any additional exploratory analyses were conducted which were not part of the (amended) protocol, but should, for example be used to inform a subsequent study, such as unplanned sub-group analyses, this should be stated as well.

21. Subject flow

A clear description on who entered the study, on the number of randomised subjects, on the number of subjects who entered and completed each study phase, on the number of drop-outs and withdrawals should be included in this section. The reasons for subjects dropping-out of the study or having been withdrawn from the study by investigators should be stated. Also, information if and in how many occasions the blind has been broken should be given here.

22. Data sets analysed

This section should include a clear description of the definition of each analysis set (e.g. ITT, PP) used for final analysis, including information on the number of subjects included in each of the analysis per time point measured. In case PP analyses are presented, information should be given to which extent subjects included in this analysis set could have deviated from the protocol and were still considered eligible for inclusion in this analysis set. Finally, the reasons for excluding subjects from analysis at each time point should be given.

23. Baseline characteristics of the study population

In this section baseline characteristics for all analysis sets should be given (e.g. ITT, PP, completers, other) - overall and by study centre.

24. Results of assessment of compliance with the intervention and the protocol

In this section results of the assessment of compliance with the intervention and the protocol should be given.

25. Statistical analysis carried out

A detailed description of the statistical analysis carried out should be given in this Section which should be in line with EFSA's guidance on statistical reporting[28] (EFSA, 2014). This description should include in particular, amongst other:

- information on the statistical programme with which the analyses were carried out (version number and operating system),
- information on the type of test or model used,
- information about the model selection,
- a discussion on the appropriateness of the test or model used for the type of data generated
- information on the handling of missing data (including a detailed description about the potential missingness mechanism of the data and how as a consequence the missing data were handled, i.e. in case it was chosen to impute data which methods were selected to do so and which sensitivity analyses were carried out),
- information on which variables or factors were used as fixed and which as random effects (if appropriate),
- information on the assumed covariance structure for longitudinal analyses,
- information on the adjustment for covariates (and justification about the covariates used),
- information on the handling of data stemming from multicentre trials,
- a discussion about whether any issue with respect to multiple comparisons arises (in case of multiple primary outcome or multiple group comparisons or if a secondary outcome is intended to be used as the primary efficacy criterion instead of the primary outcome; this should include a description of the method chosen for adjusting the analysis for multiple comparisons; information on the number of outcomes for which the analysis has been adjusted should also be given.

[28] http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/3908.pdf

26. Results of the study

Results for all endpoints studied for all analyses sets investigated should be presented. The results should be given as estimates with associated confidence intervals and p-values (if corrected for multiple comparisons both the uncorrected and corrected results (simultaneous confidence intervals, p-values accounting for multiple comparisons) should be given. Results should be presented for all groups under investigation and for each time point (if foreseen in the pre-specified analysis plan, otherwise descriptive statistics should be included). Information about the number of subjects included in each analysis at each time point should be given. The information should be presented in a tabular format as well as graphically. For multi-centre trials, results (if comparisons have been pre-specified) or descriptive statistics for the individual centres should also be presented. The number of subjects included in each analysis should be reported (including for each time point for which an analysis is presented or for which information is given). In case data have been imputed, the results of the related sensitivity analyses should be included. The full outputs of the statistical analyses together with the associated codes used for programming should be presented as an Annex. A full list of abbreviations used to denominate variables or factors in the programming should also be given, so that the statistical outputs are self-explanatory.

27. Adverse events

In case adverse events are assessed in the study, information on the outcome of this assessment should be included here.