GUIDANCE

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Scientific and technical guidance for the preparation and presentation of a health claim application (Revision 3)[1]

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Abstract

Upon request from the European Commission, the scientific and technical guidance for the preparation and presentation of an application for authorisation of a health claim initially published in 2007 and subsequently revised in 2011 and 2016 has been updated. 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, and the key issues which should be addressed in the application to substantiate the health claim. This guidance has been revised in 2020 to inform applicants of new provisions in the pre-submission phase and in the application procedure set out in Regulation (EC) No 178/2002, as amended by Regulation (EU) 2019/1381 on the transparency and sustainability of the EU risk assessment in the food chain, that are applicable to all applications submitted as of 27 March 2021. The 2016 version of this guidance remains applicable to applications submitted before 27 March 2021.

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[1] The guidance was adopted on 14 December 2016 by the former Panel on Dietetic products, Nutrition and Allergies. The present revision only aims to inform applicants of the new requirements set out in the General Food Law (Regulation (EC) No 178/2002, as amended by Regulation (EU) 2019/1381 on the transparency and sustainability of the EU risk assessment in the food chain, and to guide to EFSA's practical arrangements implementing these new requirements. For this purpose, the revision concerns only the administrative part. The scientific content remains unchanged. The present guidance (revision 3) was endorsed on 21 January 2021 by the Panel on Nutrition, Novel Foods and Food Allergens (NDA): Dominique Turck, Jacqueline Castenmiller, Stefaan de Henauw, Karen-Ildico Hirsch-Ernst, John Kearney, Helle Katrine Knutsen, Alexandre Maciuk, Inge Mangelsdorf, Harry J McArdle, Androniki Naska, Carmen Pelaez, Kristina Pentieva, Alfonso Siani, Frank Thies, Sophia Tsabouri and Marco Vinceti.

Panel members in 2016: Jean-Louis Bresson, Barbara Burlingame, Tara Dean, Susan Fairweather-Tait, Marina Heinonen, Karen Ildico Hirsch-Ernst, Inge Mangelsdorf, Harry J McArdle, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Kristina Pentieva, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Daniel Tomé, Dominique Turck, Henk Van Loveren, Marco Vinceti and Peter Willatts

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Summary

The scientific and technical guidance for the preparation and presentation of an application for authorisation of a health claim was initially published in 2007. It was subsequently revised in 2011 to include purely administrative nature modifications, and in 2016 to align with the General scientific guidance for applicants on health claim applications and to include claims that are based on the essentiality of nutrients.

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 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. Adhesion to the guidance will help the NDA Panel to deliver its scientific opinion in an effective way and avoid delay in the scientific assessment process.

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.
- Information on the characteristics of the food/constituent for which the claim is made.
- 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 to which the risk factor relates 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 variable(s) and methods of measurement which could be used to assess such changes *in vivo* in humans.
- All pertinent scientific data (published and unpublished data, data in favour and not in favour) which form the basis for substantiation of the health claim.

  For claims based on the essentiality of nutrients, data on the essential mechanistic role in a metabolic function and/or the specific clinical signs and symptoms of deficiency should be provided. 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, data from studies in humans addressing the relationship between the consumption of the food/constituent and the claimed effect are required for substantiation. 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. A comprehensive review of published human studies addressing the specific relationship between the food/constituent and the claimed effect is required. This review for the identification of pertinent studies 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.
- Data provided to substantiate a health claim should be of high quality with respect to the methodology and reporting. 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. 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), it 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, it must be obtained from a dietary source, OR

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.

Upon request from the European Commission (EC) in 2020, the guidance has been revised to inform applicants of new provisions set out in Regulation (EC) No 178/2002[2] (i.e. the General Food Law, hereafter GFL Regulation), as amended by Regulation (EU) 2019/1381[3] on the transparency and sustainability of the EU risk assessment in the food chain (hereafter Transparency Regulation). The new provisions concern the pre-submission phase and the application procedure and are applicable to all applications submitted as of 27 March 2021:

- possibility to request general pre-submission advice (Article 32a(1) of GFL Regulation);
- mandatory notification of information related to studies commissioned/carried out (Article 32b of GFL Regulation);
- publication of non-confidential version of all information submitted in support of the application and related confidentiality decision-making process (Articles 38 and 39-39e of the GFL Regulation);
- public consultation on submitted applications (Article 32c(2) of GFL Regulation).

For detailed information, please refer to EFSA's Practical Arrangements on pre-submission phase and public consultations[4] and EFSA's Practical Arrangements concerning Transparency and Confidentiality.[5]

Applicants should also note that as of 27 March 2021, applications must be submitted using the e-submission system accessible through the European Commission website or the EFSA website.[6]

Before submitting an application, applicants are also recommended to consult the EFSA Administrative guidance for the processing of applications for regulated products (EFSA, 2021a) and the General scientific guidance for applicants on health claim applications (EFSA NDA Panel, 2021).

[2] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January2002 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 amended by Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain and amending Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) No 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC, PE/41/2019/REV/1. OJ L 231, 6.9.2019, p. 1–28.

[3] Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain and amending Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) No 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC, PE/41/2019/REV/1. OJ L 231, 6.9.2019, p. 1–28.

[4] See Decision of the Executive Director of the European Food Safety Authority laying down the practical arrangements on pre-submission phase and public consultations

[5] See Decision of the Executive Director of the European Food Safety Authority laying down Practical Arrangements concerning Transparency and Confidentiality

[6] https://www.efsa.europa.eu/en/applications/toolkit

This revised guidance applies to all applications submitted as of 27 March 2021 and shall be consulted for the preparation of applications intended to be submitted from that date onwards. For applications submitted prior to 27 March 2021, the guidance adopted in 2016 remains applicable.[7]

It is intended that the guidance will be further updated as appropriate in the light of experience gained from the evaluation of health claims.

[7] https://www.efsa.europa.eu/en/efsajournal/pub/4680

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Background and Terms of Reference as provided by EFSA in 2016

Background

Regulation (EC) No 1924/2006[8] harmonises the provisions related to nutrition and health claims and establishes rules governing the Community authorisation of health claims made on foods. According to the Regulation, health claims should be only authorised for use in the Community after a scientific assessment of the highest possible standard to be carried out by the European Food Safety Authority (EFSA).

Owing to the scientific and technical complexity of health claims, the EFSA Panel on Dietetic products, Nutrition and Allergies (NDA Panel) has placed considerable efforts on developing scientific criteria for the substantiation of health claims, and has published guidance on the scientific substantiation of health claims since 2007.[9]

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[10] and through public consultations on guidance documents.[3] The NDA Panel has translated the lessons learnt from these experiences into a revised General scientific guidance for stakeholders on health claim applications,[11] which was published and represents a step forward in assisting applicants to compile their applications for health claims authorisation. In this context, the need to adapt the existing scientific and technical guidance for stakeholders[12] to new scientific and technical developments in this area is noted.

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.[13]

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.

Background and Terms of Reference as provided by the European Commission in 2020

The European Commission (EC) requested EFSA to update the Scientific and technical guidance for the preparation and presentation of a health claim application (Revision 2)[14] in order to align it to Regulation (EU) 2019/1381 on the transparency and sustainability of the EU risk assessment in the food chain[15], which applies as of 27 March 2021.

The guidance document has been identified to require updating as regards its administrative part. This request does not cover the scientific part of the document that has been left unchanged.

[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.
[9] http://www.efsa.europa.eu/en/nda/ndaclaims.htm
[10] http://www.efsa.europa.eu/it/supporting/pub/569e
[11] http://www.efsa.europa.eu/it/efsajournal/pub/4367
[12] 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
[13] http://www.efsa.europa.eu/en/efsajournal/pub/2170
[14] https://www.efsa.europa.eu/en/efsajournal/pub/4680
[15] Regulation EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain and amending Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) No 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC (OJ L 231, 6.9.2019, p. 1).

Introduction

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.

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.

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 further updated as appropriate in the light of experience gained from the scientific assessment of health claims.

General principles

This document should be read in conjunction with Regulation on Nutrition and Health Claims made on foods,[16] 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,[17] the Commission Implementing Decision (2013/63/EU) of 24 January 2013,[18] and applicable guidelines and Union legal acts, and in particular with the GFL regulation[19] which has set out new provisions in the pre-submission phase and in the application procedure that are applicable to all applications submitted as of 27 March 2021.

Before submitting an application, applicants are recommended to consult the following:

- the **General scientific guidance for stakeholders on health claim applications (Revision 1)** (EFSA NDA Panel, 2021), hereafter 'general guidance', for a better understanding of the principles and the approach used by the NDA Panel for the scientific assessment of health claims.

[16] 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.
[17] 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).
[18] 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.
[19] 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 amended by Regulation (EU) 2019/1381 of the European Parliament and of the Council of 20 June 2019 on the transparency and sustainability of the EU risk assessment in the food chain and amending Regulations (EC) No 178/2002, (EC) No 1829/2003, (EC) No 1831/2003, (EC) No 2065/2003, (EC) No 1935/2004, (EC) No 1331/2008, (EC) No 1107/2009, (EU) 2015/2283 and Directive 2001/18/EC, PE/41/2019/REV/1. OJ L 231, 6.9.2019, p. 1–28.

Cross-reference to relevant sections of the afore-mentioned 'general guidance' will be given throughout this guidance, where applicable.

- **Specific guidance on the scientific requirements for health claims**[20], which are intended to assist applicants in preparing their applications for health claims in specific areas, such as those related to:
  - the immune system, the gastrointestinal tract and defence against pathogenic microorganisms;
  - antioxidants, oxidative damage and cardiovascular health;
  - muscle function and physical performance;
  - appetite ratings, weight management and blood glucose concentrations;
  - bone, joints, skin and oral health;
  - functions of the nervous system, including psychological functions.
- **EFSA's Practical Arrangements on pre-submission phase and public consultations**[21] (EFSA, 2021b), as well as the **EFSA's Practical Arrangements concerning transparency and confidentiality**[22] (EFSA, 2021c), available on the EFSA website.
- **EFSA Administrative guidance for the processing of applications for regulated products** (EFSA, 2021a) and the **EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products** (EFSA, 2021d) for an overview of the support initiatives provided by EFSA to applicants.

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.

[20] https://www.efsa.europa.eu/en/applications/nutrition/regulationsandguidance
[21] See Decision of the Executive Director of the European Food Safety Authority laying down the practical arrangements on pre-submission phase and public consultations
[22] See Decision of the Executive Director of the European Food Safety Authority laying down practical arrangements concerning transparency and confidentiality

- **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.

3) 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 the guidance will facilitate easy access to information and scientific data in applications to help the NDA Panel to deliver its scientific opinion in an effective way and avoid delay in the evaluation process.

4) It is the duty of the applicant to provide all the available scientific data (including data in favour and not in favour, published and unpublished) which are pertinent to the health claim in order to demonstrate that the health claim is substantiated by the totality of the scientific data. In its evaluation, the NDA Panel may use data which are not included in the application if they are considered pertinent to the claim. However, the NDA Panel should not be required to undertake any additional literature reviews, 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.

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[23] 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) Where some of the information/data required by this guidance are not included in 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 claimed effect 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, 2021).

8) The application must include a proposal for the wording of the health claim and the specific conditions of use. 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 should be specified. Where appropriate, the following should 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 not only 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

[23] For example, a food product available in different flavours (e.g. vanilla, chocolate) or formats (e.g. tablets, powder, liquid).

facility which can certify the data.[24] 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 variables and methods of measurement which could be used to assess such changes *in vivo* in humans.

11) For claims based on the essentiality of nutrients,[25] data (e.g. depletion-repletion studies in human, case reports) on the essential mechanistic role in a metabolic function and/or the specific clinical signs and symptoms of deficiency should be provided. The procedure followed to identify the evidence on the essentiality of the nutrients should be depicted.

12) For claims other than those based on the essentiality of nutrients,[26] 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.

    A comprehensive review of published human studies addressing the specific relationship between the food/constituent and the claimed effect is required. This review for the identification of pertinent studies 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 pertinent human studies to the health claim should be depicted.

    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. 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.

13) 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.

    The quality of reporting should be sufficient to allow a full scientific assessment of the studies by the NDA Panel. Study reports for human efficacy studies (unpublished and/or proprietary) not complying with the requirements outlined in Appendix C may not allow a scientific assessment of the study by the NDA Panel. For transparency reasons, the registration of protocols and publication of results of the human studies submitted for the substantiation of health claims are highly recommended.[27]

    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.

[24] E.g. Information on the accreditation of the involved facility should be provided.
[25] See also section 6.1 of the 'general guidance' (EFSA NDA Panel, 2021)
[26] See also sections 6.2, 7.3 and 7.4 of the 'general guidance' (EFSA NDA Panel, 2021)
[27] http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2014.EN-569/pdf

14) 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) 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), it 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, it must be obtained from a dietary source, OR

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[28], 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.[29]

15) **Transparency and confidentiality** (Articles 38 and 39-39e of the GFL Regulation) - The Transparency Regulation introduced a general principle of proactive disclosure and transparency of information and data submitted to EFSA for scientific evaluation. In the light of this principle, and of the related provisions, EFSA must proactively disseminate all information shared by applicants for the purposes of EFSA's scientific assessment of regulated products, including that submitted during the assessment process. Specifically, EFSA is to make publicly available[30] *inter alia* the following information[31]:

- all its scientific outputs;
- scientific data, studies and other information supporting applications, including supplementary information, as well as other scientific data and information supporting requests from the Commission and the Member States for a scientific output;
- the information on which its scientific outputs are based;
- a summary of the advice provided to potential applicants at pre-submission phase, if applicable.

By derogation from the general principle of proactive disclosure and transparency, EFSA may grant confidential status to certain elements of applications dossiers, provided applicants submit a verifiable justification, and EFSA accepts the confidentiality request.

For this purpose, and for each document for which confidentiality is requested, the applicants are required to upload in the e-submission system:

- **a request to treat certain item(s) as confidential**, specifying: the confidentiality ground(s) and conditions, justification, excerpt of the text, location in the file.

[28] Consistent results obtained from studies by different research groups and/or in different settings strengthen the evidence.
[29] For claims based on the essentiality of nutrients, conditions of use are set on the basis that any significant amount of the essential nutrient in the diet will contribute to the claimed effect (e.g. conditions of use can be linked to nutrition claims). See also section 7.9 of the 'general guidance' (EFSA NDA Panel, 2021).
[30] The proactive disclosure of the above information does not imply permission or licence for their re-use, reproduction, or exploitation in breach of the relevant existing rules concerning intellectual property rights or data exclusivity. EFSA cannot be held liable or responsible for any use of the disclosed data by third parties in breach of any existing intellectual property rights.
[31] For an exhaustive list of the types of information, documents or data which is made proactively available, please refer to Articles 5 and 6 of Decision of the Executive Director of the European Food Safety Authority laying down practical arrangements concerning transparency and confidentiality (EFSA, 2021c).

- **a version of the concerned document with all information visible and no blackening applied**. In this version, all information claimed to be confidential by the applicant should be boxed or earmarked (confidential version, not for public disclosure);
- **a non-confidential version with all elements claimed to be confidential blackened** (public version).

The non-confidential (public) version of the dossier will be made publicly available in the OpenEFSA portal[32] as soon as the application is declared valid. The items on which confidentiality requests may be made are set out in Article 39(2) of the GFL Regulation. The decision on confidential treatment of information follows the procedure set out in Articles 39-39e of the GFL Regulation.

Upon publication of the non-confidential version of the application by EFSA following the implementation of EFSA's confidentiality decision, EFSA will launch **public consultation with third parties** on the EFSA website (Article 32c(2) of GFL Regulation).

Organisation and content of the dossier

The following information should be provided in the dossier, and the structure should follow the pre-filled table of content required by the e-submission system available through EFSA's[33] and European Commission's websites, to be used for submitting the application. Data provided in the dossier should be organised as follows:

- Administrative data
- Public summary (see appendix A)
- Technical dossier

This guidance details the information to be provided in the technical part of the dossier (see also General principle 15 above), that specifically should report data and scientific information as detailed below:

- Administrative and technical data 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 following administrative data should be provided via the e-submission system: applicant's contact details; contact person/person responsible for the dossier contact; subject of the request; scope of the application; existing authorisations in non-EU countries; information on data sharing agreement in place, if any;
- Information for the characterisation of the food/constituent that is the target for the claim.
- Information for the characterisation of the claimed effect.
- All pertinent scientific data (published and unpublished, data in favour and not in favour) which form the basis for substantiation of the health claim.
- An overall summary of the pertinent scientific data.
- The glossary or abbreviation of terms quoted throughout the different Parts, full copies of pertinent publications, full study protocols and study reports of unpublished pertinent data, scientific opinions of regulatory bodies outside the European Union (EU)
- List of annexes and list of references submitted to support the application

Where some of the information/data required by this guidance are not included in a particular dossier, reasons/justification must be given for the absence of such data in the dossier.

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

[32] https://open.efsa.europa.eu
[33] https://www.efsa.europa.eu/en/applications/toolkit

1. Technical dossier

1.1. Pre-application information

All relevant pre-application identification(s) received by EFSA in the pre-submission phase for the regulated product which is the subject matter of the application and information required with regard to notification of studies obligation should be provided.[34, 35]

1.2. Health claim particulars

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

1.2.2. 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

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

The proposed wording should be in English.

1.2.4. 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.[36]

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.

Supporting documents (e.g. the scientific opinion of other regulatory bodies outside the EU) should be provided in Section 6.2.

[34] See Decision of the Executive Director of the European Food Safety Authority laying down the practical arrangements on pre-submission phase and public consultations

[35] https://www.efsa.europa.eu/en/applications/toolkit

[36] For claims based on the essentiality of nutrients, conditions of use are set on the basis that any significant amount of the essential nutrient in the diet will contribute to the claimed effect (e.g. conditions of use can be linked to nutrition claims). See also sections 6.2 and 7.9 of the 'general guidance' (EFSA NDA Panel, 2021).

2. Characterisation of the food/constituent[37]

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, and where applicable to Sections 2.3 and 2.4.

☐ a food or a food category. If yes, please go to Section 2.2, and where applicable to Sections 2.3 and 2.4.

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 as described in Section 2.1.1, 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[38] 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 permitted for addition to foods, please specify:

The name of the food/constituent:

The chemical forms to which the health claim applies (one or more among those included in the Annexes to Directive 2002/46/EC[39] and to Regulation (EC) No 1925/2006[40]):

2.1.2. Food/constituents other than vitamins and minerals falling under Section 2.1.1

Name, the characteristic(s)[41], 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 facility 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.

[37] See also section 7.1 of the 'general guidance' (EFSA NDA Panel, 2021).
[38] Eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) + gamma-linolenic acid (GLA)
[39] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. OJ L 183, 12/07/2002 P. 0051 – 0057.
[40] Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods. OJ L 404, 30.12.2006, p. 26–38.
[41] Information relates to those characteristics which may influence the specific physiological effect that is the basis of the claim.

2.2. Food or category of food

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 facility 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.

2.3. Manufacturing process

Where applicable, a brief overview of manufacturing process, including e.g. information that the food/constituent can be manufactured consistently to the stated specifications, should be provided. If the production follows a quality system (e.g. GMP), the particular system should be indicated.

2.4. Stability information

Where applicable, a brief summary of the studies undertaken[42] (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.

2.5. References

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

Supporting documents should be provided in Section 6.2.

[42] Stability studies should focus on the food/constituent for which the claim is proposed (i.e. the food/constituent which is expected to exert the claimed effect). The information provided should ensure consistency and stability of the food/constituent in the final food product as consumed.

3. Characterisation of the claimed effect[43]

3.1. Function claims

The proposed health claim is based on the essentiality of a nutrient[12]

☐ 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[44], 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*[45] 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[46]

3.2.1. Definition of the claimed effect

Please specify:

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

b) how the specific risk factor can be assessed *in vivo*[47] in humans. Please indicate the outcome variable(s) and the methods of measurement proposed to assess the risk factor in human studies:

c) the disease to which the risk factor relates:

d) 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):

[43] See also section 7.2 of the 'general guidance' (EFSA NDA Panel, 2021).
[44] See section 7.2.1 of the 'general guidance' (EFSA NDA Panel, 2021).
[45] 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*.
[46] See also section 7.2.2 of the 'general guidance' (EFSA NDA Panel, 2021).
[47] It includes the measurement of outcome variables in vivo and the measurement (*ex vivo*) of outcome variables in biological samples following an intervention *in vivo*.

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

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

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 Section 3 (alphabetical order of first authors):

Full copies of the references quoted should be provided in Section 6.3.

4. Identification of pertinent scientific data

4.1. Claims based on the essentiality of nutrients[48]

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

[48] See also section 6.1 of the 'general guidance' (EFSA NDA Panel, 2021).

c) animal studies

d) *in vitro* studies

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

Full copies of references quoted should be provided in Section 6.4.

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[49]

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.[50]

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 group(s), 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 group(s), 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).

[49] See also section 7.4 of the 'general guidance' (EFSA NDA Panel, 2021).
[50] Applicants could consider the EFSA guidance on the application of systematic review methodology to food and feed safety assessments to support decision making for that purpose (EFSA, 2010).

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 copies of the above-mentioned publications should also be provided in Section 6.4.

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 **Section 6.5**.

For study reports of human efficacy studies (unpublished and/or proprietary), please see **Appendix C** for the content requirements.

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 copies of the above-mentioned publications, and the full protocol and study report for unpublished studies, should also be provided in Sections 6.4 for published studies and 6.5 for unpublished studies.

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 **Section 4** of the application.

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

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 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 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 (consistent results obtained from studies by different research groups and/or in different settings strengthen the evidence).

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 group(s) in which the effect has been demonstrated and whether study groups 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.

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 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 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

Electronic copies of all pertinent studies (published and unpublished, proprietary and not proprietary) submitted in support of the dossier, including electronic copies of protocols and of full study reports for human efficacy studies (unpublished and/or proprietary) to the applicant should be uploaded in the e-submission system (in alphabetical order of first authors) as part of the technical dossier.

EFSA strongly recommends that each document, including annexes (i.e. study reports, raw data, published studies and any other document in the technical dossier) be electronically **searchable** and accessible to allow downloading and printing of the file. This applies to **all documents or information** uploaded as part of the initial submission, or later during completeness/validity check or in the risk assessment process.

The applicant must ensure that terms and conditions asserted by any rightsholder of studies, information or data submitted to EFSA are fully satisfied. The applicant may consult with copyright licensing authorities (i.e. at national level) for guidance on purchasing the appropriate licenses to provide studies, information or data to EFSA, taking into account the proactive disclosure requirements as detailed above. For publications already available to the public upon payment of fees (e.g. studies published in scientific journals) for which the applicant does not have or cannot obtain intellectual property rights for the purposes of the proactive public disclosure requirements, the applicant must provide (a) a copy of the relevant publications along with the relevant bibliographic references/citations for scientific assessment purposes only, in the confidential version of its application and (b) these relevant bibliographic references/citations where these publications are available to the public in the non-confidential version of its application for public dissemination on the OpenEFSA portal.[51]

6.1. Glossary and abbreviations

Used throughout the different Sections. To be presented alphabetically.

[51] https://open.efsa.europa.eu

6.2. Supporting documents and copies of references related to authorisations in non-EU countries and to Section 2

If available, include here, e.g. scientific opinions of regulatory bodies outside the EU for health claim authorisation:

Supporting documents referred to in Section 2 related to characterisation of the food/constituent.

Copies should be provided by alphabetical order of first authors.

6.3. Copies of references related to characterisation of the claimed effect cited in Section 3

Copies should be provided by alphabetical order of first authors.

6.4. Copies of pertinent published data identified in Section 4

Copies of pertinent published data identified in Sections 4.1, 4.2.1 and 4.2.3 should be provided by alphabetical order of first authors.

6.5. Full study protocols and reports of pertinent unpublished data identified in Section 4

Copies of pertinent unpublished data identified in Sections 4.2.2 and 4.2.3 should be provided by alphabetical order of first authors.

References

EFSA (European Food Safety Authority), 2010. Application of systematic review methodology to food and feed safety assessments to support decision making. EFSA Journal 2010;8(6):1637, 90 pp. doi:10.2903/j.efsa.2010.1637

EFSA (European Food Safety Authority), 2014. Guidance on Statistical Reporting. EFSA Journal 2014;12 (12):3908, 18 pp. doi:10.2903/j.efsa.2014.3908

EFSA (European Food Safety Authority), 2021a. Administrative guidance for the processing of applications for regulated products. *EFSA supporting publication* 2021:EN-6471. doi:10.2903/sp.efsa.2021.EN-6471

EFSA (European Food Safety Authority), 2021b. Decision of the Executive Director of the European Food Safety Authority laying down the Practical Arrangements on pre-submission phase and public consultations. Available online: https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/210111-PAs-pre-submission-phase-and-public-consultations.pdf

EFSA (European Food Safety Authority), 2021c. Decision of the Executive Director of the European Food Safety Authority laying down practical arrangements concerning transparency and confidentiality. Available online: https://www.efsa.europa.eu/sites/default/files/corporate_publications/files/210111-PAs-transparency-and-confidentiality.pdf

EFSA (European Food Safety Authority), 2021d. EFSA's Catalogue of support initiatives during the life-cycle of applications for regulated products. *EFSA supporting publication* 2021:EN-6472. doi:10.2903/sp.efsa.2021.EN-6472

EFSA NDA Panel (EFSA Panel on Nutrition, Novel Foods and Food Allergens), 2021. General scientific guidance for stakeholders on health claim applications (Revision 1).

Glossary and Abbreviations

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
Central laboratory	In a multicentre 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
FAS	Full analysis set
GFL	General Food Law
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)
ITT	Intention-to-treat
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[52], and substances which belong to or are components of one of those categories
Other substance	Without prejudice to Regulation (EC) No 178/2002, 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 drawn

[52] 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.

PP	Per-protocol
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	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)
TR	Transparency Regulation

Appendix A – Public summary of the application [Mandatory]

Public 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[53] submitted to a Member State of the European Union for the scientific evaluation by the European Food Safety Authority (EFSA).

This document will be made available to the public and should not contain any confidential information. The public summary will be published together with the non-confidential version of the dossier on the OpenEFSA portal.[54]

General information

Applicant[55]:
(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

[53] 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.

[54] https://open.efsa.europa.eu/

[55] 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 variable(s) used to assess the claimed effect *in vivo* in humans and the methods of measurement:

Proposal for the wording of the health claim:

Specify the conditions of use:

Appendix B – Information to be presented in a full study report for human efficacy studies (unpublished and/or proprietary)

A study report can be considered complete when it contains at least the information outlined in this Appendix. This Appendix has been adapted from the International Conference on Harmonisation (ICH) guideline E3 on the structure and content of clinical study reports[56] for the purpose of health claim substantiation. Study reports which follow the full structure of ICH E3 are also acceptable.

Study reports not complying with the requirements outlined below may not allow a scientific evaluation of the study by the NDA Panel.

1. Title page

The title page should include information on the food/constituent under investigation, the primary outcome variable(s) studied, the method(s) 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 multicentre), the study group(s), the study initiation and completion date, the place in which the study was conducted, the name of the sponsor, the funding source and its exact role and contribution to the study (e.g. in the design, conduct, analysis and/or reporting of the study, if any), 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 should include information about the review and approval of the study by an ethics committee. Information about the ethical conduct of the study, about how the informed consent was obtained from participants should be provided. If a review or approval by an ethics committee was not provided, this should be specified and duly justified.

6. Trial registration

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

In this section, the name/affiliation of the investigators and 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, should be provided. The section should also include 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 on whether a contract research organisation has been tasked to carry out the work.

8. Study objectives

The objective(s) of the study and the hypothesis to be tested should be specified in this section.

9. Study design

This section should outline whether the study was planned e.g. as open-label, single-blind (specifying who was blinded) or double-blind study, as a single- or multicentre study (with a specification about the number of study sites). Information about the country setting, the type of control used (and the reasons why it was considered appropriate in the context of the study), the study duration and a discussion on the choice of the study design for investigating the selected outcome variable(s) should also be provided.

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

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 was involved in the implementation of the plan.

10. Study group

The inclusion and exclusion criteria should be described, including the diagnostic criteria (and their validation) used to select subjects, if applicable. The appropriateness of the study group for the particular purpose of the study should be discussed. Any predefined criteria for excluding subjects from the study after randomisation should also be given, together with information on how these subjects were intended to be followed-up.

11. Study products

A detailed description of the food/constituent[57] under investigation and the control used (if any), including information on the mode of administration, and the amounts used, should be provided.

12. Method of assigning subjects to groups

Details on the method used to assign subjects to the study groups (randomisation or minimisation) should be given. It should be specified 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 described here.

13. Blinding

Information on the strategy used to ensure blinding should be provided, e.g. measures taken to achieve that the study products were not distinguishable by smell, taste, colour, shape or packaging; 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 predefined circumstances in which the blinding could be broken and who from the team of investigators would be unblinded in case of such a need. If proper blinding could not be achieved, please discuss and justify why this was not possible. For 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 preplanned 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, any rescue medication allowed by the study protocol should be described here (e.g. name of medication, dose and posology; type of non-pharmacological intervention, frequency, duration).

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 predefined primary outcome variable(s), secondary outcome variable(s) and all other outcomes planned to be measured should be presented in this section.

The methods used to assess the outcome variable(s) should be specified.

[57] Sufficient information should be provided to establish that the study was performed with a food/constituent which complies with the specifications given for the food/constituent for which the claim is proposed (e.g. the microbial strain(s) used).

This section should also include information about the timing of the measurements (e.g. flow-chart), and a justification of the appropriateness of the outcome variable(s) chosen to achieve the objective(s) of the study.

17. Data quality assurance

Any measures taken with respect to the quality assurance and quality control systems implemented for data collection should be addressed here. Whenever a quality control system has been used/reported in the conduct of the studies (e.g. GCP, as relevant), the particular system should be indicated.

18. Preplanned statistical analyses

This section refers to the statistical analysis planned before the implementation of the study, and should specify whether any subgroup analyses were preplanned (e.g. whether there was a priori hypothesis of a differential effect in a particular subgroup of subjects). The choice of each statistical technique should be appropriately justified. The data analysis sets (e.g. ITT, FAS, PP) should also be defined. It should be specified which of the analyses presented have been prespecified as the main analysis in case several alternative analyses for one outcome variable are planned (e.g. ITT vs. PP or different models used). The reasons for the choice of the analysis should be given. If imputation of missing data is foreseen, 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 preplanned approach towards adjusting for multiplicity should be specified. In case of studies with an adaptive design, the number and time-points of prespecified 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 relates. 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 identified. 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

Non-adherence or changes made during or after the study with respect to the preplanned approaches or preplanned analyses should be specified here.

Any protocol amendments (i.e. a systematic change in the protocol after approval), protocol deviations and violations (i.e. unplanned unsystematic deviations from the protocol with either minor effects (deviations) or affecting the scientific integrity (violations)) should be outlined.

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 outcome variable(s), sample size, the planned statistical approaches or 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.

Protocol deviations and violations may relate, for example, to 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 variable, 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.

Any additional exploratory analyses conducted which were not part of the (amended) protocol (e.g. unplanned subgroup analyses to inform a subsequent study) should also be recorded.

21. Subject flow

A clear description of the number of subjects screened, the number of subjects recruited, the number of subjects randomised, the number of subjects who entered and completed each study phase, the number of drop-outs and the number of withdrawals should be specified. The reasons for subjects dropping-out of the study or for having been withdrawn from the study by the investigators should be stated. Information about whether and when the blind was broken (if so) should also be given here.

22. Data sets analysed

This section should include a clear definition of each analysis set used for final analysis (e.g. ITT, FAS, PP), including information on the number of subjects available for each analysis at each assessment time point. In case PP analyses are presented, information should be given on the extent to which the subjects included in this analysis set could have deviated from the protocol, and the reasons why they were still eligible for inclusion in the PP analysis set. Finally, the reasons for excluding subjects from each 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, FAS, PP, completers, other) - overall and by study centre for multicentre studies.

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

Results of the assessment of compliance with the intervention and with the protocol should be given here.

25. Statistical analysis carried out

A detailed description of the statistical analysis carried out should be provided, in line with EFSA's guidance on statistical reporting[58] (EFSA, 2014). This description should include, among other, information on:

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

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

26. Results of the study

Results for all the outcome variables assessed and for all analysis 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 the corrected results (confidence intervals and p-values accounting for multiple comparisons)) should be given. Results should be presented for all groups under investigation and for each assessment time point if foreseen in the prespecified analysis plan; otherwise descriptive statistics should be included. The information should be presented in a tabular format, and not only graphically. For multicentre trials, results or descriptive statistics for the individual centres should be presented (if prespecified). The number of subjects included in each analysis and assessment time point should be provided. In case of data imputation, 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 given as an Annex. A full list of the 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, adverse events should be clearly reported (possibly indicating those which may be related to the intervention and those which may be not related to the intervention), together with information on the (diagnostic) criteria used to ascertain them[59].

[59] For reporting of safety-related data see also ICH-E3-'Stucture and contend of study reports'.