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**SCIENTIFIC AND TECHNICAL GUIDANCE FOR THE
PREPARATION AND PRESENTATION OF THE APPLICATION FOR
AUTHORISATION OF A HEALTH CLAIM**

Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies

Adopted on 6 July 2007

(Request N° EFSA-Q-2007-066)

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**Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies
on a request from the Commission related to
scientific and technical guidance for the preparation and presentation of the
application for authorisation of a health claim**

(Request N° EFSA-Q-2007-066)

(Adopted on 6 July 2007)

SUMMARY

The European Commission has requested the European Food Safety Authority (EFSA) to issue an opinion on scientific and technical guidance for the applications for authorisations of health claims under Regulation (EC) No 1924/2006 on nutrition and health claims made on foods.

The Scientific Panel on Dietetic Products, Nutrition and Allergies has prepared a draft Opinion which was published for public consultation. After considering all comments received, the Panel has adopted this Opinion.

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 combination of nutrients/other substances); hereafter referred to as food/constituent.

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 of the Regulation, i.e. reduction of disease risk claims and claims referring to children's development and health. This guidance will be updated at a later stage to cover applications for authorisation of the health claims which fall under Article 18 of the Regulation, i.e. applications for inclusion of health claims in the Community list of permitted claims provided for in Article 13(3) which are based on newly developed scientific evidence and/or which include a request for the protection of proprietary data. It is intended that the guidance will be kept under review and will be amended and updated as appropriate in the light of experience gained from evaluation of health claim applications.

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

In accordance with the requirements of the Regulation, the application must contain:

(a) information on the characteristics of the food/constituent for which a health claim is made. Where applicable, this information should contain aspects considered pertinent to the claim, such as the composition, physical and chemical characteristics, manufacturing process, stability, and bioavailability.

(b) a proposal for the wording of the health claim, including, as appropriate, the specific

conditions of use. The following should be specified, with a rationale: the target population for the intended health claim; where appropriate, a statement addressed to persons who should avoid using the food/constituent for which the health claim is made; 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; a warning for a food/constituent that is likely to present a health risk if consumed to excess; any other restrictions of use; directions for preparation and/or use.

The application must also contain all pertinent scientific data (published and unpublished, data in favour and not in favour) identified that form the basis for substantiation of the health claim. Data from studies in humans addressing the relationship between the consumption of the food/constituent and the claimed effect will be required for substantiation of a health claim; because of the scientific uncertainties in extrapolating non-human data to humans, data from studies in animals or model systems may be included only as supporting evidence, e.g. to explain the mechanism underlying the claimed effect of the food/constituent.

A comprehensive review of the data from human studies addressing the specific relationship between the food/constituent and the claimed effect is required. This review, and the identification of data considered pertinent to the claim, should be performed in a systematic and transparent manner in order to demonstrate that the application reflects adequately the balance of all the evidence available.

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

Guidance is provided for the presentation of summaries of the data from intervention studies and non-interventional studies in humans according to a hierarchy of study designs, reflecting the relative strength of evidence that may be obtained from different types of studies. Instructions are provided for presenting summaries of data from individual studies in humans so as to highlight the relevant aspects related to the design, results and quality of the studies.

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:

- (a) the claimed effect of the food/constituent is relevant for human health,
- (b) a cause and effect relationship is established between the consumption of the food/constituent and the claimed effect in humans (such as: the strength, consistency, specificity, dose-response, and biological plausibility of the relationship),
- (c) 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,
- (d) the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.

KEY WORDS

Health claims, Regulation, food/constituent, substantiation, human data, comprehensive review

BACKGROUND

The 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 (hereafter “**the Regulation**”) entered into force on 19th January 2007¹. In relation to applications for authorisation of health claims, Article 15, paragraph 4 of the Regulation provides the following provision:

“The Commission, having first consulted EFSA, shall establish in accordance with the procedure referred to in Article 25(2) (comitology procedure) implementing rules for application of this Article, including rules concerning the preparation and presentation of the application.”

The Commission will make available administrative guidance for the preparation and the presentation of the application. This guidance needs to be complemented with scientific and technical guidelines regarding the content of the application for health claim authorisation.

Therefore the Commission requests EFSA to provide scientific guidance for the preparation and the presentation of the application for health claim authorisation.

TERMS OF REFERENCE

In accordance with Article 31 of Regulation (EC) N° 178/2002, the European Commission requests the European Food Safety Authority (EFSA) to issue an opinion on scientific and technical guidance for the application for authorisations of health claims.

OBJECTIVES

This guidance is intended to assist applicants in preparing and presenting their applications for authorisation of health claims. It presents a common format for the organisation of the information to be presented to assist the applicant in the preparation of a well-structured application.

This guidance outlines:

- the information and scientific data which must be included in the application,
- the hierarchy of different types of data and of study designs, reflecting the relative strength of evidence which may be obtained from different types of studies,
- instructions for presenting summaries of data so as to highlight the relevant aspects related to the design, results and quality of the studies, and
- the key issues which should be addressed in the application to substantiate the health claim

¹ European Parliament and Council (2006). 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. Official Journal of the European Union OJ L 404, 30.12.2006. Corrigendum OJ L 12, 18.1.2007, p. 3–18.

I. SCOPE

The guidance presented in this document is for preparing and presenting applications for authorisation of the health claims made on food/constituent 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).
- “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, and once a definition is available the guidance will be updated as appropriate.

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

This guidance will also be updated as appropriate at a later stage to cover applications for authorisation of the health claims which fall under Article 18 (or Article 13(5)) of the Regulation, i.e. applications for inclusion of health claims to the Community list of permitted claims provided for in Article 13(3) which are based on newly developed scientific evidence and/or which include a request for the protection of proprietary data.

II. GENERAL PRINCIPLES

This document should be read in conjunction with the Regulation (EC) N° 1924/2006 of the European Parliament and of the Council on nutrition and health claims made on foods, and all other pertinent elements outlined in available administrative guidance² and current and future community guidelines and regulations.

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 combination of nutrients/other substances); hereafter referred to **food/constituent**.
2. The term **application** hereafter means a stand-alone dossier containing the information and the scientific data submitted for authorisation of the health claim in question.
3. It is the duty of the applicant to provide all of the available scientific data (including data in favour and not in favour) that 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 Scientific Panel on Dietetic Products, Nutrition and Allergies (NDA Panel) should not be required to consider other data that are not part of the application, to undertake any additional literature reviews, or assemble, or process data to evaluate the application. As such, the application substantiating a proposed health claim should be comprehensive and complete. Each application will be considered on a case by case basis.

² E.g.: EFSA Pre-submission guidance for applicants intending to submit applications for authorisation of health claims (http://www.efsa.europa.eu/en/science/nda/Pre_submission_guidance.html)

4. This guidance presents a common format for the organisation of the information to assist the applicant in the preparation of a well-structured application. Adherence to this format will also 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 advice in an effective and consistent way.
5. **Not all the information and data specified in this guidance will be required for each application. In cases where some of the data that are required as 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.**
6. The application must contain information on the characteristics of the food/constituent for which a claim is made. Where applicable, this information should contain aspects such as the composition, physical and chemical characteristics, manufacturing process, stability, and bioavailability. Measurements should be performed in a competent laboratory that can certify the data. Whenever a quality system is in place for control/documentation (e.g.: good manufacturing practices (GMP), good laboratory practices (GLP), applicable ISO standard), it should be indicated.
7. The application must contain a proposal for the wording of the health claim, including, as appropriate, the specific conditions of use. The following should be specified, with a rationale: the target population for the intended 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; and where appropriate, a statement addressed to persons who should avoid using the food/constituent for which the health claim is made; a warning for a food/constituent that is likely to present a health risk if consumed to excess; any other restrictions of use; directions for preparation and/or use.
8. 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. Data from studies in humans addressing the relationship between the consumption of the food/constituent and the claimed effect will be required for substantiation of a health claim; 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 to substantiate the health claim but may be included only as supporting evidence, e.g. to explain the mechanism underlying the claimed effect of the food/constituent.
9. A comprehensive review of the data from human studies addressing the specific relationship between the food/constituent and the claimed effect is required. This review, and the identification of data considered pertinent to the health claim, should be performed in a systematic and transparent manner in order to demonstrate that the application reflects adequately the balance of all the evidence available.
10. The data from intervention studies and observational studies in humans should be organised according to a hierarchy of study designs, reflecting the relative strength of evidence which may be obtained from different types of studies.
11. Data provided to substantiate a health claim should be of the quality expected from a peer-reviewed journal. Whenever a quality system has been used/reported in the conduct of the studies (e.g.: GLP, good practices for the collection and analysis of human data, including good clinical practices (GCP), as relevant), it should be indicated.

12. 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:
 - (a) the claimed effect of the food/constituent is relevant for human health,
 - (b) a cause and effect relationship is established between the consumption of the food/constituent and the claimed effect in humans (such as: the strength, consistency, specificity, dose-response, and biological plausibility of the relationship),
 - (c) 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,
 - (d) the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.
13. The application in itself cannot be confidential. Sections considered as confidential by the applicant should be kept to a minimum and clearly identified. As defined in the Regulation, EFSA will make public the summary of the application as provided by the applicant upon its receipt. EFSA will also make public, once adopted, its scientific Opinion on the data and information included in the application, excluding those considered as confidential.
14. One application should be prepared for each individual health claim; this means that only a 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 as candidates to bear the health claim in the same application, provided the scientific evidence is valid for all proposed formulations of a food/constituent bearing that same health claim.

III. 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-heading)**. Data provided in the application should be organised into **five Parts** (see **Diagram 1**).

- **Part 1** contains the specific requirements for the administrative and technical data, such as the application form, information related to the applicant and the nature of the application including the national and international regulatory status of the health claim, health claim particulars, and the summary of the application.
- **Part 2** contains information specific to the food/constituent and its characteristics (such as the composition, physical and chemical characteristics, manufacturing process, stability, and bioavailability data).
- **Part 3** contains summaries (tabulated summary of all pertinent studies identified and of data from pertinent human studies, and written summary of data from pertinent human studies and of non-human studies) and overall conclusions, which follow the scope and the outline of the body of scientific data identified under Part 4.
- **Part 4** contains all pertinent scientific data (published and unpublished, data in favour and not in favour) identified that form the basis for substantiation of the health claim.

- **Part 5** comprises the glossary or abbreviations of terms quoted throughout different Parts, copies/reprints of pertinent publications identified, full study reports of unpublished pertinent data, and scientific opinions of national/international regulatory bodies.

Where some of the data that are required as described below in this guidance document 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.

Suggested steps for the preparation of the application are given below (**Diagram 2**).

Diagram 1: Representation of the organisation of the application*

* Appendices corresponding to the related Parts/Sections of the guidance document are also indicated.

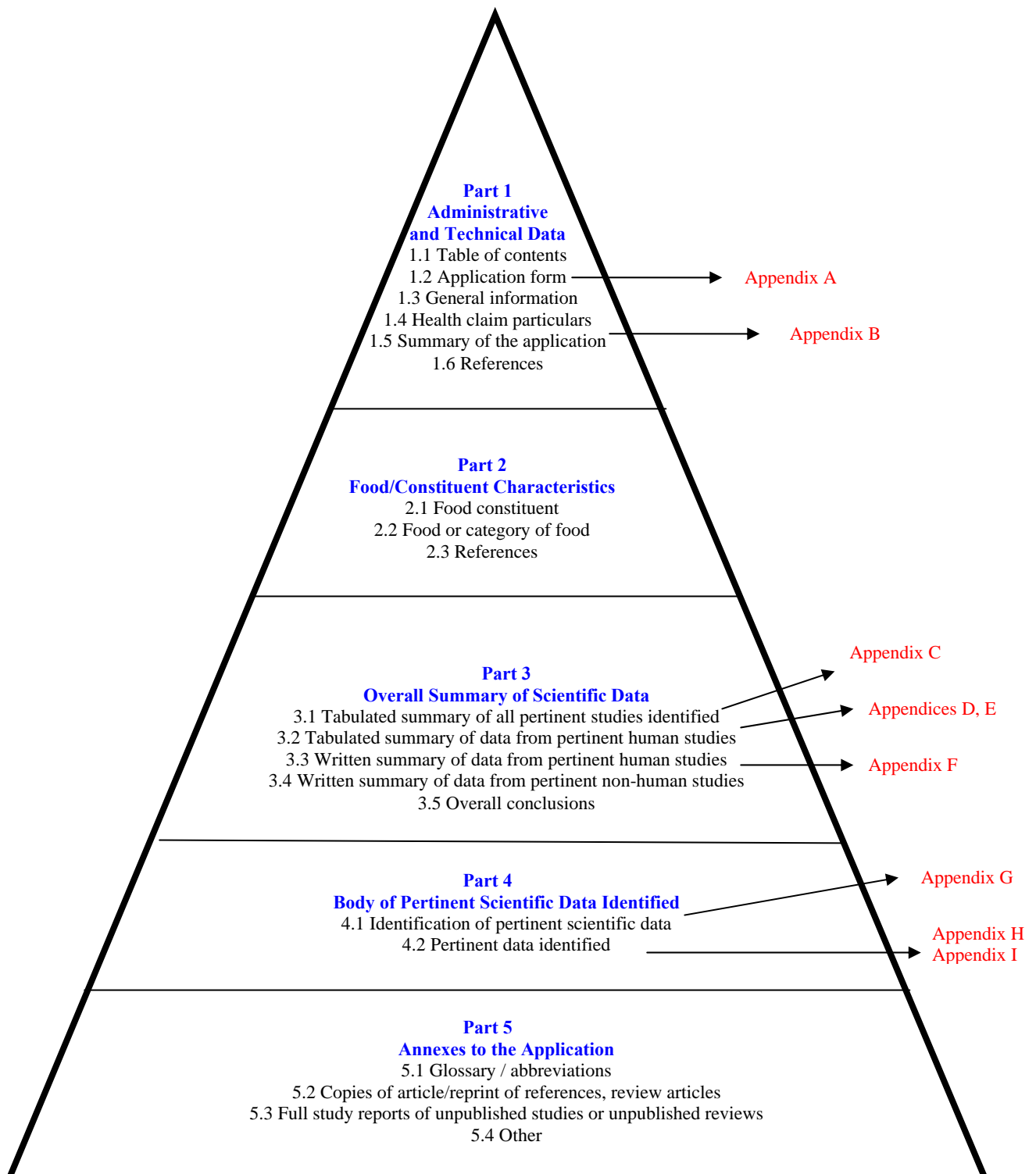
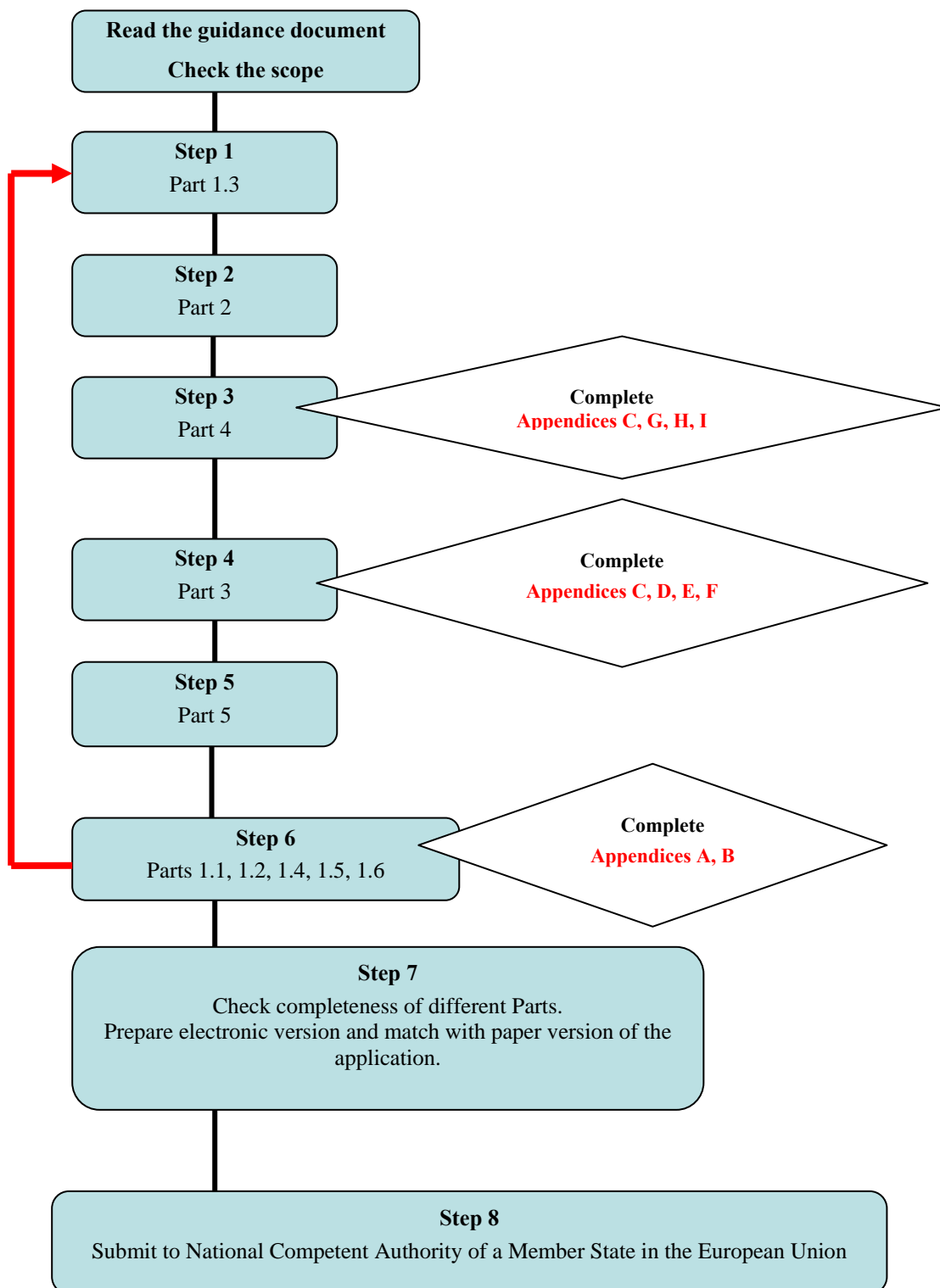


Diagram 2: Suggested steps for the preparation of the application



PART 1: ADMINISTRATIVE AND TECHNICAL DATA

1.1 *Comprehensive table of contents of the application*

1.2 *Application form*

Please use the application form provided in **Appendix A**.

1.3 *General information*

1.3.1 *Applicant*³

1.3.1.1 Provide the name and address of the company or organisation

1.3.1.2 Indicate the contact person⁴ authorised to communicate with EFSA on behalf of the applicant

1.3.2 *Nature of the application*

1.3.2.1 Application for authorisation of a health claim pursuant to Article 14 of the Regulation

Indicate whether it is a disease risk reduction claim

If yes, please specify the health claim

Indicate whether it is referring to children's development and health

If yes, please specify the health claim

State whether it includes proprietary data

If yes, please specify and locate the related Part in the application, section and page number:

Please provide verifiable justification/declaration

State whether it includes confidential data

If yes, please specify & locate the related Part in the application, section and page number:

Please provide verifiable justification/declaration

1.3.3 *National and international regulatory status*

Indicate whether this health claim or a similar one has been scientifically evaluated, either within or outside the European Union. If so, provide a copy of the scientific evaluation.

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

³ In case more than one company or organisation submit an application: provide their names and addresses. EFSA requires **only one contact person authorised to communicate with EFSA**.

⁴ To facilitate communication, EFSA requires having **only one contact person per application**.

- Under consideration
Provide the wording of the claim submitted, the date of submission, the formulation and specify the food/constituent for which the claim has been submitted. Indicate the name of the regulatory body for health claim authorisation dealing with the application.
- Approved
Provide the wording of the claim approved, the date of approval, the formulation and specify the food/constituent for which the claim has been approved. Indicate the name of the regulatory body for health claim authorisation.
If available, provide a copy of the scientific opinion of the regulatory body authorising the health claim (in [Part 5, Section 5.4](#)).
- Rejected
Provide the wording of the claim which was rejected, the date of rejection and the reasons for rejection. Indicate the name of the regulatory body for health claim authorisation which rejected the health claim.
If available, provide a copy of the scientific opinion of the regulatory body rejecting the health claim (in [Part 5, Section 5.4](#)).
- Withdrawn
Provide the wording of the claim that was withdrawn, the date of submission, date of withdrawal and the reason for withdrawal. Indicate the name of the regulatory body for health claim authorisation at the time of withdrawal.

1.4 Health claim particulars

1.4.1 Specify the food/constituent for which a health claim is made

1.4.2 Describe the relationship between the food/constituent and the claimed effect

1.4.3 Provide a proposal for the wording of the health claim for which authorisation is sought

The proposed wording should be in English (For language requirement, please refer to the available administrative guidance⁵).

1.4.4 Specific conditions of use:

1.4.4.1 Specify the target population for the intended health claim and provide a rationale

⁵ EFSA Pre-submission guidance for applicants intending to submit applications for authorisation of health claims (http://www.efsa.europa.eu/en/science/nda/Pre_submission_guidance.html)

- Cross references should be given for the scientific data provided in Parts 3 and 4 (i.e. the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended).
- 1.4.4.2 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 a rationale, with cross-referencing to the scientific data provided in Parts 3 and 4 (i.e. claimed effect observed with the amount of food/constituent and pattern of consumption proposed).
- 1.4.4.3 Provide, where appropriate, a statement addressed to the category(ies) of population who should avoid using the food/constituent for which the health claim is made, and include the rationale.
- 1.4.4.4 Specify, where applicable, the warning for food/constituent that is likely to present a health risk if consumed to excess, and provide a rationale.
- 1.4.4.5 Specify, where applicable, other restrictions of use, and provide a rationale.
- 1.4.4.6 Specify, where applicable, directions for preparation and/or use.

1.5 Summary of the application

Please use the form provided in **Appendix B**.

1.6 References

References quoted under Part 1 should be given here (alphabetical order of first authors).

PART 2: FOOD/CONSTITUENT CHARACTERISTICS

2.1 Food constituent

Characterise the food constituent (e.g. the nutrient or other substance, or a combination of nutrients/other substances) for which the health claim is made. For food or category of food, go directly to **Part 2, Section 2.2**.

2.1.1 Name and characteristics

The source and specifications (e.g. physical and chemical properties, composition, and where applicable microbiological constituents) of the food constituent 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 system is in place for control/documentation (e.g.: GLP, ISO17025), please indicate the system.

2.1.2 *Manufacturing process*

Where applicable, provide a brief overview, and if the production follows a quality system (e.g. GMP) please indicate the system.

2.1.3 *Stability information*

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

2.1.4 *Bioavailability data*

Where applicable, provide the relevant data and rationale that the 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 absorption is not necessary to produce the claimed effect (e.g.: plant sterols, fibres, lactic acid bacteria), please provide the relevant data and rationale that the constituent reaches the target site.

Data on any factors (e.g.: formulation, processing) that could affect the absorption or utilisation in the body of the constituent for which the health claim is made should be provided, if available.

2.2 *Food or category of food*

The food or category of food for which the health claim is made should be described.

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 constituent(s) related to the health claim.

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 control/documentation (e.g.: GLP, ISO17025), please indicate the system.

2.2.2 *Manufacturing process*

Where applicable, provide a brief overview, and if the production follows a quality system (e.g. GMP) please indicate the system.

2.2.3 *Stability information*

Where applicable, provide a brief summary of the studies undertaken (e.g. conditions, batches, analytical procedures) and of the results and conclusions

of the stability studies. Conclusions with respect to storage conditions and shelf-life should be given.

2.2.4 *Bioavailability data*

Where applicable provide the relevant data and rationale that the constituent related to the health claim is in a form that is available to be used by the human body (e.g.: absorption studies).

If absorption is not necessary to produce the claimed effect (e.g.: plant sterols, fibres, lactic acid bacteria), please provide the relevant data and rationale that the constituent related to the health claim reaches the target site.

Data on any factors (e.g.: formulation, processing, other constituents of the food) that could affect the absorption or utilisation in the body of the constituent related to the health claim should be provided, if available.

2.3 *References*

References quoted under **Part 2** should be given here (alphabetical order of first authors).

PART 3: OVERALL SUMMARY OF PERTINENT SCIENTIFIC DATA

The overall summary follows the scope and the outline of the body of scientific data identified in **Part 4**. Provide the information in the following order:

3.1 *Tabulated summary of all pertinent studies identified*

Use the form provided under **Appendix C**.

3.2 *Tabulated summary of data from pertinent human studies*

Use the form provided under **Appendix D** for human intervention studies and the form provided under **Appendix E** for human observational studies.

3.3 *Written summary of data from pertinent human studies*

The scope of this section is to clarify to which extent the relationship between the food/constituent and the claimed effect is supported by the totality of human data identified as pertinent to the health claim in **Part 4 (Section 4.2.1)** of the application and summarised in section 3.2. Cross-references to pertinent human studies (intervention or observational) should be given, when and as appropriate in this section. See **Appendix F** for guidance.

3.4 *Written summary of data from pertinent non-human studies*

This section should address how, and to which extent, the pertinent non-human studies (resulting from Part 4, Section 4.2.2) identified or performed may help

to support the relationship between the food/constituent and the claimed effect in humans (e.g.: bioavailability, mechanisms of action).

3.5 *Overall conclusions*

By taking into account the totality of the data (including evidence in favour and not in favour) and by weighing the evidence, the overall conclusions should clearly define to which extent:

- (a) the claimed effect of the food/constituent is relevant for human health,
- (b) a cause and effect relationship is established between the consumption of the food/constituent and the claimed effect in humans (such as: the strength, consistency, specificity, dose-response, and biological plausibility of the relationship),
- (c) the quantity of the food/constituent and pattern of consumption required to obtain the claimed effect could reasonably be consumed as part of a balanced diet,
- (d) the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.

PART 4: BODY OF PERTINENT SCIENTIFIC DATA IDENTIFIED

Part 4 contains all pertinent scientific data which form the basis for substantiation of the health claim.

4.1 *Identification of pertinent scientific data*

Pertinent data means all human and non-human studies, published or unpublished, that are relevant for the substantiation of health claim applied for, i.e. addressing the relationship between the food/constituent and the claimed effect, including data in favour and data not in favour of such relationship. Pertinent published human data should be identified through a comprehensive review.

Important notice:

- a. Journal abstracts and articles published in newspapers, magazines, newsletters or handouts that have not been peer-reviewed **should not** be cited.
- b. Books or chapters of books for consumers or the general public **should not** be cited.

4.1.1 *Comprehensive review of published human data*

A comprehensive review of the published human data addressing the relationship between the food/constituent and the claimed effect in a systematic and transparent manner is required.

Please provide the following information on the comprehensive review, as appropriate:

4.1.1.1 Authorship

Indicate name, affiliation, declaration of interests and signature of the reviewer(s) responsible for the comprehensive review.

4.1.1.2 Background

Clearly define the food/constituent for which the health claim is made and the claimed effect. In case of a claimed effect that cannot be measured directly, define any marker(s) being selected as surrogate of the claimed effect, if any, e.g.: plasma cholesterol concentrations being used as surrogate marker of cardiovascular disease risk, bone density being used as surrogate marker of osteoporosis risk, etc. In addition, provide information and a rationale for selecting the above as surrogate marker(s) of the claimed effect, stating their relevance and whether they are methodologically valid with respect to their analytical characteristics.

4.1.1.3 Clearly describe the relationship between the food/constituent and the claimed effect (or surrogate markers of the claimed effect), that is being addressed in the comprehensive review.

4.1.1.4 Clearly define exclusion and inclusion criteria that will be applied by the applicant to select pertinent publications.

4.1.1.5 Literature search

List the databases that have been searched and provide details about the search strategy (including the terms used, limits used such as dates of publication, publication types, languages, population subgroups or default tags). Other sources of data should be acknowledged (web sites, hand searching, etc).

4.1.1.6 Identification of pertinent published human data

Please indicate, by using the form provided in **Appendix G**, how many of the identified publications have been included (considered pertinent to the health claim) and excluded (considered not pertinent to the health claim) by applying the inclusion and exclusion criteria defined in **Section 4.1.1.4**.

List of references (but not copies/reprints) of the publications **being** considered as not pertinent to the health claim and therefore **excluded** should be provided here (alphabetical order of first authors).

In addition, for publications considered as pertinent to the health claim, please proceed as follows:

- For original research publications, please indicate the number of pertinent published human studies identified by study design using the form provided under **Appendix C** (to be presented in **Part 3, Section 3.1**); and go to **Part 4, Section 4.2** to provide the synopsis of each pertinent study.
- For published systematic reviews, pooled analyses and meta-analyses, please indicate the number of individual human studies included by

study design using the form provided under **Appendix C** (to be presented in **Part 3, Section 3.1**).

ONLY if the research question addressed by the systematic review, pooled analysis or meta-analysis is directly relevant to the health claim applied for, go to **Part 3, Section 3.2** to present such publications. IF NOT, individual studies included in the above publications should be treated and presented as individual original research publications in **Part 4, Section 4.2**.

- For other review publications, guidelines, or consensus opinions, please refer to them in **Part 3, Section 3.5** as appropriate.

4.1.2 Unpublished human data

Unpublished human studies addressing the relationship between the food/constituent and the claimed effect and considered as pertinent to the health claim applied for, should be mentioned here.

In addition:

Please indicate the number of unpublished human studies identified by study design, by using the form provided under **Appendix C** (to be presented in **Part 3, Section 3.1**); and go to **Part 4, Section 4.2** to provide the synopsis of each pertinent study.

4.1.3 Identification of published non-human data

Please depict the strategy followed to identify published non-human studies that are considered as pertinent to the health claim and state the reasons for selecting them as supporting evidence.

In addition:

Please indicate the number of published non-human studies identified as pertinent to the health claim applied for, by using the form provided under **Appendix C** (to be presented in **Part 3, Section 3.1**); and go to **Part 4, Section 4.2** to organise the pertinent data identified.

4.1.4 Unpublished non-human data

Unpublished non-human studies addressing the relationship between the food/constituent and the claimed effect and considered as pertinent to the health claim applied for, should be mentioned here.

In addition:

Please indicate the number of unpublished non-human studies, by using the form provided under **Appendix C** (to be presented in **Part 3, Section 3.1**); and go to **Part 4, Section 4.2** to organise the pertinent data identified.

4.2 Pertinent data identified

Organise the data identified as pertinent in [Sections 4.1.1 to 4.1.4](#) in the following order: human data, followed by non-human data if appropriate.

4.2.1 *Human data*

Classify human data in accordance with hierarchy of study design.

4.2.1.1 Human intervention studies

Present each study by using the form provided under [Appendix H](#).

4.2.1.1.1 Randomised controlled studies

4.2.1.1.2 Other randomised studies (non-controlled)

4.2.1.1.3 Controlled, non-randomised studies

4.2.1.1.4 Other intervention studies

4.2.1.2 Human observational studies

Present each study by using the form provided under [Appendix I](#).

4.2.1.2.1 Cohort studies

4.2.1.2.2 Case-control studies

4.2.1.2.3 Cross-sectional studies

4.2.1.2.4 Other observational studies (e.g.: case reports)

4.2.1.3 Other

E.g.: Human studies dealing with the mechanisms by which the food/constituent could be responsible for the claimed effect. These studies also include those on bioavailability (cross-reference to [Part 2](#) should be given, if appropriate).

4.2.1.4 List of references of the pertinent published human studies (those studies being included after the comprehensive review) and unpublished human studies should be given (alphabetical order of first authors)

Copies/reprints of pertinent publications should be given under [Part 5, Section 5.2](#). Full study reports of unpublished studies should be annexed under [Part 5, Section 5.3](#).

4.2.2 *Non-human data*

Animal data (including studies investigating aspects related to absorption / distribution / metabolism / excretion of the food/constituent, mechanistic studies, other studies), *ex vivo* or *in vitro* data (meaning studies based on either human or animal biological samples related to the mechanisms of action by which the food/constituent could be responsible for the claimed effect), and other non-human studies, if available, should be presented here. The main objectives, the study design, the nature of the intervention, main results and their relevance to humans should be clearly and concisely summarised for each individual study.

4.2.2.1 List of references related to pertinent published and unpublished non-human data should be given (alphabetical order of first authors)

Copies of article/reprint of references of published studies should be given under **Part 5, Section 5.2**. Full study reports of unpublished studies should be annexed under **Part 5, Section 5.3**.

PART 5: ANNEXES TO THE APPLICATION

5.1 Glossary / Abbreviations

Used throughout different Parts. To be presented alphabetically.

5.2 Copies /reprints of pertinent published data

5.3 Full study reports of pertinent unpublished data

5.4 Other

If available, include here e.g.:

- Scientific opinions of national/international regulatory body for health claim authorisation if available as referred to in **Part 1, Section 1.3.3**.

REFERENCES

Aggett PJ, Antoine JM, Asp NG, Bellisle F, Contor L, Cummings JH, Howlett J, Müller DJG, Persin C, Pijls LTJ, Rechkemmer G, Tuijtelaars S, Verhagen H (2005). Process for the Assessment of Scientific Support for Claims on Foods (PASSCLAIM): Consensus on criteria. *Eur J Nutr* 44 (supplement 1): 5-30.

Des Jarlais DC, Lyles C, Crepaz N; TREND Group (2004). Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: the TREND statement. *Am J Public Health* 94:361-6.

Food Standards Australia and New Zealand:

<http://www.foodstandards.gov.au/foodmatters/healthnutritionandrelatedclaims/index.cfm>

Health Canada:

Interim Guidance Document - Preparing a Submission for Foods with Health Claims: Incorporating Standards of Evidence for Evaluating Foods with Health Claims.

http://www.hc-sc.gc.ca/fn-an/label-etiquet/nutrition/claims-reclam/index_e.html;

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Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, et al. (1999) Improving the quality of reports of meta-analyses of randomised controlled trials: The QUOROM statement. Quality of Reporting of Meta-Analyses. *Lancet* 354: 1896–1900.

QUOROM (Quality of Reporting of Meta-Analyses) [statement checklist](#). A checklist of items which systematic review authors can address in their review to assure readers of the reliability of the review's findings.

SCF (Scientific Committee for Food) (2000). Guidelines of the Scientific Committee on Food for the development of tolerable upper intake levels for vitamins and minerals. Opinion expressed on 19 October 2000. http://ec.europa.eu/food/fs/sc/scf/out80_en.html

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB (2000). Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283: 2008-2012.

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<http://www.cochrane.org/resources/handbook/index.htm>

U.S. Food and Drug Administration (2007). Draft Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims; Availability. Office of Nutrition, Labeling and Dietary Supplements of the FDA Center for Food Safety and Applied Nutrition. <http://www.cfsan.fda.gov/~dms/hclmgui5.html>

PANEL MEMBERS

Jean-Louis Bresson, Albert Flynn, Marina Heinonen, Karin Hulshof, Hannu Korhonen, Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley, Andreu Palou, Hildegard Przyrembel, Seppo Salminen, J (Sean) J Strain, Stephan Strobel, Inge Tetens, Henk van den Berg, Hendrik van Loveren, and Hans Verhagen.

GLOSSARY USED IN THE GUIDANCE DOCUMENT

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 the claim is included in the list of permitted health claims by Commission Decision.
Application	Means a stand-alone dossier containing the information and the 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).
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 the Regulation (EC) No 1924/2006).
Nutrient	Means protein, carbohydrate, fat, fibre, sodium, vitamins and minerals listed in the Annex to Directive 90/496/EEC, and substances which belong to or are components of one of those categories (as defined in the Regulation (EC) No 1924/2006).
Other substance	Without prejudice to Regulation (EC) No 178/2002 ⁶ , it means a substance other than a nutrient that has a nutritional or physiological effect (as defined in the Regulation (EC) No 1924/2006).

⁶ 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.

APPENDICES

Notes to users:

- **Information requested in Appendices A and B are mandatory. Applicants are advised to follow the instructions given and use the forms provided.**
- For the remaining Appendices: Instructions are given to assist applicants in preparing and presenting in a well-structured format pertinent data that have been identified and acquired to substantiate the health claim and to facilitate review and evaluation of the results.
- For preparation of the application, refer also to suggested steps in Diagram 2.

Content:

Appendix A	Application form [Mandatory]
Appendix B	Summary of the application [Mandatory]
Appendix C	Tabulated summary of all pertinent studies identified
Appendix D	Tabulated summary of data from pertinent human intervention studies
Appendix E	Tabulated summary of data from pertinent human observational studies
Appendix F	Written summary of data from pertinent human studies
Appendix G	Results of the review of human data
Appendix H	Synopsis of pertinent individual human intervention studies
Appendix I	Synopsis of pertinent individual human observational studies

APPENDIX A – APPLICATION FORM

APPLICATION FORM



The application form should be used for an application for authorisation of a health claim submitted pursuant to Article 14 of the Regulation (EC) No 1924/2006⁷ to (a) a Member State in the European Union and (b) for the scientific evaluation by the European Food Safety Authority (EFSA).

A separate application form for each health claim is required. It is to be completed by the applicant for inclusion under **Part 1, Section 1.2**.

Information should be provided where applicable. For ease of completion, references to the related part of the application are given.

DECLARATION and SIGNATURE

Application pursuant to Article 14 of the Regulation (EC) No 1924/2006 submitted to:
<Specify the Member State's Competent Authority>

Food/constituent⁸ (specify as appropriate):

Proposed wording of the health claim:

Applicant⁹:

Contact person¹⁰:

It is hereby confirmed to its 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

Name

Function

Place and date (yyyy-mm-dd)

⁷ European Parliament and Council (2006). 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. Official Journal of the European Union OJ L 404, 30.12.2006. Corrigendum OJ L 12, 18.1.2007, p. 3–18.

⁸ “food/constituent” refers to the food category, a food, or constituents (including a nutrient or other substance, or a combination of nutrients/other substances) for which the health claim is made.

⁹ In case more than one company or organisation submitting an application: provide their names and addresses.
EFSA requires only one contact person authorised to communicate with EFSA.

¹⁰ To facilitate communication, EFSA requires having **only one contact person per application.**

GENERAL INFORMATION (Part 1, Section 1.3)

APPLICANT (Part 1, Section 1.3.1)

Applicant¹¹:

(Company) Name:
Address:
Country:

Person authorised for communication on behalf of the applicant with EFSA during the procedure (*Notes: To facilitate communication, EFSA requires having only one contact person*):

Name:
Company name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

SCOPE (Part 1, Section 1.3.2)

This application concerns:

- Application pursuant to Article 14 of the Regulation (EC) 1924/2006**
Please specify:
- Reduction of disease risk claim
 - Claim referring to children's development and health

Indicate whether the health claim applied for complies with:

- The general principles referred to in Art 3 of the Regulation (EC) No 1924/2006
- The general conditions referred to in Art 5 of the Regulation (EC) No 1924/2006
- The specific conditions referred to in Art 10 of the Regulation (EC) No 1924/2006

¹¹ In case more than one company or organisation submit an application, provide their names and addresses.

Indicate whether the application includes:

Proprietary data:	<input type="checkbox"/> Yes	<input type="checkbox"/> No
If yes, has verifiable justification/declaration been provided?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
If yes, has the proprietary data in the application been located?	<input type="checkbox"/> Yes	<input type="checkbox"/> No

Confidential data:	<input type="checkbox"/> Yes	<input type="checkbox"/> No
If yes, has verifiable justification/declaration been provided?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
If yes, has the confidential data in the application been located?	<input type="checkbox"/> Yes	<input type="checkbox"/> No

NATIONAL AND INTERNATIONAL REGULATORY STATUS (Part 1, Section 1.3.3)

State whether approval for this health claim or similar one has been already sought through any regulatory body for health claim authorisation, either within or outside the European Union.

<input type="checkbox"/> Yes	<input type="checkbox"/> No	
If yes, specify the regulatory status:		
Under consideration:	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Approved:	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Rejected:	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Withdrawn:	<input type="checkbox"/> Yes	<input type="checkbox"/> No

HEALTH CLAIM PARTICULARS (Part 1, Section 1.4)

SPECIFY THE FOOD/CONSTITUENT:

(Part 1, Section 1.4.1)

--

DESCRIBE THE RELATIONSHIP BETWEEN THE FOOD/CONSTITUENT AND THE HEALTH CLAIM:

(Part 1, Section 1.4.2)

--

PROPOSAL OF THE WORDING OF THE HEALTH CLAIM:

(Part 1, Section 1.4.3)

SPECIFY THE CONDITIONS OF USE:

(Part 1, Section 1.4.4)

CONTENT OF THE APPLICATION

Please provide the below information, by ticking the “Yes” or “No” boxes as appropriate:

	Is the object of the application for a single claimed effect only?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Parts/sections of the application:			
2.1	Has the food/constituents for which the health claim is made been characterised?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
2.1.1	Has the specification of the constituent for which the health claim is made been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
2.1.2	Has an overview of the manufacturing process of the constituent for which the health claim is made been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
2.1.3	Has the stability information of the constituent for which the health claim is made been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
2.1.4	Have relevant data and rationale that the constituent for which the health claim is made is in a form available to be used by the body been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
2.2	Has the food or category of food for which the health claim is made been characterised?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
2.2.1	Has the specification of the food or category of food for which the health claim is made been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
2.2.2	Has an overview of the manufacturing process of the food or category of food for which the health claim is made been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
2.2.3	Has the stability information of the food or category of food for which the health claim is made been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
2.2.4	Have relevant data and rationale that the constituent related to the health claim is in a form available to be used by the body been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
3.1	Has a tabulated summary of all pertinent studies identified been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
3.2	Has a tabulated summary of data from pertinent human studies been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
3.3	Has a written summary of data from pertinent human studies been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
3.4	Has a written summary of data from pertinent non-human studies been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
3.5	Have the overall conclusions clearly defining the relationship between the food/constituent and the claimed effect as demonstrated by the totality of the data and weighing of the evidence been provided?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
4.1.1	Has the totality of the available scientific human data been reviewed comprehensively?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
4.1.1.6	Have any pertinent published human data been identified?	Yes <input type="checkbox"/>	No <input type="checkbox"/>

4.1.2	Have any pertinent unpublished human data been identified?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
4.1.3	Have any pertinent published non-human data been identified?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
4.1.4	Have any pertinent unpublished non-human data been identified?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
4.2	Have all pertinent data identified been presented?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
5	Have the glossary/abbreviations, copies/reprint of pertinent publications identified, full study reports of unpublished pertinent data, and scientific opinions of national/international regulatory bodies been annexed?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Have reasons/justification been given for the absence of the above requested data in the application?		Yes <input type="checkbox"/>	No <input type="checkbox"/>
Templates provided in the Appendices:			
A	Has the application form been provided under Part 1-Section 1.2?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
B	Has the summary of the application been provided under Part 1-Section 1.5?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
C	Has the tabulated summary of all pertinent studies identified been provided under Part 3-Section 3.1?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
D	Has the tabulated summary of data from pertinent human intervention studies been provided under Part 3-Section 3.2?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
E	Has the tabulated summary of data from pertinent human observational studies been provided under Part 3-Section 3.2?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
F	Has the written summary of data from pertinent human studies been provided under Part 3-Section 3.3?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
G	Has the results of the review of human data been provided under Part 4-Section 4.1.1.6?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
H	Has a synopsis of each pertinent human intervention study been provided Part 4-Section 4.2.1.1?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
I	Has a synopsis of each pertinent human observational study been provided Part 4-Section 4.2.1.2?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Overall conclusions			
	Is there sufficient evidence that the claimed effect of the food/constituent is relevant for human health?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
	Is there sufficient evidence that a cause and effect relationship is established between the consumption of the food/constituent and the claimed effect in humans (such as: the strength, consistency, specificity, dose-response, and biological plausibility of the relationship)?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
	Is there sufficient evidence that 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?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
	Is the specific study group(s) in which the evidence was obtained representative of the target population for which the claim is intended?	Yes <input type="checkbox"/>	No <input type="checkbox"/>

APPENDIX B – SUMMARY OF THE APPLICATION

According to Articles 15(2b) and 15(3g) of the Regulation, the application shall be accompanied by a Summary of the application, and EFSA shall make the Summary of the application available to the public.

Instructions for use:

To be completed by the applicant for inclusion under [Part 1, Section 1.5](#).

The form provided specifies the format of the Summary of the application. It is **mandatory** to use the form provided in this Appendix

- The Summary of the application shall be preferably presented in English in an easily comprehensible and legible form,
- It should be brief and concise, and reflect the information in the application.
- The Summary of the Application shall not contain parts which are considered to be confidential as it will be published on the EFSA Website following receipt of the application from a National Competent Authority of a Member State.
- Acknowledging the above, applicants are encouraged for transparency purpose to make publicly available a maximum of information submitted in the Summary of application.
- An electronic version of the Summary of the Application should be provided.

SUMMARY OF THE APPLICATION



The Template provided should be used for the Summary for the application for authorisation of a health claim submitted pursuant to Article 14 of the Regulation (EC) No 1924/2006¹² to (a) a Member State in the European Union and (b) for the scientific evaluation by the European Food Safety Authority (EFSA).

GENERAL INFORMATION

APPLICANT:

Applicant¹³:

Name:

Address:

SCOPE:

This application concerns:

APPLICATION PURSUANT TO ARTICLE 14 OF THE REGULATION (EC) 1924/2006

Please specify:

- Reduction of disease risk claim
- Claim referring to children's development and health

MEMBER STATE OF APPLICATION:

<Specify the Member State's Competent Authority>

¹² European Parliament and Council (2006). 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. Official Journal of the European Union OJ L 404, 30.12.2006. Corrigendum OJ L 12, 18.1.2007, p. 3–18

¹³ In case more than one company or organisation submitting an application: provide their names and addresses.

HEALTH CLAIM PARTICULARS

SPECIFY THE FOOD/CONSTITUENT¹⁴:

DESCRIBE THE RELATIONSHIP BETWEEN THE FOOD/CONSTITUENT AND THE HEALTH CLAIM:

PROPOSAL OF THE WORDING OF THE HEALTH CLAIM:

SPECIFY THE CONDITIONS OF USE:

¹⁴ “food/constituent” refers to the food category, a food, or constituents (including a nutrient or other substance, or a combination of nutrients/other substances) for which the health claim is made.

APPENDIX C – TABULATED SUMMARY OF ALL PERTINENT STUDIES IDENTIFIED

To be completed by the applicant for inclusion under **Part 3, Section 3.1** based on the information identified in **Part 4, Sections 4.1.1 to 4.1.4**. All pertinent studies identified should be included (published and unpublished); individual studies included in any review publication should be counted separately.

Study type	Number of pertinent studies (published)	Number of pertinent studies (unpublished)
1. Human studies¹ (Total 1.1 to 1.4)		
1.1 Experimental intervention studies (Total a to c)		
a. RCT (full randomisation ²)		
b. RCT (concealed allocation)		
c. RT (non-controlled)		
1.2 Quasi-experimental intervention studies (Total a+b)		
a. Non-randomised, controlled		
b. Non-randomised, non-controlled		
1.3 Observational studies (Total a to d)		
a. Cohort studies		
b. Case-control studies		
c. Cross-sectional studies		
d. Other (e.g. Case reports)		
1.4 Other ³		
2. Non-human studies (Total 2.1 to 2.3)		
2.1 Animal studies ⁴		
2.2 <i>ex vivo/in vitro</i> studies ⁵		
2.3 Other ⁶		
Total (1 + 2)		

RCTs = Randomised controlled trials

RT = Randomised trials

¹ Human studies dealing with the relationship between the consumption of the food/constituent and the claimed effect.

² Method of randomisation reported as coin toss, computer generated numbers, random number tables or similar.

³ Human studies dealing with the mechanisms by which the food/constituent could be responsible for the claimed effect (mechanistic studies), or studies on bioavailability.

⁴ Animal studies dealing with, e.g., the mechanisms by which the food/constituent could be responsible for the claimed effect (mechanistic studies), including studies on bioavailability.

⁵ These include: *ex vivo* and *in vitro* studies based on either human or animal biological samples.

⁶ Studies reporting any combination of the above or non classifiable among the above.

APPENDIX D – TABULATED SUMMARY OF DATA FROM PERTINENT HUMAN INTERVENTION STUDIES

This guidance is applicable to **Part 3, Section 3.2**

1. Provide a table summarising the results of all pertinent human intervention studies addressing the relationship between the consumption of the food/constituent and the claimed effect. If more than one intervention (i.e. different doses of a food/constituent) is reported in the same study, use more than one line for that study indicating which intervention group is being considered (see table below as an example). List intervention studies by hierarchy of study design as follows: randomised controlled studies, other randomised studies (non-controlled), controlled non-randomised studies, other intervention studies.

Claimed effect (or surrogate marker of the claimed effect)*:

Studies**	Intervention***	Intervention n/N	Control n/N	RR (95%CI)
Study 1	Intervention 1			
Study 1	Intervention 2			
Study 2				
Study n				

* This table is only an example and could be adapted to accommodate different types of study design. However, one table clustering the individual studies investigating the relationship between the consumption of the food/constituent and EACH outcome (either the claimed effect or a surrogate marker of the claimed effect) is required.

**Indicate first author and publication year.

*** To be filled only for studies with more than one intervention groups

n/N = number of subjects receiving the intervention or control / total number of subjects

RR (95%CI) = Relative risk (95% confidence interval)

2. If possible, provide a graphical analysis (e.g. forest plot) summarising the results of human intervention studies addressing the relationship between the consumption of the food/constituent and the claimed effect. Specify whether the graphical analysis is presented:

- a. Without meta-analysis
- b. With meta-analysis (fixed effect model)
- c. With meta-analysis (random effects model)

In cases b. and c., where a meta-analysis of the studies is performed, a full report detailing the protocol followed in conducting the analysis should be provided under **Part 5, 5.3** (see Moher *et al.*, 1999; Des Jarlais *et al.*, 2004; and related articles for guidance).

3. If available, published systematic reviews, pooled analyses or meta-analyses of human intervention studies investigating the relationship between the consumption of the food/constituent and the claimed effect should be presented in **Part 3, Section 3.3**, indicating the protocol used to conduct the systematic review or analyses, and summarising the relevant results. ONLY when the question addressed by the systematic review, pooled analysis or meta-analysis is directly relevant to the health claim applied for, the individual studies included in the systematic review, pooled analysis or meta-analysis need not be presented separately in the application (i.e.: **Part 4, Section 4.2.1.1**). Copies/reprints of the systematic

reviews, published pooled analyses and meta-analyses, together with copies/reprints of the individual, original studies included in those should be annexed under **Part 5, Section 5.2**.

APPENDIX E – TABULATED SUMMARY OF DATA FROM PERTINENT HUMAN OBSERVATIONAL STUDIES

This guidance is applicable to **Part 3, Section 3.2**

1. Provide a table summarising the results of observational studies addressing the relationship between the consumption of the food/constituent and the claimed effect. If more than one level of exposure (i.e. different doses of food/constituent) is reported in the same study, use more than one line for that study indicating which exposure group is being considered (see table below as an example). List observational studies by hierarchy as follows: cohort studies, case-control studies, cross-sectional studies, other observational studies.

Claimed effect (or surrogate marker of the claimed effect)*:

Studies**	Exposure***	Exposure n/N	Control n/N	RR (95%CI)
Study 1	Exposure 1			
Study 1	Exposure 2			
Study 2				
Study n				

* This table is only an example and could be adapted to accommodate different types of study designs. However, one table clustering the individual studies investigating the relationship between the consumption of the food/constituent and EACH outcome (either the claimed effect or a surrogate marker of the claimed effect) is required.

**Indicate first author and publication year.

*** To be filled only for studies with more than one level of exposure

n/N = number of subjects in the exposure or control group / total number of subjects

RR (95%CI) = Relative risk (95% confidence interval)

2. If possible, provide a graphical analysis (e.g. forest plot) summarising the results of observational studies addressing the relationship between the consumption of the food/constituent and the claimed effect. Specify whether the graphical analysis is presented:

- a. Without meta-analysis
- b. With meta-analysis (fixed effect model)
- c. With meta-analysis (random effects model)

In cases b. and c., where a meta-analysis of the studies is performed, a full report detailing the protocol followed in conducting the analysis should be provided under **Part 5, Section 5.3**. (for guidance, see Stroup *et al.*, 2004)

3. If available, published systematic reviews, pooled analyses or meta-analyses of observational studies investigating the relationship between the consumption of the food/constituent and the claimed effect should be presented in **Part 3, Section 3.3**, indicating the protocol used to conduct the systematic reviews or analyses, and summarising the relevant results. ONLY when the question addressed by the systematic review, pooled analysis or meta-analysis is directly relevant to the health claim applied for, the individual studies included in the systematic reviews, pooled analyses or meta-analyses need not be presented separately in the application (i.e.: **Part 4, Section 4.2.1.2**). Copies/reprints of published

systematic reviews, pooled analyses and meta-analyses, together with copies/reprints of the individual, original studies included in those should be annexed under **Part 5, Section 5.2**.

APPENDIX F – WRITTEN SUMMARY OF DATA FROM PERTINENT HUMAN STUDIES

(i) Instructions for use:

This guidance is applicable to **Part 3, Section 3.3** and is intended to assist applicants in summarising the scientific data that have been acquired under Part 4, Section 4.2.1.

Therefore, it is advisable to start with the preparation and completion of Part 4, Section 4.2.1 prior to starting Part 3, Section 3.3.

(ii) General principles and sequence of information:

The written summary is intended to provide a summary of the human data presented under Part 4 (Section 4.2.1) and in the tabulated format under Section 3.2 of the application. The summary should include pertinent information resulting from the comprehensive review of published data, unpublished data, including studies in favour and not in favour.

Cross-references to pertinent human studies (intervention or observational) provided in Part 4 (Section 4.2.1) and in the Tabulated Summary (Section 3.2) should be given, when and as appropriate, to address the points below:

First, the relationship between the consumption of the food/constituent and the claimed effect **should be characterised** by considering, i.e.:

- the magnitude of the effect and its physiological relevance,
- the study population in which the effect has been observed and whether it is representative of the target population,
- the conditions under which the effect has been achieved or observed (metabolic room, clinical setting, free-living subjects, etc.),
- the sustainability of such effect over time,
- the amount of food/constituent used to achieve the effect, the usual intakes of food/constituent in the target population and whether these amounts could be reasonably consumed as part of a balanced diet.

Second, to what extent the data substantiate a **causal relationship** between the consumption of the food/constituent and the claimed effect should be addressed by considering:

- the consistency of results across studies,
- the magnitude of the effect, its statistical significance, the presence/absence of equally strong evidence, neutral or against,
- if available, an effective dose.
- Elements to be considered are the biological plausibility, alternate explanations for the observed effect and the specificity of the cause-effect relationship.

APPENDIX G – RESULTS OF THE REVIEW OF HUMAN DATA

To be completed by the applicant for inclusion under **Part 4, Section 4.1.1.6.**

Please indicate the number of pertinent publications identified in the comprehensive review of human data by publication type

Publication type	Number of pertinent publications identified	Number of publications excluded
Human data¹ (Total 1 to 8)		
1 Original research (Total a+b)		
a. Intervention studies		
b. Observational studies		
2 Pooled analysis of human intervention studies		
3 Meta-analysis of human intervention studies		
4 Pooled analysis of human observational studies		
5 Meta-analysis of human observational studies		
6 Systematic reviews		
7 Other review publications		
8 Guidelines/consensus opinions/text book chapters		
9 Other ²		

¹ Articles reporting Human studies dealing with the effect of the food/constituent on the health outcome underlying the claim.

² Articles reporting Human studies dealing with the mechanisms by which the food/constituent could be responsible for the health outcome (mechanistic studies), or studies on bioavailability.

APPENDIX H – SYNOPSIS OF PERTINENT INDIVIDUAL HUMAN INTERVENTION STUDIES

Please provide one synopsis for each study.

Data below should be extracted from copies/reprints of published studies and from full study reports of unpublished studies. Since not all data below may be available in all cases, please state “not available” as appropriate.

To be included under **Part 4, Section 4.2.1.1.**

1. Identification of the study

- 1.1. Authors:
- 1.2. Article title:
- 1.3. Source (journal, conference, etc.) Year/Volume/pages/Country of origin:
- 1.4. Institutional affiliation (first author) and/or contact address:
- 1.5. Declaration of interests:
- 1.6. Source of funding:
- 1.7. Good Clinical Practice status / ethical approval:

2. Report status. Please check as appropriate:

Published Accepted for publication Unpublished

3. Verification of study eligibility (check if the intervention study meets inclusion criteria defined in Part 4, Section 4.1.1 on Comprehensive Review of Human Data):

4. Objective(s) of the study

5. Description of the study population

- 5.1. Population subgroup (if not general population):
- 5.2. Age range(s):
- 5.3. Sex:
- 5.4. Ethnicity:
- 5.5. Inclusion criteria:
- 5.6. Exclusion criteria:
- 5.7. Setting(s):
- 5.8. Geographical region(s):

6. Study design:

- 6.1. Design: randomised controlled trials, cross-over studies, other.
- 6.2. Intervention arm(s): *(fill boxes below as appropriate. Use N/A when not applicable)*

	Food/co nstituent	Food matrix, if applicable	Daily intake (constituent)	Daily intake (food/food category, if applicable)	Duration of intervention	Duration of follow-up
Intervention 1 = control						
Intervention 2						
Intervention <i>n</i>						

- 6.3. Number of subjects allocated to each intervention arm:
- 6.4. Primary outcome: State the variable used for power calculations, if any.
- 6.5. Secondary outcome(s): variable 1, variable 2, variable *n*
- 6.6. Comparability of subjects between study groups (arms) at baseline. Variables checked for: variable 1, variable 2, variable *n*

7. Study results:

- 7.1. Drop outs by intervention arm (including controls, if applicable):
- 7.2. Adverse effects in the control and intervention arms, if any reported:
- 7.3. Pre-test and post-test values (means/medians± SD/SEM/interquartile ranges), mean differences (± SD/SEM/95% C) for primary/secondary outcomes, and statistical significance of the results.

Variable 1	Pre-test	Post-test	Mean difference	P-1*	P-2**	Follow up	Mean difference	P-1*	P-2**
Controls									
Intervention 1									
Intervention 2									
Intervention <i>n</i>									
Variable 2	Pre-test	Post-test	Mean difference	P-1*	P-2**	Follow up	Mean difference	P-1*	P-2**
Controls									
Intervention 1									
Intervention 2									
Intervention <i>n</i>									

This table is only an example and could be adapted to accommodate different types of study design. Values are expressed as: (state means/medians ± SD/SEM/interquartile ranges/95% CIs, as appropriate)
 * **P-1**= Significance for changes in the variable considered during each treatment.
 ****P-2** = Significance for changes in the variable considered during each treatment **as compared to the control group.**

7.4. Address the biological relevance of the results.

8. Study quality. Please check the appropriate columns in the table below. If copies/reprints of published studies or full study reports of unpublished studies do not contain enough data to assess some of the points below, please tick the “No” or “Unknown” boxes as appropriate

	Yes	Partially	No	Unknown	N/A ¹
1. Power calculations performed					
2. Baseline characteristics of subjects reported					
3. Subjects inclusion and exclusion criteria specified					
2. Information on background dietary habits provided					
3. Information on physical activity provided					
4. Information on smoking/alcohol drinking provided					
5. Information on medication use provided					
6. Information on other risk factors provided					
7. Randomisation					
a. Random sequence generation					
b. Treatment allocation concealed					
8. Control and intervention(s) group(s) comparable at baseline for relevant risk factors/outcome variables.					
9. Blinding of subjects					
10. Blinding of care givers ²					
11. Blinding of outcome assessors ³					
12. Compliance of subjects with the intervention reported					
13. Duration of intervention(s) adequate to test the hypothesis					
14. Point estimates and variability of main outcome variable reported.					
15. Surrogate markers of the claimed effect validated analytically					
16. Surrogate markers of the claimed effect validated biologically					
17. Analyses include an intention to treat analysis					
18. Adjustment for potential confounders performed					

¹ N/A=Not applicable

² Appropriate placebo available

³ Investigators in charge of assigning laboratory values and of evaluating complementary exams (ECG, ultrasounds, etc.) blinded to subjects' allocation arm.

9. Applicant's conclusions (15 lines maximum)

APPENDIX I – SYNOPSIS OF PERTINENT INDIVIDUAL HUMAN OBSERVATIONAL STUDIES

Please provide one synopsis for each study.

Data below should be extracted from copies/reprints of published studies and from full study reports of unpublished studies. Since not all data below may be available in all cases, please state “not available” as appropriate.

To be included under **Part 4, Section 4.2.1.2.**

1. Identification of the study

- 1.1. Authors:
- 1.2. Article title:
- 1.3. Source (journal, conference, etc.) Year/Volume/pages/Country of origin:
- 1.4. Institutional affiliation (first author) and/or contact address:
- 1.5. Declaration of interests:
- 1.6. Source of funding:
- 1.7. Ethical approval:

2. Report status. Please check as appropriate:

Published Accepted for publication Unpublished

3. Verification of study eligibility (check if observational study meets inclusion criteria defined in Part 4, Section 4.1.1 on Comprehensive Review of Human Data):

4. Objective(s) of the study

5. Description of the population

- 5.1. Population subgroup (if not general population):
- 5.2. Age range(s):
- 5.3. Sex:
- 5.4. Ethnicity:
- 5.5. Inclusion criteria (for cases and controls, if appropriate):
- 5.6. Exclusion criteria (for cases and controls, if appropriate):
- 5.7. Recruitment procedures used (consecutive, arbitrary, unreported, other):
- 5.8. Setting(s):
- 5.9. Geographical region(s):

6. Study design:

- 6.1. Design: cohort, case-control, case-reports, cross-sectional
- 6.2. Data collection (prospective, retrospective, unreported, other).
- 6.3. Exposure (s): *(fill boxes below as appropriate. Use N/A when not applicable)*

	Food/constituent	Food matrix, if applicable	Daily intake (constituent)	Daily intake (food/food category, if applicable)	Duration of exposure
Exposure 1= control					
Exposure 2					
Exposure <i>n</i>					

- 6.4. Number of subjects (total, per cohort, per group):
- 6.5. Primary outcome: State the variable used for power calculations, if any.
- 6.6. Secondary outcome(s): variable 1, variable 2, variable *n*
- 6.7. Comparability of subjects between study groups (arms) at baseline. Variables checked for: variable 1, variable 2, variable *n*

7. Outcome measures and results:

- 7.1. Duration of follow-up, if applicable:
- 7.2. Drop outs in total, by group:
- 7.3. Adverse effects being reported:

- 7.4. Measure of effect of the exposure: report measure of effect for outcome variables as appropriate.
 6.5. Address the biological relevance of the results.

8. Study quality. Please check the appropriate columns in the table below. If copies/reprints of published studies or full study reports of unpublished studies do not contain enough data to assess some of the points below, please tick the “No” or “Unknown” boxes as appropriate

	Yes	Partially	No	Unknown	N/A ¹
1. Power calculations performed					
2. Baseline characteristics of subjects reported					
3. Subjects inclusion and exclusion criteria specified					
4. Definition of cases explicit					
5. Condition of cases reliably assessed and validated					
6. Controls selected from the source of population of the cases					
7. Information on background dietary habits provided					
8. Information on physical activity provided					
9. Information on smoking/alcohol drinking provided					
10. Information on medication use provided					
6. Information on other risk factors provided					
11. Information on the distribution of prognostic factors provided					
12. Groups comparable at baseline for relevant risk factors/potential confounding variables					
13. Exposure ascertained					
14. Dose-response relationship between exposure and outcome demonstrated					
15. Outcome assessors blinded to exposure status					
16. Appropriate duration of follow-up for outcome to occur					
17. Surrogate markers of the claimed effect validated analytically					
18. Surrogate markers of the claimed effect validated biologically					
19. Drop out rates and reasons similar among groups					
20. Adequate adjustment for the effects of confounding variables					
21. Statistical methods appropriate					
22. Dose-response relationship between exposure and outcome statistically significant					

¹ N/A=Not applicable

9. Applicant’s conclusions (15 lines maximum)