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

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

Agreed on 3 May for release for public consultation

(Request N° EFSA-Q-2007-066)

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Comments should be submitted on-line by 17 June 2007, at the latest.

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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)

(Agreed on 3 May 2007 for release for public consultation)

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. In this context, a 'food' may be a nutrient or other substance, or a combination of nutrients/substances, or a food or a category of food.

The Scientific Panel on Dietetic Products, Nutrition and Allergies has prepared a draft Opinion which is published for consultation and which will be adopted following amendment, as considered appropriate, in the light of comments received.

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 for which a health claim is made. This information should contain aspects considered pertinent to the claim, such as, manufacturing process, composition, physical and chemical characteristics, 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 for which the health claim is made; the quantity of the food and pattern

of consumption required to obtain the claimed beneficial effect, and whether this quantity could reasonably be consumed as part of a balanced diet; a warning for foods that are likely to present a health risk if consumed to excess; any other restrictions of use. The application should also include examples of how the claim will be presented, where the claim will be used, e.g. labelling, advertising, and a rationale (and data, if available) in support of consumer understanding of the health claim.

The application must also contain all pertinent scientific data (published and unpublished, including proprietary data) identified that form the basis for substantiation of the health claim. Data from studies in humans 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 health effect of the food.

A comprehensive review of the data from human studies pertaining to the specific food-health relationship 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 observational 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. Templates are provided for presenting summaries of data from individual studies in humans so as to highlight the relevant aspects related to the design, outcome 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 beneficial effect of the food is relevant for human health,

(b) a cause and effect relationship is established between the consumption of the food and the health outcome in humans (including the strength, consistency, specificity, dose-response, and biological plausibility of the relationship),

(c) the quantity of the food and pattern of consumption required to obtain the claimed beneficial effect could reasonably be achieved as part of a balanced diet,

(d) the evidence obtained from the specific study group(s) can be generalised to the target population for which the claim is intended.

KEY WORDS

Health claims, Regulation, food(s), 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 2007[1]. 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,
- templates for presenting summaries of data so as to highlight the relevant aspects related to the design, outcome 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 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.
- "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 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 guidance[2] and current and future community guidelines and regulations.

1. The term "**food**" hereafter means a nutrient or other substance, or a combination of nutrients/substances, or a food or a category of food, for which a health claim is made.
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. Assessors 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.
4. This guidance presents a common format for the organisation of the information to assist the applicant in the preparation of a well-structured dossier for applications that will be

[2] 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)

submitted to EFSA for evaluation, so that EFSA can deliver scientific advice (i.e. scientific Opinion) in an effective and consistent way.

5. To facilitate easy access to information and scientific data in applications and to help the evaluator become quickly oriented to the application contents, information and data should be presented in conformity with the format and requirements given in this guidance document.

6. Not all the points included in this guidance document may apply to every case. In cases where some of the data that are required as described 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.

7. The application must contain information on the characteristics of the food for which a claim is made. This information should contain aspects such as the manufacturing process, composition, physical and chemical characteristics, stability, and bioavailability.

8. 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; where appropriate, a statement addressed to persons who should avoid using the food for which the health claim is made; the quantity of the food and pattern of consumption required to obtain the claimed beneficial effect, and whether this quantity could reasonably be consumed as part of a balanced diet; a warning for foods that are likely to present a health risk if consumed to excess; any other restrictions of use. The application should include examples of how the claim will be presented, where the claim will be used, e.g. labelling, advertising, and a rationale (and data if available) in support of consumer understanding of the health claim.

9. The application must contain all pertinent scientific data (published and unpublished, including proprietary data) which form the basis for substantiation of the health claim. Data from studies in humans 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 health effect of the food.

10. A comprehensive review of the data from human studies pertaining to the specific food-health relationship 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.

11. 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.

12. Data provided to substantiate a health claim should be of the quality expected from a peer-reviewed journal.

13. 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 beneficial effect of the food is relevant for human health,

(b) a cause and effect relationship is established between the consumption of the food and the health outcome in humans (including the strength, consistency, specificity, dose-response, and biological plausibility of the relationship),

(c) the quantity of the food and pattern of consumption required to obtain the claimed beneficial effect could reasonably be achieved as part of a balanced diet,

(d) the evidence obtained from the specific study group(s) can be generalised to the target population for which the claim is intended.

14. The application in itself cannot be confidential. Sections considered as confidential by the applicant should be kept to a minimum. As defined in the Regulation, EFSA will make public the summary of the application 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 by the applicant.

15. One application should be prepared for each individual health claim; this means that only a relationship between a food and **a single health outcome can be the object of each application**. However, multiple formulations of a food 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 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(s) and the nature of the application including its national and international status, health claim particulars, the summary of the application, model health claim, and aspects related to consumer understanding.
- **Part 2** contains information specific to the food and its characteristics (such as the manufacturing process, composition, physical and chemical characteristics, stability, and bioavailability data).
- **Part 3** contains summaries (the overall summary of pertinent human data and the overall summary of pertinent non-human data) 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 including proprietary data) identified that form the basis for substantiation of the health claim.
- **Part 5** comprises the glossary or abbreviations of terms quoted throughout different Parts, including copy of reprints of those pertinent references identified, and study reports.

Where requested information is not applicable or is not submitted on any of the points set out below, justification should be given for any omission.

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

Acronyms and abbreviations should be defined the first time they are used, and should also be listed in **Part 5.1**.

Any reference to published information, considered pertinent by the applicant after performing the review of the data, should be accompanied in **Part 5.2** by full reprints, or easily readable copies of such information.

Study reports of pertinent data (including proprietary data) should be enclosed in **Part 5.3**.

If available, scientific Opinions of national/international authorising body and relevant data related to consumer understanding should be enclosed in **Part 5.4.**

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

Diagram 1: Representation of the organisation of the application*

** The numbering of each Appendix corresponds to the related Part/Section of the guidance document.*

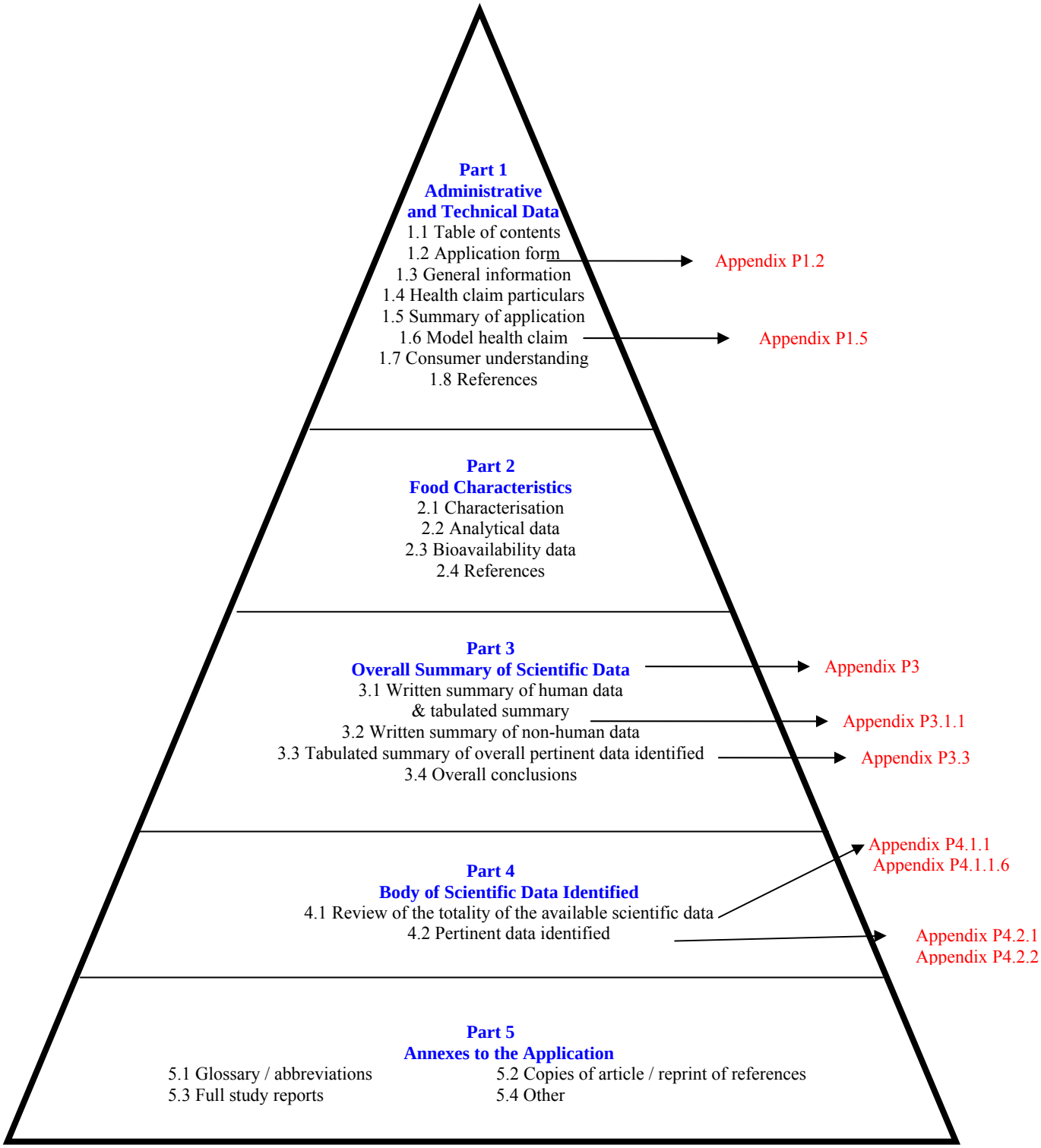
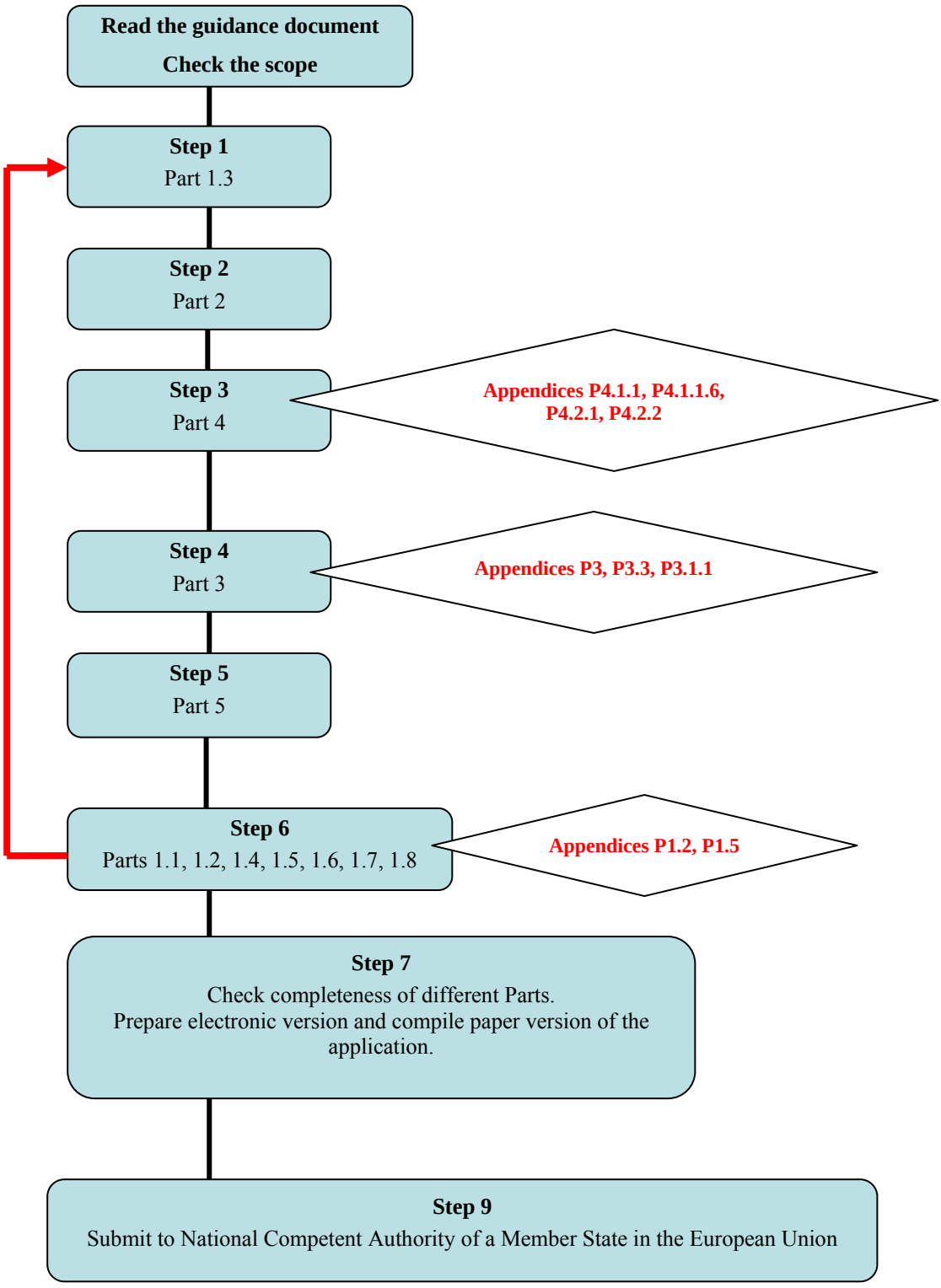


Diagram 2: Suggested steps for the preparation of the application



PART 1: ADMINISTRATIVE AND TECHNICAL DATA

1.1 Comprehensive table of contents of the application

1.2 Application form

Please use the **Template provided in Appendix P1.2**.

1.3 General information

1.3.1 Applicant

1.3.1.1 Provide the name and address of the company or organisation:

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

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

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 & 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 status

State whether approval for the health claim in this application has been already sought through any regulatory body, either in or outside the European Union. If so, please indicate the status of **each** application for the proposed health claim (in case of submission to more than one regulatory body) as appropriate:

- ☐ Under consideration

  Provide the wording of the claim submitted, the date of submission, the formulation and nutrient content of the food(s) for which the claim has been submitted. Indicate the regulatory body dealing with the application for authorisation.

- ☐ Approved

Provide the wording of the claim approved, the date of approval, the formulation and nutrient content of the food(s) for which the claim has been approved. Indicate the regulatory body authorising the health claim.

If possible, provide the scientific Opinion of the regulatory body authorising the health claim (in Part 5.4).

☐ Rejected

Provide the wording of the claim which was rejected, the date of rejection and the reasons for rejection. Indicate the regulatory body which rejected the health claim.

If possible, provide the scientific Opinion of the regulatory body rejecting the health claim (in Part 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 regulatory body evaluating the health claim at the time of withdrawal.

1.4 Health claim particulars

1.4.1 Specify the food (as defined in the General Principles) for which a health claim is made

1.4.2 Describe the relationship between the food and the health claim

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 EFSA Pre-submission guidance for applicants intending to submit applications for authorisation of health claims).

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

Cross-referencing should be given for the scientific data provided in Parts 3 and 4 (i.e. study groups are representative of target group).

1.4.5 Specific conditions of use:

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

1.4.5.2 Indicate the quantity of the food and pattern of consumption required to obtain the claimed beneficial effect, and whether this quantity could reasonable 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 and pattern of consumption proposed).

1.4.5.3 Specify, where applicable, warning for foods that are likely to present a health risk if consumed to excess, and provide a rationale.

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

1.5 Summary of the application

Please use the **Template provided in Appendix P1.5.**

1.6 Model health claim

1.6.1 Provide a model health claim (mock-up), if available, that may be used for a food

1.6.2 Indicate where the health claim is intended to be used, as appropriate:

- ☐ Labelling
- ☐ Brochure
- ☐ Internet marketing directed at consumers
- ☐ Expert documentation
- ☐ Advertisements
- ☐ Other forms of marketing, specify

1.7 Consumer understanding

1.7.1 Rationale to support consumer understanding

Provide here a supporting rationale.

1.7.2 Indicate whether surveys on consumer understanding of the health claim have been carried out

Provide relevant data if available in Part 5.4.

1.8 References

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

PART 2: FOOD CHARACTERISTICS

2.1 Characterisation

2.1.1 Characterise the nutrient or combination of nutrients and/or other substance for which the health claim is made:

This section is only applicable to the nutrient(s)/other substance intentionally added to foods. Otherwise, go directly to Part 2.1.2.

2.1.1.1 Name and general properties (i.e. physicochemical characterisation and other relevant properties)

2.1.1.2 Manufacturing process

Provide a brief overview and indicate whether the production is in compliance with good manufacturing practice (GMP).

Provide specifications.

2.1.1.3 Stability information

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

2.1.2 Characterise the food or category of food (i.e. the final product(s)) for which the health claim is made:

2.1.2.1 Composition and specifications of final product(s)

A description of the final product(s) and its composition, including characterisation of the food matrix, should be provided.

2.1.2.2 Manufacturing process of the final product(s)

Provide a brief overview and indicate whether the production is in compliance with good manufacturing practice (GMP).

2.1.2.3 Stability information

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

2.2 Analytical data

Provide analytical data for the final product(s) for which the health claim is made.

Using relevant analytical methods, investigations should focus especially on:

the determination of the content and the amount of the nutrient(s) (macro- and micronutrients)/other substance(s), including the nutrient/combination of nutrients/other substance for which the health claim is made, that are contained in the final products determined in a representative number of samples of food and covering the period up to the end of its shelf-life;

the variability of the nutrient(s) content from batch to batch (or from different foods).

Analytical methods applied have to be valid/scientifically sound to ensure quality and consistency of the data. The results of the validation studies must be provided. Indicate whether the analytical study has been conducted in compliance with relevant International Standards (e.g.: ISO 17025).

2.3 Bioavailability data

If available, provide the relevant data and/or a supporting rationale that the food 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).

In the case where the food is not absorbed (e.g.: plant sterols, fibres, lactic acid bacteria), provide if available the relevant data and/or a supporting rationale that the food reaches the target site.

Any factors (e.g.: formulation, processing, other ingredients of the product) that could impair the absorption or utilisation in the body of the food on which a health claim is based should be provided, if available (e.g.: interaction studies).

2.4 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 is a summary that follows the scope and the outline of the body of scientific data identified in Part 4. Provide the information in the following order. See **Appendix P3** for guidance.

3.1 Written summary of human data [resulting from 4.2.1]

The written summary is intended to provide a factual summary of the human data presented under Part 4.2.1 and which are deemed pertinent to the health claim in the intended population. See **Appendix P3** for guidance.

3.1.1 Tabulated summary of human data

Use the **Templates provided under Appendix P3.1.1**.

3.2 Written summary of non-human data [resulting from 4.2.2]

This section should present an integrated summary of the pertinent non-human studies identified or performed that support the claimed effect.

3.3 Tabulated summary of overall pertinent data identified [resulting from 4.2.1 and 4.2.2]

Use the **Templates provided under Appendix P3.3**.

3.4 Overall conclusions

The overall conclusions should clearly define the health effects of the food as demonstrated by the totality of the data (including evidence in favour and not in favour) and by weighing the evidence to arrive at logical, well-argued

conclusions substantiating the relationship between the food and the health effect. In particular, the evidence should demonstrate the extent to which:

(a) the claimed beneficial effect of the food is relevant for human health,

(b) a cause and effect relationship is established between the consumption of the food and the health outcome in humans (including the strength, consistency, specificity, dose-response, and biological plausibility of the relationship),

(c) the quantity of the food and pattern of consumption required to obtain the claimed beneficial effect, and whether this quantity could reasonably be consumed as part of a balanced diet,

(d) the evidence obtained from the specific study group(s) can be generalised to the target population for which the claim is intended.

PART 4: BODY OF PERTINENT SCIENTIFIC DATA IDENTIFIED

Part 4 contains all pertinent scientific data (published and unpublished, including proprietary data) which form the basis for substantiation of the health claim.

Unpublished or proprietary data must be clearly indicated (see also **Part 1,** i.e. 1.3.2.1).

Studies with inconclusive or negative results must also be considered and included.

4.1 Review of the totality of available scientific data

All references identified and considered as pertinent after review should be compiled and listed alphabetically under **Part 4.1.1.5**, and accompanied by copies of article/reprint of references under **Part 5.2**. Full study reports for unpublished studies should be annexed under **Part 5.3** and cross-reference should be given.

In addition, these references should be presented as follow:

- They should be clustered and listed under **Part 4.2.1.4** if they are related to human data
- They should be clustered and listed under **Part 4.2.2.1** if they are related to non-human data

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

4.1.1 Processing a comprehensive review of human data

For assistance in completing the required information below, please refer to the guidance given under **Appendix P4.1.1 on Comprehensive Review of Human Data**.

Please provide the following information:

4.1.1.1 Authorship

4.1.1.2 Background

4.1.1.3 Food-health relationship

4.1.1.4 Literature search

4.1.1.5 Identification of pertinent literature

List here all references identified (excluded and included) following the comprehensive review. The list comprises those references selected, **which are excluded** (by exclusion criteria) and **which are included** (by inclusion criteria) and considered as pertinent for the food-health relationship (see also **sections (ii) 5.1-5.2 of Appendix P4.1.1**).

4.1.1.6 Results of the comprehensive review

Please use the **Template provided in Appendix P4.1.1.6**.

In addition, go to Part 4.2 to organise the data which have been identified as pertinent following the comprehensive review.

4.1.2 *Other pertinent data, including proprietary data*

Data not considered in the comprehensive review (i.e. unpublished data not identified under 4.1.1.6) and considered as pertinent (including proprietary data), should be mentioned here.

In addition, go to Part 4.2 to organise the data which have been identified under Part 4.1.2.

4.2 ***Pertinent data identified***

Organise the data identified as pertinent (i.e. resulting from **4.1.1 and 4.1.2**) in the following recommended order: human data, followed by non-human data if appropriate.

For presentation of human data, please refer to **Appendix P4.2.1** for guidance.

For presentation of non-human data, please refer to **Appendix P4.2.2** for guidance.

4.2.1 *Human data*

Classify human data in accordance with hierarchy of study design.

Individual studies should be presented using the **Templates provided in Appendix P4.2.1 - Synopsis of individual human studies**.

4.2.1.1 Human intervention studies

Present each study by using the **Template provided in Appendix P4.2.1.1**.

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 **Template provided in Appendix P4.2.1.2**.

4.2.1.2.1 Cohort studies

4.2.1.2.2 Case-controlled 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 could be responsible for the health outcome. These studies also include those on bioavailability (cross-reference should be given to Part 2.3, if appropriate).

4.2.1.4 List of references of the pertinent human data should be given (alphabetical order of first authors)

Copies of article/reprint of references should be given under **Part 5.2**. Full study reports for unpublished studies should be annexed under **Part 5.3** and cross-reference should be given.

4.2.2 Non-human data

A brief and concise overview of individual studies should be provided. Please refer to **Appendix P4.2.2** for guidance.

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

Copies of article/reprint of references should be under **Part 5.2**. Full study reports for unpublished studies should be annexed under **Part 5.3** and cross-reference should be given.

PART 5: ANNEXES TO THE APPLICATION

5.1 Glossary / Abbreviations

Used throughout different Parts. To be presented alphabetically.

5.2 Copies of article/reprint of references

- those considered as pertinent after the comprehensive review conducted under Part 4.1.1
- those identified under Part 4.2.2.

5.3 Full study reports

Include here the full study reports identified under Part 4.1.2

5.4 Other

If available, include here e.g.:

- Scientific opinions of national/international authorising body if available as referred to in Part 1.3.4.
- Relevant data following surveys of consumer understanding as referred to in Part 1.5.2.

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.

Food Standards Australia and New Zealand:
http://www.foodstandards.gov.au/foodmatters/healthnutritionandrelatedclaims/index.cfm

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

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

U.S. Food and Drug Administration:
http://www.cfsan.fda.gov/~dms/lab-hlth.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.

668 **GLOSSARY AND ABBREVIATION USED IN THE GUIDANCE DOCUMENT**

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

Application	Means a stand-alone dossier containing the information and the scientific data submitted for auhorisation 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).
Food	Means a nutrient or other substance, or a combination of nutrients/substances, or a food or a category of food, for which a health claim is made.
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.
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	A substance other than a nutrient that has a nutritional or physiological effect (as defined in the Regulation (EC) No 1924/2006).

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APPENDICES

Notes to users:

- **Information requested in Appendices P1.2 and P1.5 are mandatory. Applicants are advised to follow the instructions given and use the Templates provided.**
- For the remaining Appendices: Instructions are given for guidance to applicants. This guidance is intended to assist applicants in preparing and presenting in a well-structured format pertinent data that have been identified and acquired to substantiate the claimed effect and to facilitate review and evaluation of the results.
- Please note that the numbering of each Appendix corresponds to the related Part/Section of the guidance document (see Diagram 1).
- For preparation of the application, refer also to suggested steps in Diagram 2.

Content:

Appendix P1.2	**Application form [Mandatory]**
Appendix P1.5	**Summary of the application [Mandatory]**
Appendix P3	**Overall summary of scientific data**
Appendix P3.1.1	**Tabulated summary of human data**
Appendix P3.3	**Tabulated summary of overall pertinent data identified by study type**
Appendix P4.1.1	**Comprehensive review of human data**
Appendix P4.1.1.6	**Template provided to display the results of the review of human data**
Appendix P4.2.1	**Synopsis of individual human studies**
Appendix P4.2.2	**Guidance for presenting non-human data**

APPENDIX P1.2 – APPLICATION FORM

(i) Instructions for use:

To be completed by the applicant for inclusion under **Part 1.2**.

It is **mandatory** to use the Template under (ii) of this Appendix and to give the required information.

(ii) Template (provided in the next page):

Template P1.2

APPLICATION FORM

●●●●●

The application form should be used for an application for authorisation of a health claim made on food(s) for human use submitted pursuant to Article 14 of the Regulation (EC) No 1924/2006 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.
Information should be provided where appropriate.

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[1] (specify, provide common name and brand name as appropriate):

Proposed wording of the health claim:

Applicant[2]:

Contact person[3]:

It is hereby confirmed 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 date (yyyy-mm-dd)

[1] "**food**" means a nutrient or other substance, or a combination of nutrients/substances, or a food or a category of food, for which a health claim is made.

[2] 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.

[3] To facilitate communication purposes, EFSA requires having **only one contact person per application.**

1. GENERAL INFORMATION

1.1 APPLICANT

1.1.1 Applicant[4]:

(Company) Name:
Address:
Country:

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

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

1.2 SCOPE

1.2.1 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

1.2.2 INDICATE WHETHER THE APPLICATION INCLUDES:

Proprietary data:	☐ Yes	☐ No
If yes, has verifiable justification/declaration been provided?	☐ Yes	☐ No
If yes, has the proprietary data in the application been located?	☐ Yes	☐ No

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

Confidential data:	☐ Yes	☐ No
If yes, has verifiable justification/declaration been provided?	☐ Yes	☐ No
If yes, has the confidential data in the application been located?	☐ Yes	☐ No

1.3 NATIONAL AND INTERNATIONAL STATUS

State whether approval for the health claim in this application has been already sought through any authorising body, either in or outside the European Union.

☐ Yes	☐ No	
If yes, specify the status:		
Under consideration:	☐ Yes	☐ No
Approved:	☐ Yes	☐ No
Rejected:	☐ Yes	☐ No
Withdrawn:	☐ Yes	☐ No

2. HEALTH CLAIM PARTICULARS

2.1 SPECIFY THE FOOD[5]

2.2 DESCRIBE THE RELATIONSHIP BETWEEN THE FOOD AND THE HEALTH CLAIM

2.3 PROPOSAL OF THE WORDING OF THE HEALTH CLAIM

2.4 SPECIFY THE TARGET POPULATION FOR THE HEALTH CLAIM

2.5 SPECIFY THE CONDITIONS OF USE

[5] "**food**" means a nutrient or other substance, or a combination of nutrients/substances, or a food or a category of food, for which a health claim is made.

2.6 INDICATE WHETHER THE HEALTH CLAIM 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

3. MARKETING / PROMOTION STATUS

☐ Labelling
☐ Brochure
☐ Internet marketing directed at consumers
☐ Expert documentation
☐ Advertisements
☐ Other forms of marketing, specify:

4. CONSUMER UNDERSTANDING

4.1 INDICATE WHETHER SUPPORTING RATIONALE IS PROVIDED

☐ Yes	☐ No

4.2 INDICATE WHETHER SURVEYS ON CONSUMER UNDERSTANDING HAVE BEEN CARRIED OUT

☐ Yes	☐ No

5. CONTENT OF THE APPLICATION

Please provide the below information:

	Is the object of the application for a single health outcome only?	Yes ☐	No ☐
Parts/sections of the application:			
2.1.1	Has the nutrient or combination of nutrients and/or other substances for which the health claim is made been characterised?	Yes ☐	No ☐
2.1.2	Has the food or category of food (i.e. the final product(s)) for which the health claim is made been characterised?	Yes ☐	No ☐
2.2	Have analytical data for the final product for which the health claim is made been provided?	Yes ☐	No ☐
2.3	Have relevant data and / or a supporting rationale that the food for which the health claim is made is in a form available to be used by	Yes ☐	No ☐

	the body been provided?		
3.1	Has a written summary of human data been provided?	Yes ☐	No ☐
3.1.1	Has a tabulated summary of human data been provided?	Yes ☐	No ☐
3.2	Has a written summary of non-human data been provided?	Yes ☐	No ☐
3.3	Has a tabulated summary of overall pertinent data identified been provided?	Yes ☐	No ☐
3.4	Have the overall conclusions clearly defining the health effects of the food as demonstrated by the totality of the data and weighing of the evidence been provided?	Yes ☐	No ☐
4.1.1	Has the totality of the available scientific data been reviewed comprehensively?	Yes ☐	No ☐
4.1.2	Has any proprietary data been identified?	Yes ☐	No ☐
4.2	Have all pertinent data been identified?	Yes ☐	No ☐
4.2.1.1	Are pertinent data coming from human intervention studies?	Yes ☐	No ☐
4.2.1.2	Are pertinent data coming from human observational studies?	Yes ☐	No ☐
4.2.2	Have any pertinent non-human data been identified?	Yes ☐	No ☐
Templates provided in the Appendices:			
P 1.2	Has the application form been provided?	Yes ☐	No ☐
P1.5	Has the summary of the application been provided?	Yes ☐	No ☐
P 3.1.1a	Has the tabulated summary of intervention studies in humans been provided?	Yes ☐	No ☐
P 3.1.1b	Has the tabulated summary of observational studies in humans been provided?	Yes ☐	No ☐
P 3.3	Has the tabulated summary of overall pertinent data identified by study type been provided?	Yes ☐	No ☐
P 4.1.1.6	Have the tabulated results of the review of human data been provided?	Yes ☐	No ☐
P 4.2.1.1	Has a synopsis of each human intervention study been provided?	Yes ☐	No ☐
P 4.2.1.2	Has a synopsis of each human observational study been provided?	Yes ☐	No ☐
	Is there sufficient evidence that the claimed beneficial effect of the food is relevant for human health?	Yes ☐	No ☐
	Is there sufficient evidence that a cause and effect relationship is established between the consumption of the food and the health outcome in humans (including the strength, consistency, specificity, dose-response, and biological plausibility of the relationship)?	Yes ☐	No ☐
	Is there sufficient evidence that the quantity of the food and pattern of consumption required to obtain the claimed beneficial	Yes ☐	No ☐

	effect could reasonably be achieved as part of a balanced diet?		
	Is there sufficient evidence that the study group(s) in which the evidence was obtained is representative of the target population for which the health claim is intended?	Yes ☐	No ☐

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APPENDIX P1.5 – 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.

(i) Instructions for use:

To be completed by the applicant for inclusion under **Part 1.5**.

The Summary of the application should be presented in a standardised form. The language used should be English. It shall be presented in an easily comprehensible and legible form. It should be brief and concise. An electronic version of the Summary of the Application should be provided.

The Summary of the Application should 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.

It is **mandatory** to use the Template provided under (ii) of this Appendix and to give the required information.

(ii) Template (provided in the next page):

Template P1.5

SUMMARY OF THE APPLICATION

●●●●●

The Template provided should be used for the Summary for the application for authorisation of a health claim made on food(s) for human use submitted pursuant to Article 14 of the Regulation (EC) No 1924/2006 to (a) a Member State in the European Union and (b) for the scientific evaluation by the European Food Safety Authority (EFSA).

Information should be provided where appropriate.

1. GENERAL INFORMATION

1.1 APPLICANT

Applicant[1]:

(Company) Name:

Address:

Country:

1.2 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

1.3 MEMBER STATE OF APPLICATION

<Specify the Member State's Competent Authority>

1.4 NATIONAL AND INTERNATIONAL STATUS

State whether approval for the health claim in this application has been already sought through any authorising body, either in or outside the European Union.

☐ Yes	☐ No

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

If yes, specify the status:		
Under consideration:	☐ Yes	☐ No
Approved:	☐ Yes	☐ No
Rejected:	☐ Yes	☐ No
Withdrawn:	☐ Yes	☐ No

2. HEALTH CLAIM PARTICULARS

2.1 SPECIFY THE FOOD[2]

2.2 DESCRIBE THE RELATIONSHIP BETWEEN THE FOOD AND THE HEALTH CLAIM

2.3 PROPOSAL OF THE WORDING OF THE HEALTH CLAIM

2.4 SPECIFY THE TARGET POPULATION FOR THE HEALTH CLAIM

2.5 SPECIFY THE CONDITIONS OF USE

3. CONSUMER UNDERSTANDING

SUMMARISE SUPPORTING RATIONALE, AND/OR RELEVANT DATA IF AVAILABLE

<NOTES: Filling of this section should not exceed 550 words (~ 3500 characters with spaces>

4. FOOD CHARACTERISTICS

<NOTES: Filling of the sections 4.1 to 4.3 should not exceed 1100 words (~ 7000 characters with spaces>

4.1 CHARACTERISATION

The nutrient or combination of nutrients and/or other substance – intentionally

[2] *"**food**" means a nutrient or other substance, or a combination of nutrients/substances, or a food or a category of food, for which a health claim is made.*

added to foods – for which the health claim is made:
The food or category of food for which the health claim is made:

4.2 SUMMARISE RELEVANT ANALYTICAL INFORMATION

4.3 SUMMARISE RELEVANT INFORMATION AND/OR SUPPORTING RATIONALE ON BIOAVAILABILITY

5. SCIENTIFIC SUBSTANTIATION OF THE HEALTH CLAIM

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.

SUMMARISE TO WHICH EXTENT:

<NOTES: Filling of the sections 5.1 to 5.4 should not exceed 1100 words (~ 7000 characters with spaces>

5.1 THE CLAIMED BENEFICIAL EFFECT OF THE FOOD IS RELEVANT FOR HUMAN HEALTH

5.2 A CAUSAL AND EFFECT RELATIONSHIP IS ESTABLISHED BETWEEN THE CONSUMPTION OF THE FOOD AND THE HEALTH OUTCOME IN HUMANS (INCLUDING THE STRENGTH, CONSISTENCY, SPECIFICITY, DOSE-RESPONSE, AND BIOLOGICAL PLAUSIBILITY OF THE RELATIONSHIP)

5.3 THE QUANTITY OF THE FOOD AND THE PATTERN OF CONSUMPTION REQUIRED TO OPTAIN THE CLAIMED BENEFICIAL EFFECT COULD REASONABLY BE ACHIEVED AS PART OF A BALANCED DIET

5.4 THE EVIDENCE OBTAINED FROM THE SPECIFIC STUDY GROUP(S) CAN BE GENERALISED TO THE TARGET POPULATION FOR WHICH THE CLAIM IS INTENDED

APPENDIX P3 – OVERALL SUMMARY OF SCIENTIFIC DATA

(i) Instructions for use:

This guidance is applicable to **Part 3** and is intended to assist applicants in summarising the scientific data that have been acquired under Part 4.2.

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

(ii) General principles:

The overall summary is intended to provide a summary of all the pertinent scientific data identified in Part 4.2, and which form the basis for the substantiation of the health claim. The summary of the data identified should establish that the relationship between the food and the health claim is substantiated by the totality of the scientific data and by weighing the evidence.

(iii) Sequence of information:

The overall summary of the totality of pertinent data identified (including the data in favour and the data not in favour) should be presented in the following order:

- *Written summary of human data*
- *Tabulated summary of human data*
- *Written summary of non-human data*
- *Tabulated summary of overall pertinent data identified*
- *Overall conclusions*

Written summary for human data

This section is applicable to **Part 3.1.**

The written summary is intended to provide a summary of the human data presented under Part 4.2.1. The summary should include pertinent information resulting from the comprehensive review, including unpublished or proprietary data. Cross-referencing to more detailed presentations provided in Part 4.2.1 is encouraged.

The results from all pertinent studies, including studies with inconclusive or negative results, which were considered for evaluation of the health claim should be summarised as follows, quoting the appropriate references identified in section 4.2 when needed:

First, **the relationship** between the consumption of the food and the claimed health outcome **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 a broader generalisation of the results to the target population is possible,
- 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 used to achieve the effect, the usual intakes of food in the target population and whether these amounts could be reasonable consumed as part of a healthy diet.

Second, to what extent the data substantiate **a causal relationship** between the consumption of the food and the claimed health outcome 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.

Tabulated summary for human data

This section is applicable to **Part 3.1.1.** Please use the Templates and follow the guidance provided in **Appendix P3.1.1**.

Written summary for non-human data

This section is applicable to **Part 3.2.** It is recommended to complete the Overview of individual non-human studies presented in Part 4.2.2 prior to starting the Written Summary required in Part 3.2. The written summary is intended to provide an overall integrated summary of the non-human data presented under Part 4.2.2

The results from all pertinent studies considered to support the health claim, should be summarised, and should be arranged in a logical order so that all relevant data elucidating a certain effect are brought together.

Cross-referencing to more detailed information provided in Part 4.2.2 should be given.

Tabulated summary of overall pertinent data identified

This section is applicable to **Part 3.3** and is based on the human data presented under Part 4.2.1 and includes non-human data presented under Part 4.2.2**.**

Please use the Template provided in the **Appendix P3.3**.

Overall conclusions

This section is applicable to **Part 3.4.**

The overall conclusions should clearly define how and to what extent human data are supported by other available data. Any important limitations of the studies presented should be discussed here.

The analyses provided in previous sections should not be reiterated here. **This section can be brief**, but it should clearly define the health effects of the food as demonstrated by the totality of the data (including evidence in favour and not in favour) and by weighing the evidence to arrive at logical, well-argued conclusions substantiating the relationship between the food and the health effect.

APPENDIX P3.1.1 – TABULATED SUMMARY FOR HUMAN DATA

(i) Instructions for use:

This guidance is applicable to **Part 3.1.1**.

It is advisable to start with the preparation and completion of Part 4.2.1 prior to preparing Part 3.1.1.

It is advisable to use the Templates below as appropriate: **Appendix P3.1.1.a** for human intervention studies and Appendix **P3.1.1.b** for observational studies.

(ii) Appendix P3.1.1.a - Template provided for "Tabulated summary of intervention studies in humans"

1. Provide a table summarising the results of human intervention studies for the health outcome. If more than one intervention (i.e. different doses of food) 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.

Outcome:

Studies*	Intervention**	Intervention n/N	Control n/N	RR (95%CI)	Cross-reference to relevant sections within Parts 4 and 5
Study 1	Intervention 1				
Study 1	Intervention 2				
Study 2					
Study *n*					

**Indicate first author and publication year.*

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

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 for the health outcome. 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 metaanalysis of the studies is identified/performed, the protocol followed in conducting the analysis should be clearly detailed.

3. If available, published pooled analyses or meta-analyses of human intervention studies should be presented here (in **Part 3.1.1**), indicating the source and the protocol used to conduct the meta-analysis, and summarising the relevant results. A full report, if available, should be annexed under **Part 5.2**, and cross-reference should be given.

(iii) Appendix P3.1.1.b - Template provided for "Tabulated summary of human observational studies"

1. Provide a table summarising the results of observational studies for the health outcome. If more than one level of exposure (i.e. different doses of food) 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.

Outcome:

Studies*	Exposure**	Exposure n/N	Control n/N	OR (95%CI)	Cross-reference to relevant sections within Parts 4 and 5
Study 1	Exposure 1				
Study 1	Exposure 2				
Study 2					
Study *n*					

**Indicate first author and publication year.*

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

OR (95%CI) = Odd ratio (95% confidence interval)

2. If possible, provide a graphical analysis (e.g. forest plot**)** summarising the results of observational studies for the health outcome. 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 identified/performed, the protocol followed in conducting the analysis should be clearly detailed.

3. If available, published pooled analyses or meta-analyses of observational studies should be presented here (in **Part 3.1.1**), indicating the source and the protocol used to conduct the meta-analysis, and summarising the relevant results. A full report, if available, should be annexed under **Part 5.2**, and cross-reference should be given.

APPENDIX P3.3 – TABULATED SUMMARY OF OVERALL PERTINENT DATA

(i) Instructions for use:

This guidance is applicable to **Part 3.3**.

It is advisable to start with the preparation and completion of Parts 4.2.1 and 4.2.2 prior to preparing Part 3.3. Please use the Template below under (ii).

(ii) Appendix P3.3 - Template provided for "Tabulated summary of overall pertinent data identified by study type"

To be completed by the applicant for inclusion under **Part 3.3**. Individual studies included in any meta-analysis should be presented separately.

Study type	**Number of pertinent studies**	**Cross-reference to relevant sections within Parts 4 and 5**
1. Human studies[1] **(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 *ex vivo*/*in vitro* studies[5]		
2.3 Other [6]		
Total **(1 + 2)**		

RCTs = Randomised controlled trials
RT = Randomised trials

[1] Human studies dealing with the effect of the food on the health outcome.
[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 could be responsible for the health outcome (mechanistic studies), or studies on bioavailability.
[4] Animal studies dealing with e.g.: the mechanisms by which the food could be responsible for the health outcome (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.

Do not include numbers in grey rows in totals of columns. **Several cells in the above table might not be applicable.**

APPENDIX P4.1.1 – COMPREHENSIVE REVIEW OF HUMAN DATA

(i) Instructions for use

This guidance is applicable to **Part 4.1.1.** Applicants are advised to read this carefully to complete Part 4.1.1.

It is intended to assist applicants in conducting a comprehensive review of the totality of scientific data in a systematic and transparent manner in order to identify the pertinent human data to substantiate the claimed effect.

(ii) Information required in Part 4.1.1 when conducting a comprehensive review of the totality of scientific data:

To be completed by the applicant and presented under Part 4.1.1:

1. **Authorship.** Name, affiliation, conflict of interests' declaration and signature of the reviewer(s) responsible for the comprehensive review.
2. **Background**
   - 2.1. Define the nutrient(s)/substance/food/food category relevant to the effect for which a health claim is made
   - 2.2. Define the health outcome relevant to the effect for which a health claim is made
   - 2.3. In case of a health outcome that cannot be measured directly, define any marker(s) being selected as surrogate of the health outcome, if any, e.g.: plasma cholesterol concentrations being used as marker of cardiovascular disease risk, bone density being used as marker of osteoporosis risk, etc.
   - 2.4. Provide information and a rationale for selecting the above marker(s) of health function (if any) as surrogate for the health outcome in point 2.2. State their relevance to the health claim. For both endpoints and markers of health outcome, state whether they are methodologically valid with respect to their analytical characteristics.
3. **Brief description of the hypothesis tested, i.e.: Food-health relationship**
4. **Literature search**
   - 4.1. <u>List of electronic databases searched</u>
     - 4.1.1. General Health and Medical databases
     - 4.1.2. Selected databases with a specific focus
     - 4.1.3. Research registers
     - 4.1.4. Review registers
     - 4.1.5. Other
   - 4.2. <u>Search strategy</u>
     - 4.2.1. Standard search terms (and combination of terms) used.
     - 4.2.2. Additional search terms (for databases not allowing complex search strategies)

4.2.3. Search limits. Specify whether (and which) search limits were used, if any.

a. Dates of publication.

b. Publication type

c. Language

d. Population subgroup (s)

e. Default tag (Title, Abstract, Full text, other)

f. Other

4.2.4. Website searches (for relevant organisations publishing reviews /guidelines /consensus opinions relevant to the topic).

4.2.5. Hand searching and grey literature. Specify what efforts were made to obtain scientific data that are not indexed in the major electronic databases.

4.3. Identify when the search was performed

5. Identification of pertinent literature

5.1. Detailed **exclusion and inclusion criteria** applied to select pertinent references with clear identification of the references excluded by each exclusion criteria either before or after evaluation of the full text.

5.2. List of all references identified potentially pertinent to the topic. Indicate author(s), title, journal/book/other, publication year, volume, pages. For book and book chapters indicate also editor, publisher and city.

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.

APPENDIX P4.1.1.6 – TEMPLATE PROVIDED TO DISPLAY THE RESULTS OF THE REVIEW OF HUMAN DATA

"Number of pertinent references identified by publication type"

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

Publication type	**Number of pertinent publications**
Human data[1] **(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 Review articles	
7 Guidelines/consensus opinions/text book chapters	
8 Other[2]	

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

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

Do not include numbers in grey rows in total of columns. **Some cells in the above table might not be applicable.**

APPENDIX P4.2.1 – SYNOPSIS OF INDIVIDUAL HUMAN STUDIES

(i) Instructions for use:

Applicants are advised to use the following Templates for presenting the synopsis of individual human studies requested under **Part 4.2.1**.

For human intervention studies (randomised controlled, randomised non-controlled, and controlled non-randomised studies), go to (ii)-**Appendix P4.2.1.1**.

For human observational studies, go to (iii)-**Appendix P4.2.1.2**.

(ii) Appendix P4.2.1.1: Template provided for "Synopsis of each human intervention study"

Please provide one synopsis for each study.

To be included under **Part 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. Conflict(s) of interest declared:
   - 1.6. Good Clinical Practice status / ethical consideration:
2. **Report status.** Please check as appropriate:
   Published □ Unpublished □
3. **Verification of study eligibility** (check if the intervention study meets inclusion criteria defined in 5.1 of the Appendix P4.1.1 on Comprehensive Review of Human Data):
4. **Description of the study population**
   - 4.1. Population subgroup (if not general population):
   - 4.2. Age range:
   - 4.3. Sex:
   - 4.4. Ethnicity:
   - 4.5. Inclusion criteria:
   - 4.6. Exclusion criteria:
   - 4.7. Setting:
   - 4.8. Geographical region:
5. **Study design:**
   - 5.1. Design: randomised controlled trials, cross-over studies, other.
   - 5.2. Intervention arm(s): (*fill boxes below as appropriate. Use N/A when not applicable)*

	Food	Food matrix, if applicable	Daily intake (nutrient(s)/substance)	Daily intake (food/food category, if applicable)	Duration of intervention
Intervention 1 = control					
Intervention 2					
Intervention *n*					

   - 5.3. Number of subjects allocated to each intervention arm:
   - 5.4. Primary outcome: State the variable used for power calculations, if any.
   - 5.5. Secondary outcome(s): variable 1, variable 2, variable *n*

5.6. Comparability of subjects between study groups (arms) at baseline. Variables checked for: variable 1, variable 2, variable *n*

6. Study outcomes:

6.1. Duration of follow-up:

6.2. Drop outs by intervention arm (including controls, if applicable):

6.3. Adverse effects in the control and intervention arms, if any reported:

6.4. 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****
Controls					
Intervention 1					
Intervention 2					
Intervention *n*					
Variable 2	Pre-test	Post-test	Mean difference	**P-1***	**P-2****
Controls					
Intervention 1					
Intervention 2					
Intervention *n*					

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.**

6.5. Address the biological relevance of the results.

7. Study quality. Please check the appropriate columns in the table below

	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. Endpoints/Markers of health outcome(s) validated analytically					
16. Endpoint/Markers of health outcome(s) 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.

8. Conclusions (15 lines maximum)

(iii) Appendix P4.2.1.2: Template provided for "Synopsis of each observational human study"

Please provide one synopsis for each study.

To be included under **Part 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. Conflict(s) of interest declared:
- 1.6. Good Epidemiological Practice status / ethical consideration:

2. Report status. Please check as appropriate:
Published ☐ Unpublished ☐

3. Verification of study eligibility (check if observational study meets inclusion criteria):

4. Description of the population
- 4.1. Population subgroup (if not general population):
- 4.2. Age range(s):
- 4.3. Sex:
- 4.4. Ethnicity:
- 4.5. Inclusion criteria (for cases and controls, if appropriate):
- 4.6. Exclusion criteria (for cases and controls, if appropriate):
- 4.7. Recruitment procedures used (consecutive, arbitrary, unreported, other):
- 4.8. Setting(s):
- 4.9. Geographical region(s):

5. Study design:
- 5.1. Design: cohort, case-control, case-reports, cross-sectional
- 5.2. Data collection (prospective, retrospective, unreported, other).
- 5.3. Exposure (s): (*fill boxes below as appropriate. Use N/A when not applicable)*

	Food	Food matrix, if applicable	Daily intake (nutrient(s)/substance)	Daily intake (food/food category, if applicable)	Duration of exposure
Exposure 1= control					
Exposure 2					
Exposure *n*					

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

6. Outcome measures and results:

6.1. Duration of follow-up:

6.2. Drop outs in total, by group:

6.3. Adverse effects being reported:

6.4. Measure of effect of the exposure: report measure of effect for outcome variables as appropriate.

6.5. Address the biological relevance of the results.

7. Study quality. Please check the appropriate columns in the table below.

	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. Endpoint/Markers of health outcome(s) validated analytically					
18. Endpoint/Markers of health outcome(s) 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*

8. Conclusions (15 lines maximum)

APPENDIX P4.2.2 – GUIDANCE FOR PRESENTING NON-HUMAN STUDIES

(i) Instruction for use:

This guidance is applicable to **Part 4.2.2** and is intended to assist applicants in the preparation and presentation of non-human data that have been identified and acquired to support the health claim.

(ii) Sequence of information:

The sequence of information to be presented under Part 4.2.2 is described below:

- Animal data
  - Studies investigating aspects related to absorption / distribution / metabolism / excretion
  - Mechanistic studies
  - Other
- *Ex vivo* or *in vitro* data (i.e. meaning studies based on either human or animal biological samples related to the mechanisms of action)
- Other studies
- List of references

(iii) Content of information:

For each individual study, a **brief and concise overview should be given**, addressing if applicable:

- Testing model
- Good Laboratory Practice status where appropriate
- The quality and relevance of "test food(s)", dose, route of administration, duration of exposure
- The principal findings (e.g. mechanism of action) and their relevance for humans.
- Any potential side effects identified

Copies of article/reprint of references and full study reports for unpublished studies should **not** be given under Part 4.2.2. They should be annexed in **Part 5.2**. Full study reports for unpublished studies should be annexed under **Part 5.3.** Cross-reference should be given.