Guidance Document for Preparing a Submission for Food Health Claims

Bureau of Nutritional Sciences
Food Directorate, Health Products and Food Branch
Health Canada

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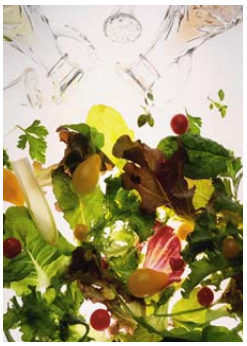


Canada

TABLE OF CONTENTS

LIST OF TABLES

1.0 BACKGROUND INFORMATION

1.1 Purpose of the Guidance Document

This document updates the *Interim Guidance Document Preparing a Submission for Foods with Health Claims: Incorporating Standards of Evidence for Evaluating Foods with Health Claims*, which has been available for use since 2002. The purpose of this updated document is to ensure that health claims for foods are substantiated in a systematic, comprehensive and transparent manner. When petitioners are preparing submissions for the use of new health claims on food products, they are required to follow the format set out in this guidance document. A common submission format among petitioners will ensure a comprehensive and well-organized submission and an improved efficiency in the review process.

A health claim is a statement or representation that states, suggests or implies that a relation exists between a food or component of that food and health (Codex Alimentarius Commission, 1997). Authorization or acceptability of a health claim requires evaluation of evidence on:

- Causality – consumption of the food affects a health outcome;
- Generalizability – the claimed effect is physiologically meaningful and is applicable to the general population or a subgroup of the population; and
- Quality assurance – the food is produced according to quality standards and consistently meets predefined specifications.

The safety of a food must also be assured for health claim authorization. As such, the subject of a health claim application must be for a food approved for safe use; or, if a novel food is the subject of the health claim, a novel food application must be completed and submitted to Health Canada preceding or concurrent with this application. This guidance document is focused on demonstrating causality and generalizability of a health claim. Additionally, key aspects related to quality assurance are addressed.

1.2 Relevant Regulations

The *Food and Drugs Act* governs the use of health claims on food products in Canada. The *Food and Drugs Act* (the *Act*) includes definitions and provisions that are relevant to health claims, specifically:

- The definition of a food (Section 2 of the *Act*)
- The definition of a drug (Section 2 of the *Act*)[1]
- Prohibition of advertising for any condition stated in Schedule A (Section 3 of the *Act*)

1 A drug is defined as "any substance or mixture of substances manufactured, sold or represented for use in the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals; or, restoring, correcting or modifying organic functions in human beings or animals."

- Prohibition of deceptive advertising (Section 5 of the *Act*)
- Authorization of drug-like claims on food (Section 30 (j) of the *Act*).

A food bearing health claims deemed to meet the definition of a drug is subject to the drug-related regulations in the *Food and Drug Regulations*. However, provisions have been included in the *Food and Drugs Act (*Section 30 (j)) and *Food and Drug Regulations* to exempt foods with drug-like claims from the provisions of the *Act* and its Regulations with respect to drugs, and from Section 3 of the *Act* (Schedule A). This exemption was applied to approve Canada's existing five food health claims that mention a disease (see B.01.601 in the *Food and Drug Regulations*). New health claims that would fall under the definition of a drug can be added to the table following Section B.01.603 of the *Food and Drug Regulations* through regulatory amendments following review of a health claim submission and adoption of a regulatory amendment by the Government of Canada.

1.3 When to Use this Guidance Document

This guidance document should be used in the preparation of a health claim submission for any food where the health claim applied for brings the food under the definition of a drug – *i.e.,* the claim is related to the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms; or restoration, correction or modification of organic functions. Such health claims require approval by Health Canada and regulatory amendments before the food can be marketed with the intended health claim.

Health claims that do not bring the food under the definition of a drug do not require pre-market approval or regulatory amendment. However, such claims must be truthful and not misleading (Section 5 of the *Act*) and manufacturers are expected to have evidence (in-house) substantiating the health claim should they be questioned by enforcement agencies. They are thus advised to follow this guidance document to ensure the health claim is properly substantiated and/or to prepare a voluntary submission to Health Canada.

1.4 Guiding Principles

Substantiation of a food health claim and the assessment of whether it is valid is guided by the following principles:

a. **Systematic Approach**: A methodical, consistent approach is applied to substantiate a health claim.

b. **Transparency:** Search strategies, literature selection and evaluation, as guided by the document, are fully disclosed, to increase the credibility of the submission and to permit reproducibility.

c. **Comprehensiveness:** All original research in humans, pertaining to the health claim, is captured, including evidence in favour and not in favour of the health claim.

d. **Human Evidence:** The focus is on original research in humans that measures the food and health effect of interest.

e. **High level of Certainty**: The health claim is supported by a high level of certainty. This means that the majority of high quality human studies support a statistically significant favourable effect. Consideration will be given to statistical significance achieved at $p \leq 0.05$.

f. **Demonstration of Causality:** Demonstration of causality will consider the quality and quantity of original research in humans that support a beneficial effect of the food (*i.e.*, direction of effect); the strength of the association between the food and health effect (*i.e.*, statistical significance of the favourable effect) and the relationship between the amount of the food and the health effect (*i.e.*, dose-response).

g. **Biological Relevance of the Claimed Effect:** The claimed effect of the food is biologically/physiologically relevant and expected to benefit the health of the target population. To ensure biological relevance of the claimed effect, surrogate markers of the claimed effect must have both methodological validity and biological validity. Markers must additionally be part of the causal pathway between the food and the health outcome.

h. **Feasibility of Consumption of Effective Dose:** The amount of food to be consumed to achieve a beneficial effect can be incorporated into a healthy, balanced diet by the target population.

i. **Health Claim Wording:** The health claim wording communicates the health outcome that is substantiated in the submission, i.e., it is specific to the substantiated health outcome. If, for example, the submission supports a reduced risk of infectious diarrhea, this does not mean that the product "supports healthy immune function". The correct claim wording would more directly make a statement to the effect that the product "reduces risk of infectious diarrhea".

j. **Substantiation of one food-health relationship in a submission:** One food/health relationship is to be addressed per submission. Multiple formulations/matrices of a food can be proposed by the petitioner, provided the scientific evidence is valid for all proposed formulations/matrices, but only a single health effect can be the object of a submission. However, more than one biomarker of a single health effect may be used – *e.g.*, using total cholesterol and LDL cholesterol as biomarkers of one health effect – heart disease.

1.5 Study Designs and Evidence of Interest

a. Human Studies

Health Canada's evaluation of a health claim will be based on human studies – intervention and/or prospective observational studies. As such, the literature search strategy should be established with a focus on retrieving human studies. The scientific uncertainties in extrapolating non-human data to humans limit the usefulness of non-human studies, such as animal and *in vitro* studies. A submission guided by this document should thus be based on the retrieval and evaluation of human studies. If desired, non-human studies may be used to support the discussion on biological plausibility. This is, however, optional.

b. Validity of Study Designs

The research design of human studies is a critical factor in interpreting the evidence for a health claim. Certain research designs can present biases that skew the interpretation of the evidence in an erroneous fashion and/or are not useful in inferring causality. Characteristics of research designs that limit the interpretation of the validity of the evidence are, for intervention studies, the absence of randomization and/or a control group. For observational studies, the use of retrospective studies (retrospective cohort, case-control), cross-sectional, and descriptive studies (ecologic, time series, demographic) does not allow determination of a causal relationship.

This document provides guidance on how human studies with different research designs should be dealt with. For intervention studies, non-randomized studies may be included during literature filtering; however, their subsequent quality rating will affect their contribution to supporting consistency. For observational studies, only those with a prospective design (*i.e.*, prospective cohort and nested case-control studies) should be included; all other observational studies should be excluded.

Finally, if the subject of a health claim is a food constituent (*i.e.*, not a food or a food category), the submission must at least include intervention studies; relevant observational studies would also be included, if available. Observational studies may be of greatest relevance for substantiation of health effects related to foods or food categories, but without intervention studies, observational studies alone generally do not allow for a causal inference to be made on the relationship between a food constituent and a health effect.

1.6 Definitions

Definitions for commonly used terms in the guidance document are provided below.

- The term "food" hereafter means a food category; a food (whole or processed); or, a food constituent, added or inherent.

- "Food exposure" and "food intake" are used interchangeably in this document. In both experimental and epidemiological studies, the assessment of food intake may be supported by a biomarker of exposure (*e.g.*, intake of lutein from foods may be supported by measurement of blood lutein levels).

- A "bioactive substance" is a substance that is demonstrated or purported to have a favourable effect on health. In the context of food, bioactive substances include nutrients (*e.g.*, vitamins and mineral nutrients) and non-nutrients (*e.g.*, lycopene, live microbes) that may be inherent in or added to food.

- The term "health effect" refers to a body function, health condition or disease risk, or mental or physical performance. With regard to disease risk, it refers to an effect on a true disease endpoint, such as heart disease mortality, or to an effect on a recognized surrogate marker of disease or a disease risk factor, such as blood LDL cholesterol. With regard to normal physiological function, or mental or physical performance, it refers to an effect associated with the maintenance or enhancement of health (*e.g.*, promotes regularity, builds and repairs muscles), and not to a therapeutic effect (*e.g.*, relieves constipation, restores mental alertness).

- The terms "health effect" and "health outcome" are used interchangeably in the document.

- The term "submission" means a stand-alone dossier containing all the required information for substantiation of a food/health relationship (*i.e.*, a health claim).

- The term "food/health relationship" refers to a biologically plausible association between a food and a health outcome.

1.7 Organization of Submission

The submission should meet the requirements below:

- The submission should include all components outlined in the checklist (Table 16).
- Pagination must be sequential for the entire submission.
- Paper copies must be bound or organized in a binder.
- The applicant's identification (*e.g.*, company name) should be included on all pages of the submission.
- Submissions must be in English or French. Relevant submission material in other languages must be translated into English or French.
- Applicants are responsible for clearly indicating parts of the application that contain proprietary or confidential data (*e.g.*, results from an unpublished clinical trial, details on manufacturing, *etc.*).
- Applicants are responsible for the accuracy of all cited references, published or unpublished. An established style for citing references must be used.

- The application must be signed by the person responsible for the submission. The submission must be signed by the petitioner or by his/her attorney or agent, or, if a corporation, by an authorized official.

All submissions will be screened for completeness. The petitioner will be informed of deficiencies regarding completeness. In cases where deficiencies are major, the file will be closed, until a revised and complete submission is received at which time the Food Directorate can continue with its review.

1.8 Submission to Health Canada

Two hard copies of the submission must be forwarded by mail to the address below.

Submission Management and Information Unit
Food Directorate, Health Products and Food Branch, Health Canada
251, Sir Frederick Banting Driveway
Postal Locator: 2202E
Ottawa, Ontario K1A 0K9

An electronic submission may be forwarded to the following e-mail address in addition to, but not in place of, hard copies: smiu-ugdi@hc-sc.gc.ca

1.9 Contact for Questions / Pre-Submission Meeting

Questions may be directed to

Nutrition Labelling and Claims Section
Food Directorate, Health Products and Food Branch, Health Canada
251, Sir Frederick Banting Driveway
Postal Locator: 2202E
Ottawa, Ontario K1A 0K9

The following email address may also be used
healthclaims-allegationssante@hc-sc.gc.ca

Submission requirements regarding characterization of the food will be contingent on the nature of the food (Section 3). To ascertain whether these requirements apply or to clarify requirements on any part of an application, it is recommended that petitioners arrange a pre-submission meeting and provide relevant information to Health Canada in advance.

1.10 Review Process Following a Submission

Within 15 days of receipt of the submission, Health Canada will notify the petitioner by letter that the submission has been received.

1.11 Re-Evaluation of a Health Claim

Health Canada may re-evaluate an approved health claim in response to a petitioner or on its own initiative due to new scientific evidence that brings into question the certainty of the claim or the conditions for its use.

2.0 SUBMISSION REQUIREMENTS

2.1 Contact Information

Objective: To identify the organization submitting the health claim and to provide the coordinates of a person that can be contacted for scientific and/or regulatory issues/concerns/questions.

Procedure:

- Complete Table 1 – Applicant Information.

Table 1. Applicant information

	Applicant (Organization/ Company)	Contact Person
Name		
Affiliation		
Position		
Address		
Telephone Number		
Fax Number		
E-mail		
Website		

If information requested is not applicable, please indicate NA.

2.2 Details Pertaining to Proposed Health Claim

Objective: To communicate important aspects related to the health claim up front.

Procedure:

- Complete Table 2 – Details pertaining to the proposed health claim.

Table 2. Details pertaining to the proposed health claim		
Item	**Details (State N/A where necessary)**	
Food/bioactive substance of interest		
Health outcome of interest (include surrogate markers if used)		
Human studies used to support health claim	Intervention Studies	Prospective Observational Studies
	☐ Yes ☐ No	☐ Yes ☐ No
Proposed health claim (claim wording)		
Voluntary submission	☐ Yes ☐ No	
Mandatory submission (for a claim that brings food under definition of a drug, or for <u>any claim</u> intended for use on Infant Formula)	☐ Yes ☐ No	
Minimum effective intake of the food/bioactive substance to obtain the claimed effect		
Proposed daily intake of the food		
Proposed qualifying criteria for foods to carry a health claim (*e.g.*, minimum or maximum allowable levels of nutrients)		
Target population for the proposed claim		
Rationale for the target population		
Potential adverse effects related to food intake (from human studies)		
Proposed restrictions on use of food (*e.g.*, a subgroup of population, mode of consumption of food)		
Proposed risk management strategies to address adverse effects and/or restrictions on use of food (*e.g.*, indicate wording of recommended warning statements)		

Abbreviations: N/A, not applicable

2.3 Regulatory Status of the Health Claim in Other Jurisdictions

Objective: To understand the regulatory status of the health claim in other jurisdictions in addition to the claim wording and conditions for use of approved claims.

Procedure:

- Complete Table 3 – Regulatory status of the health claim in other jurisdictions.

Table 3. Regulatory status of the health claim in other jurisdictions

Country	Regulatory Body	Date of Submission (day/month/year)	Status of Health Claim Application[1]	Details for Approved Claims		
				Wording of approved claim	Conditions for use of the claim	Date of claim authorization

[1] State "under review", "withdrawn", or "rejected"

3.0 CHARACTERIZATION OF THE FOOD

Objective: To understand the composition and manufacturing of the food/bioactive substance and to ensure it meets quality standards and pre-defined specifications.

Background

The nature of the food that is the subject of the proposed health claim will guide the type and extent of information required to be provided in this section. More information will be required if the subject of the health claim is a food containing a bioactive substance (added to or inherent in the food) *versus* a food category or a whole food.

Procedure:

- Fulfill the information requirements outlined in Table 4 – Information requirements for characterization of the food. Note that the requirements differ depending on the subject of the claim.

Table 4. Information requirements for characterization of the food	
Subject of Claim	**Information Requirements**
Applicable to any of the following categories	Dietary intake estimates • Current intakes of the food or constituent (should be based on Canadian intake data, where possible)
Food category (*e.g.*, fruits)	• State the food category. • Consider the range of foods that typically fall under the food category and state the foods proposed for the health claim and those not proposed for the claim.
Whole (unprocessed) food *(e.g.*, apple)	• State the food. • State the amount of calories and levels of macronutrients and micronutrients per 100 g, per Canada's Food Guide serving, and per minimum effective intake (the minimum quantity of food shown to be effective in the human studies)[1].
Foods containing an inherent bioactive substance *(e.g.*, galacturonic acid (pectin) in apples)	• State the common or usual name of the food. • State the amount of calories and levels of macronutrients and micronutrients, and bioactive substance per 100 g, per Canada's Food Guide serving, per minimum effective intake (the minimum quantity of food shown to be effective in the human studies), and per reference amount of the food[1]. • State the ingredients, and their amounts, that comprise the food. • Summarize the specifications for the food (*e.g.*, chemical, physical, microbiological characteristics and levels of bioactive substance inherent in the food) and include a certification of this data in an Appendix. • Summarize the manufacturing process of the food and indicate whether it follows a quality system (*e.g.*, Good manufacturing practices). • Describe the tests, and their results, used to ensure the food meets pre-defined specifications (*e.g.*, batch to batch variability tests). • Describe the studies, and their results, used to ensure stability of the bioactive substance inherent in the food, during its shelf-life and under the recommended storage conditions.
Food containing an added bioactive substance[2] (*e.g.*, yogurt with L. casei 431)	<u>End Product (Food with added bioactive substance)</u> • Describe the common or usual name of the food. • State the amount of calories and levels of macronutrients and micronutrients, and added bioactive substance per 100 g, per Canada's Food Guide serving, per minimum effective intake (the minimum quantity of food shown to be effective in the human studies), and per reference amount of the food[1]. • State the ingredients, and their amounts, that comprise the food (including the added bioactive substance). • Summarize the specifications for the food (*e.g.*, chemical, physical, microbiological characteristics) and include a certification of this data in an Appendix. • Summarize the manufacturing process of the food and indicate whether it follows a quality system (*e.g.*, Good manufacturing practices). • Describe the tests, and their results, used to ensure the food meets pre-defined specifications (*e.g.*, batch to batch variability tests). • Describe the studies, and their results, used to ensure stability of the added bioactive substance during the shelf-life of the food and under the recommended storage conditions.

Table 4. Information requirements for characterization of the food	
Subject of Claim	**Information Requirements**
	Bioactive substance (added to the food) • Summarize the specifications (*e.g.*, chemical, physical, microbiological characteristics) for the bioactive substance and include a certification of this data in an Appendix. • Summarize the manufacturing process of the bioactive substance and indicate whether it follows a quality system (*e.g.*, Good manufacturing practices). • Describe the tests, and their results, used to ensure the bioactive substance meets pre-defined specifications (*e.g.*, batch to batch variability tests). • Describe the studies, and their results, used to ensure stability of the bioactive substance under the recommended storage conditions of the bioactive substance.

[1]The Canadian Nutrient File is the preferred source for this information. Alternatively, the USDA National Nutrient Database may be used.
[2] Information is required for the end product (with the added bioactive substance) and for the added bioactive substance, individually. Requirements for each are separately outlined.

4.0 CHARACTERIZATION OF THE HEALTH EFFECT

Objective: The purpose of this section is to provide information on the health effect, the validity of biomarkers used, and the relevance of the health effect to the Canadian population.

Procedure:

- Describe the health effect and all relevant biomarkers of the health effect with a rationale for the selection of biomarkers to be used. Discuss the methodological and biological validity of the health effect/its biomarkers.
- Discuss data on the prevalence of the health effect/its biomarkers in the Canadian population and provide a rationale on the cause for concern about the health effects/its biomarkers.

5.0 EVALUATION OF CLAIM VALIDITY

The purpose of this section is to guide the retrieval and evaluation of the totality of relevant evidence on the food/health relationship, to allow for an assessment of causality (*i.e.*, whether intake of the food causes the health effect of interest) and generalizability (*i.e.*, applicability of the food/health relationship to the target group), as well as the biological relevance of the health effect and the feasibility of consuming an effective intake of the food. See Figure 1 for an outline of the steps to be completed. The remainder of this document describes the requirements for each step in detail.

Figure 1. Required Steps to Address Claim Validity

Step 1. Describe the search strategy for literature retrieval
Step 2. Implement the search strategy for literature retrieval
Step 3. Develop inclusion and exclusion criteria to filter the literature retrieved
Step 4. Filter the literature
Step 5. Generate reference lists of included and excluded studies
Step 6. Tabulate studies
Step 7. Evaluate study quality
Step 8. Tabulate study findings per health outcome
Step 9. Assess causality
- **Step 9a. Rate consistency**
- **Step 9b. Rate the strength of the association**
- **Step 9c. Discuss the relationship between the food exposure and the health effect**

Step 10. Discuss generalizability of the data to the target population
Step 11. Discuss the physiological meaningfulness of the effect of the food exposure
Step 12. Discuss the feasibility of consuming an effective amount of the food
Step 13. Make conclusions

5.1 Details of the Steps

5.1.1 Step 1. Describe the Search Strategy for Literature Retrieval

Objective: To develop a relevant, comprehensive (*i.e.*, minimizing exclusion of relevant evidence), and reproducible strategy that will be used to retrieve the totality of evidence from human studies on the food/health relationship.

Procedure:

- **It is highly recommended to seek the assistance of a librarian to develop a relevant and comprehensive search strategy.**

- Brainstorm relevant keywords related to the food and health effect that will be used to retrieve the literature. Consider alternate terminologies/synonyms (*e.g.*, scientific/technical terms and/or Latin terms) and alternate spellings of common terms. Electronic databases may be a helpful reference to learn of alternate terminologies of common terms.
  - Literature retrieval will <u>not</u> be limited at this point to the target population in order to maintain a broad evidence base on the food/health relationship as much as possible and to address applicability of the relationship to a

population group. Therefore, keywords related to the target population do not require brainstorming.

- Decide on relevant keywords to be used to retrieve the literature and how they will be combined to search the literature within electronic databases.

- Decide on relevant electronic databases that will be used to search the literature. Examples include: MEDLINE, Cochrane Library, EMBASE, CINAHL, Food Science and Technology Abstracts, Current Contents, Scopus, Cab health (Global Health), Web of Science, Scholars Portal Search, PsycInfo, AGRICOLA, Science Citation Index. The use of at least MEDLINE and two additional electronic databases is recommended.

- Decide on whether you will consider non-electronic methods to retrieve relevant literature – *e.g.*, unpublished literature; hand-searching (systematic reviews, meta-analyses or other relevant articles).

- Decide on your search limitations, such as the date range; languages; whether you will limit the search to publications in humans; etc.

- Complete Table 5 – Identification of databases and search parameters used for literature retrieval.

- Complete Table 6 – Keywords and their combinations used to retrieve literature on the food/health relationship from electronic databases.

Table 5. Identification of databases and search parameters used for literature retrieval	
A. Electronic Databases • List electronic databases used and identify fields searched within each database	
Database	**Fields searched in database (*e.g.*, title, abstract, subject headings, descriptors)**
B. Non-Electronic Methods/Sources • State whether the below were conducted/considered	
Hand Searching	☐ Yes ☐ No
Unpublished Studies	☐ Yes ☐ No
C. Humans • State whether a search parameter was used to limit retrieval to human studies	
☐ Yes ☐ No	If yes, search parameter used:
D. Publication Years • State the publication years considered for your electronic/non-electronic searches and justify the start date.	
Start date (*i.e.*, year):	
End date (*i.e.*, year):	
Justification for start date (*i.e.*, year), and if necessary, for end date if different from the current year:	
E. Languages • State the languages considered for your electronic/non-electronic searches.	
Languages considered for search:	

Table 6. Keywords and their combinations used to retrieve literature on the food/health relationship from electronic databases[1]	
A. Food	
Indicate keywords used (*e.g.*, Oat, oats, beta-glucan, beta glucan, Avena sativa):	
B. Health effect(s)	
1. Final health effect	**2. Biomarker/Surrogate marker of health effect**
Indicate keywords used (*e.g.*, heart disease, coronary heart disease, cardiovascular death):	**Indicate keywords used** (*e.g.*, myocardial infarction, ischemia, atherosclerosis, total cholesterol, LDL cholesterol):
C. Combinations of keywords used	
Indicate combinations of keywords used – *e.g.*, A and B1; A and B2; [(A and B1) or (A and B2)], *etc.*:	
D. Justification for exclusion of potentially relevant terms	
Please specify and justify the disuse of relevant terms as keywords – *e.g.*, Opting to only use keywords related to the surrogate marker of a health effect, rather than using keywords related to both the health effect and its surrogate marker:	

[1]State N/A if not applicable.

5.1.2 Step 2. Implement the Search Strategy for Literature Retrieval

Objective: To implement the search strategy consistently across all electronic databases, to maintain a record of all literature retrieved prior to literature filtering and to organize the retrieval of the literature in a systematic way.

Procedure:

- Implement the search strategy outlined in Step 1 in each electronic database.

- Include a copy of the 'search history' in an Appendix (the record of the keywords used, their combinations, and the limitations imposed on the search) by printing it directly from the electronic database.

- Include a copy of the entire literature search in an Appendix by printing it directly from the electronic database.

- Complete Table 7 – Number of references retrieved from electronic and non-electronic sources.

Table 7. Number of references retrieved from electronic and non-electronic sources	
Source	**# of References**
A. Retrieved from Electronic Databases	
B. Retrieved from Non-Electronic Databases (*e.g.*, unpublished literature; hand-searched)	
C. Duplicates	
TOTAL (A+B-C):	

5.1.3 Step 3. Develop Inclusion and Exclusion Criteria to Filter the Literature Retrieved

Objective: To develop inclusion/exclusion criteria that will be applied to all references retrieved from electronic and non-electronic databases so that not relevant/non-useful references can be excluded.

Procedure:

- Specify your inclusion and exclusion criteria in Table 8a using Table 8b as a guide. You can simply re-state what is written in Table 8b in Table 8a if similar criteria were used (where examples are included in Table 8b, you can substitute the example with information relevant to the health claim in Table 8a).

Table 8a. Inclusion and exclusion criteria used for literature filtering		
Factor	**Inclusion Criteria**	**Exclusion Criteria**
Source		
Report type		
Language		
Publication Year		
Duplicate		
Treatment (Food)		
Control (if used)		
Route of exposure		
Health effect		
Population health status/study setting		
Ages		
Statistical significance		

Table 8b. Guidance on appropriate inclusion and exclusion criteria for literature filtering		
Factor	**Inclusion Criteria**	**Exclusion Criteria**
Source	• Published or in press in a peer-reviewed journal, or unpublished	• Published in a non-peer-reviewed source (magazine, website, *etc.*)
Report type	• Full length article/study report of original research in humans: • Human intervention studies • Prospective observational studies (cohort and nested case-control studies) • Systematic reviews, or meta/pooled analysis of original research in humans • Authoritative statement (position papers by a credible scientific body, such as the Institute of Medicine, the World Health Organization, *etc.*)	• Animal and *in vitro* studies • Published abstract, short communication, opinion letter, consumer letter, testimonials • Abbreviated unpublished study report • Retrospective studies (retrospective cohort, case-control, cross-sectional, ecological, time-series, or demographic studies)
Language	• *e.g.*, English	• *e.g.*, All but English
Publication Year	• *e.g.*, Start date of database (*e.g.*, 1967) to date of search (*e.g.*, January 31, 2009)	• *e.g.*, N/A
Duplicate	• N/A	• Publication is a duplicate

Table 8b.	Guidance on appropriate inclusion and exclusion criteria for literature filtering	
Factor	**Inclusion Criteria**	**Exclusion Criteria**
Treatment (Food)[1]	• Food of interest quantified: dose of food known (intervention studies); amount of food consumed calculated (prospective observational studies). • For intervention studies, food of interest administered independently of other nutritional and/or pharmacological interventions • Biomarker of food biologically/methodologically relevant	• Food of interest not quantified: dose of food not known (intervention studies); amount of food consumed not calculated (observational studies). • For intervention studies, food of interest not administered independently of other nutritional and/or pharmacological interventions • Biomarker of food not biologically/methodologically relevant
Control	• Control group included and use of a control/placebo appropriate to design	• No control or comparison group or inappropriate control used
Route of exposure	• Oral	• Non-oral (*e.g.*, intravenous)
Health effect[1]	• Health effect of interest measured • Biomarker(s) of health effect biologically and methodologically relevant	• Health effect of interest not measured • Biomarker(s) of health effect not biologically/methodologically relevant
Population health status/study setting	• Representative of target population – *e.g.*, free-living, generally healthy adults	• Not representative of target population – *e.g.*, hospitalized or free-living sick or diseased individuals
Ages	• Representative of target population – *e.g.*, Adults ≥18 years	• Not representative of target population – *e.g.*, Individuals <18 years
Statistical significance	• Reported	• Not reported

Abbreviations: N/A, not applicable

[1]You may find it helpful to articulate terminologies (in a footer to the table) that could be used in publication titles and that could indicate a relevant publication – *e.g.*, a publication title may reference "cholesterol-lowering foods" rather than "oats", or "dyslipidemia" rather than "cholesterol-lowering".

5.1.4 Step 4. Filter the Literature

Objective: To exclude references that based on their title, abstract, or full-text, meet the exclusion criteria/do not meet the inclusion criteria specified in Table 8a.

Procedure:

Title-Filtering

- Apply the inclusion/exclusion criteria to the titles of all retrieved references.*

- Count the number of references excluded at the title filtering stage and complete the applicable section of Table 9 – Results of literature filtering.

* **It is highly recommended that two people independently apply the inclusion/exclusion criteria.** Their results can be compared and disagreements can be resolved through discussion. **It is recommended to err on the side of over-inclusion at the title-filtering stage to minimize the likelihood of excluding relevant/useful literature early on.** When deciding on inclusion/exclusion at the title-filtering stage, in addition to using the reference title to determine relevance/usefulness, the name of the journal may be helpful. For example, if the food/health relationship of interest is oats and cholesterol-lowering, a correct inference would be that a reference appearing in the "International Journal of Cancer" is not relevant/useful.

Abstract-filtering:

- Apply the inclusion/exclusion criteria to the abstracts of references which were not excluded during title filtering.

- Count the number of references excluded at the abstract-filtering stage and complete the applicable section of Table 9 – Results of literature filtering.

Full-text filtering:

- Apply the inclusion/exclusion criteria to the full text of references which were not excluded during abstract filtering.

- Count the number of references excluded at the full text-filtering stage, noting the reason for exclusion of each reference (Table 11).

- Complete the applicable section of Table 9 – Results of literature filtering.

Table 9. Results of literature filtering	
Factor	**Number of References**
References prior to applying inclusion/exclusion criteria	
References excluded at title-filtering stage	
References excluded at abstract-filtering stage	
References excluded at full-text filtering stage	
TOTAL References Excluded (after applying inclusion/exclusion criteria):	
TOTAL References Included (after applying inclusion/exclusion criteria):	

5.1.5 Step 5. Generate Reference Lists of Included and Excluded Studies

Objective: To indicate the references that met the inclusion criteria and those that met the exclusion criteria at the full-text filtering stage.

Procedure:

- Produce a reference list of all studies that met the inclusion criteria at the full-text filtering stage and include it in Table 10 – List of references that met the inclusion criteria at the full-text filtering stage.

- Produce a reference list of all studies that were excluded on the basis of the exclusion criteria at the full-text filtering stage and include it in Table 11 – References excluded at the full-text filtering stage and reason(s) for exclusion. Note the reason for exclusion for each reference. Count the total number of excluded studies per reason for exclusion and include the tally in Table 11.

- Ensure you have the full-text copy of all publications that have met the inclusion criteria at the full-text filtering stage. Full-text copies of all included publications should be included with your submission in an Appendix. If studies in languages other than English or French were included, then translations of the studies in either English of French must be provided.

Note: Only original research will be evaluated in the remaining steps. Systematic reviews and meta-analyses lack sufficient detail on individual studies to be used in these steps. Systematic reviews, meta-analyses and authoritative statements may, however, be used in the last step of the systematic approach to support concluding statements.

Table 10.	List of references that met the inclusion criteria at the full-text filtering stage

Table 11.	List of references excluded at the full-text filtering stage and reason(s) for exclusion
Reference (Full citation)	**Reason(s) for Exclusion[1]**
Total number of excluded studies per reason	*e.g.*, Source (n=2); Report type (n=5), *etc.*

[1]Reason(s) for exclusion include: Source, report type, language, publication year, duplicate, treatment, control, route of exposure, health effect, population health status/study setting, age, statistical significance, or other (specify).

5.1.6 Step 6. Tabulate Studies

Objective: To provide a synopsis of the relevant information from intervention and observational studies in a standardized and objective manner.

Procedure:

- Group the included studies according to publication type as follows:
  A) Intervention/Experimental studies
  B) Observational studies
    i) Prospective cohort studies
    ii) Nested case-control studies (case-control within a cohort)

- Summarize relevant information from each of the intervention and observational studies that met the inclusion criteria at the full-text filtering stage using Table 12a (for intervention studies) and 12b (for observational studies) as templates.

Table 12a. Summary of intervention studies addressing the food/health relationship (*e.g.*, oats beta glucan fibre and heart disease risk).

<table>
<tr><th>Reference and Quality Rating

(Author, year)</th><th>Aim of Study</th><th>Design

• R (Randomized)
• NR (Non-randomized)
• C (Control group)
• SB (Single-blind)
• DB (Double-blind)
• P (Parallel)
• CO (Crossover)</th><th>Sample Characteristics

• Country
• Health status
• Setting (metabolic unit, free-living subjects)
• Age range
• Gender (M, F)
• No. recruited
• No. randomized
• No. in final sample</th><th>Exposure and Duration

• Food matrix
• Food dose; method and frequency of consumption
• Duration of intervention
• Design and/or duration of stabilization period , washouts, follow-ups</th><th>Background Diet & Assessment Tool</th><th>Results & Statistics

• Changes in health effect
• Adverse effects</th><th>Relevant Authors' Conclusions</th></tr>
<tr>
<td>Biorklund et al., 2005

Quality:</td>
<td>• To investigate whether cholesterol-lowering effect of a beverage enriched with 10g beta-glucans is more pronounced compared to a beverage providing half that amount (5g).

• To compare the effect of products enriched with beta-glucan from oats and barley on the serum lipoprotein profile and postprandial concentrations of glucose and insulin.</td>
<td>• R, C, SB, P</td>
<td>• Netherlands and Sweden

• BMI: 20-30;
No history of CAD or heart failure; No diabetes;
Hypercholesterolemia:
Total Chol 5.5-8.0mmol/L,
LDL Chol 4.1-5.7mmol/L

• Free-living

• 18-70 yrs

• M and F

• 100 recruited and randomized

• 89 in final sample</td>
<td>• Fruit beverage

• Oat Dose High
10g beta-glucan from oats/d: two 250 ml beverages, to be consumed with two main meals (breakfast, lunch or dinner)

• Oat Dose Low
5g beta-glucan from oats/d: two 250 ml beverages, to be consumed with two main meals (breakfast, lunch or dinner)

• Control Dose
0g beta-glucan from oats/d; 22.5g rice starch/d from two 250 ml beverages, to be consumed with two main meals (breakfast, lunch or dinner)

• 3-wk run-in period with control (rice starch) beverage

• 5-wk treatment in one of 5 grps:
1. 10g beta-glucans from oat (Oat-10) + usual diet
2. 5g beta-glucans from oat (Oat-5)+ usual diet
3. 10g beta-glucans from barley (Barley-10) + usual diet
4. 5g beta-glucans from barley (Barley-5) + usual diet
5. control beverage + usual diet</td>
<td>• Usual diet

• 3-day food record or food frequency lists</td>
<td>Mean ± SD of lipid outcomes (mmol/l) at end of run-in and intervention, and change from run-in.

<table>
<tr><th></th><th>Oat-5 (n=19)</th><th>Oat-10 (n=15)</th><th>Control (n=20)</th></tr>
<tr><td>Total Chol</td><td></td><td></td><td></td></tr>
<tr><td>Run-in</td><td>6.64± 1.06</td><td>6.33± 1.05</td><td>6.54± 0.81</td></tr>
<tr><td>Intervention</td><td>6.33± 0.92</td><td>6.21± 0.77</td><td>6.71± 1.02</td></tr>
<tr><td>Change</td><td>-0.32± 0.39[a]</td><td>-0.12± 0.54</td><td>0.17± 0.49</td></tr>
<tr><td>LDL Chol</td><td></td><td></td><td></td></tr>
<tr><td>Run-in</td><td>4.32± 0.87</td><td>4.02± 0.82</td><td>4.43± 0.76</td></tr>
<tr><td>Intervention</td><td>4.07± 0.81</td><td>3.91± 0.67</td><td>4.48± 0.93</td></tr>
<tr><td>Change</td><td>-0.24± 0.35[b]</td><td>-0.11± 0.54</td><td>0.05± 0.38</td></tr>
<tr><td>HDL Chol</td><td></td><td></td><td></td></tr>
<tr><td>Run-in</td><td>1.60± 0.50</td><td>1.45± 0.41</td><td>1.42± 0.30</td></tr>
<tr><td>Intervention</td><td>1.59± 0.44</td><td>1.52± 0.42</td><td>1.49± 0.36</td></tr>
<tr><td>Change</td><td>-0.01± 0.15</td><td>0.06± 0.10[b]</td><td>0.07± 0.14[b]</td></tr>
<tr><td>TAG</td><td></td><td></td><td></td></tr>
<tr><td>Run-in</td><td>1.59± 0.78</td><td>1.87± 1.13</td><td>1.53± 0.53</td></tr>
<tr><td>Intervention</td><td>1.45± 0.67</td><td>1.73 ±0.98</td><td>1.63± 0.67</td></tr>
<tr><td>Change</td><td>-0.14±0.37</td><td>-0.14 ±0.45</td><td>0.10± 0.40</td></tr>
<tr><td colspan="4">[a]ANOVA and Tukey's post hoc test: significant change compared to control (p<0.01). [b]Paired samples t-test: significant change between run-in and intervention period, p<0.05.</td></tr>
<tr><td colspan="4">Adverse Effects: Subjects recorded AE in a diary. Some subjects reported GI discomfort during study. Major complaints included bloating, flatulence, diarrhea reported for both control and oat grps. GI problems were more frequent in oat (10g) grp (11 complaints) compared to other grps (7-8 complaints) but the problems decreased gradually for all subjects after 1-2 wks of consumption.</td></tr>
</table>
</td>
<td>A daily consumption of 5g of oat beta-glucans in a beverage improved lipid metabolism.

Compared to control, LDL Chol was non- significantly lowered by 5g (6.7%) and 10g (3.7%) beta-glucan oat beverages.

Compared to control, Total Chol was significantly lowered by the 5g beta-glucan oat beverage (7.4%) but not by the 10g beta-glucan oat beverage (4.5%).

The study was unable to show a dose-response effect of 5g compared with 10g of beta-glucans from oats and barley. The amount of beta-glucan does not necessarily predict its effect on serum Chol concentrations.</td>
</tr>
</table>

Table 12b. Summary of observational studies addressing the food/health relationship (*e.g.*, dietary fibre and heart disease risk)

<table>
<tr><th>Reference and Quality Rating

(Author, year)</th><th>Aim of Study</th><th>Design

• PROS (Prospective cohort)

• Nested Case-control within a cohort</th><th>Sample Characteristics

• Country
• Health status
• Setting (free-living subjects)
• Age range
• Gender (M, F)
• No. in final sample</th><th>Exposure and Duration

• Food exposure
• Duration of follow-up (for measurement of health effects)</th><th>Diet Assessment Tool</th><th>Results & Statistics

• Changes in health effect</th><th>Relevant Authors' Conclusions</th></tr>
<tr><td>Wolk et al., 1999

Quality:</td><td>• To examine the association between long term intake of total dietary fiber as well as fiber from different sources and risk of CHD in women.</td><td>• PROS</td><td>• USA

• Mean BMI at baseline: 24;
At baseline, no previous diagnosis of angina, myocardial infarction, stroke, cancer, hypercholesterolemia, diabetes

• Free-living

• 37-64 yrs

• F

• 68 782 in final sample</td><td>• Mean energy adjusted daily intake of total dietary fiber was:

Year 0: 16.2 (4.8) g
Year 2: 17.5 (5.3) g
Year 6: 18.0 (5.5) g

• 10-year follow-up on health effect</td><td>• Semi-quantitative food frequency questionnaire</td><td>Table 1. Relative Risk of CHD by Quintiles of Long-term Dietary Fiber Intake Among Women During 10 Years of Follow-up
<table>
<tr><th></th><th colspan="5">Quintiles of Energy-Adjusted Long-Term Total Dietary Fiber Intake, 1984-1990</th><th></th></tr>
<tr><th></th><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th><th>p-value for trend</th></tr>
<tr><td>Median fiber intake for 1984 to 1990, g/d</td><td>11.5</td><td>14.3</td><td>16.4</td><td>18.8</td><td>22.9</td><td></td></tr>
<tr><td>Age-adjusted RR (95% CI) for Non-Fatal MI</td><td>1.0 (Referent)</td><td>0.80 (0.61-1.06)</td><td>0.68 (0.51-0.90)</td><td>0.57 (0.42-0.77)</td><td>0.57 (0.42-0.77)</td><td><0.001</td></tr>
<tr><td>Age-adjusted RR (95% CI) for Fatal CHD</td><td>1.0 (Referent)</td><td>0.83 (0.52-1.31)</td><td>0.74 (0.46-1.18)</td><td>0.73 (0.46-1.16)</td><td>0.41 (0.23-0.70)</td><td>0.002</td></tr>
<tr><td>Age-adjusted RR (95% CI) for Total CHD</td><td>1.0 (Referent)</td><td>0.81 (0.64-1.02)</td><td>0.69 (0.54-0.89)</td><td>0.61 (0.47-0.79)</td><td>0.53 (0.40-0.69)</td><td><0.001</td></tr>
<tr><td>Multivariate RR (95% CI) for Total CHD[a]</td><td>1.0 (Referent)</td><td>0.98 (0.77-1.24)</td><td>0.92 (0.71-1.18)</td><td>0.87 (0.66-1.15)</td><td>0.77 (0.57-1.04)</td><td>0.07</td></tr>
<tr><td colspan="7">[a]Multivariate model controlled for age, study period, BMI, smoking, menopausal status, hormone use, aspirin use, multivitamin supplement use, vitamin E supplement use, exercise, hypertension, parental history of MI, alcohol intake, energy intake, saturated fat intake, carbohydrate intake.</td></tr>
</table></td><td>A significant inverse association between intake of dietary fiber and risk of CHD found. This association confined to fiber from cereal sources.

In age adjusted analysis, women in the highest quintile of long-term total dietary fiber intake had a 43% lower risk of nonfatal MI and a 59% lower risk of fatal coronary disease compared with the lowest quintile (Table 1).

Cigarette smoking accounted for most of the difference between the age-adjusted and multivariate analysis.

In multivariate analysis, women in the highest quintile of cereal fiber intake had a 34% lower risk of total CHD compared with those in the lowest quintile. Intakes of fibre from vegetables and from fruits were not appreciably associated with risk of total CHD.</td></tr>
</table>

5.1.7 Step 7. Evaluate Study Quality

Objective: To discriminate between studies that have a high or low internal validity and risk of bias. A quality appraisal tool can help in the critical appraisal of individual studies and help identify studies that are more likely to generate unbiased results (*i.e.*, higher quality studies). Bias may occur in the selection of subjects (bias affected by study design; subject inclusion/exclusion criteria), the measurement of the exposure (the food) and health outcomes (bias affected by study design; identification and analysis of food and health effect), and in data analysis (bias affected by confounding variables; inappropriate group comparisons). While both higher and lower quality studies are considered in the following sections, substantiation for claim validity should be largely based on higher quality studies.

Procedure:

- **It is highly recommended that two independent raters appraise the quality of each study. If scores are different, the source of the differences should be discussed, and disagreements resolved through discussion, to result in a single score**.

- Apply the quality appraisal tool outlined in Table 13a to each of the intervention studies that met the inclusion criteria during full-text filtering.

- Apply the quality appraisal tool outlined in Table 13b to each of the observational studies that met the inclusion criteria during full-text filtering.

- Rate the quality as "higher quality" or "lower quality" where indicated based on the quality score.

- Add the quality score for each study to the "Reference and Quality Rating" column in corresponding Tables 12a or 12b.

- Attach a copy of the completed quality appraisal to the full-text copy of the article in the Appendix. If two raters rated the quality of each study, then attach a consensus quality appraisal.

Table 13a. Quality appraisal tool for intervention studies			
Assign a score of 1 for each "Yes", and a score of 0 for each "No/NR".			
Reference (Author, year):			
Item	**Question**	**Score**	
		Yes	No/NR
1. Inclusion/ Exclusion Criteria	Were the inclusion and/or exclusion criteria for study participation reported (*e.g.*, age greater than 50 years, no history of heart disease)?		
2. Group Allocation[1]	Was the study described as randomized?		
	Was the randomization method reported?		
	Was the randomization method appropriate?[2]		
	Was allocation concealed?[3]		
3. Blinding	Were the study subjects blinded to the intervention received?		
	Were the research personnel blinded to the intervention received by the subjects?		
4. Attrition	Was attrition numerically reported?		
	Were the reasons for withdrawals and dropouts provided?[4]		
5. Exposure/ Intervention	Was the type of food described (e.g., composition, matrix)?		
	Was the amount of food described (i.e., dose)?		
6. Health Effect	Was the methodology used to measure the health effect reported?		
7. Statistical Analysis	Was a between-group statistical analysis of the health effect conducted (*i.e.*, control vs. intervention)?		
	Was an intention-to-treat analysis conducted?[5]		
8. Potential Confounders	Were potential confounders of the food/health relationship considered?[6]		
TOTAL SCORE (maximum of 15):			
Higher quality (Score ≥ 8)		☐	
Lower quality (Score ≤ 7)		☐	

Abbreviation: NR, not reported

[1] Studies without an appropriate control group would be excluded at Step 3, page 19.

[2] Examples of appropriate randomization include the use of computer-generated random number table, while date of birth and alternate allocation are examples of inappropriate methods of randomization.

[3] Allocation concealment is not the same as blinding. Allocation concealment refers to the method used to implement the random allocation sequence, *e.g.*, numbered envelopes containing the assignment. It protects the assignment sequence before and until allocation. Blinding protects the sequence after subjects have been allocated.

[4] If the study reported no attrition, (*i.e.*, no subjects were lost to follow-up, withdrew or were excluded) then reasons for withdrawals/dropouts is a "non-applicable" factor. In such a circumstance, please check "yes" so as to not unfairly lose a point.

[5] If there was no subject attrition, a per-protocol analysis is appropriate and an intention-to-treat analysis not applicable. In such a circumstance, please check "yes" so as to not unfairly lose a point.

[6] Specify the confounders considered in a footer to this table. Confounding could have occurred during subject selection (*e.g.,* inclusion/exclusion criteria), study conduct *(e.g.,* specific dietary/physical activity restrictions), or data analysis *(e.g.,* use of co-variates). If randomization is successful (*i.e.*, no difference in baseline characteristics between the intervention and control groups) and between-group differences that may have occurred during study conduct *(i.e.,* post-randomization between-group differences) are considered during statistical analysis, then confounders were "considered". See the Appendix for more information on confounders.

Table 13b. Quality appraisal tool for prospective observational studies			
Assign a score of 1 for each "Yes", and a score of 0 for each "No/NR".			
Reference (Author, year):			
Item	**Question**	**Score**	
		Yes	No/NR
1. Inclusion/ Exclusion Criteria	Were the inclusion and/or exclusion criteria for study participation reported (*e.g.*, age greater than 50 years, no history of heart disease)?		
2. Attrition	Was attrition numerically reported?		
	Were the reasons for withdrawals and dropouts provided?[1]		
3. Exposure	Was the methodology used to measure the exposure reported?		
	Was the exposure assessed more than once?		
4. Health Outcome	Was the methodology used to measure the health outcome reported?		
	Was the health outcome verified (*e.g.*, through assessment of medical records, confirmation by a health professional)?		
5. Blinding	Were the outcome assessors blinded to the exposure status?		
6. Baseline Comparability of groups	Were the subjects in the different exposure levels compared at baseline?		
7. Statistical Analysis	Was the statistical significance of the trend reported?		
8. Potential Confounders	Were key confounders related to subjects' demographics accounted for in the statistical analysis?[2,3]		
	Were key confounders related to other risk factors of the health outcome accounted for in the statistical analysis?[2,4]		
TOTAL SCORE (maximum of 12):			
Higher quality (Score ≥ 7)		☐	
Lower quality (Score ≤ 6)		☐	

Abbreviation: NR, not reported

[1] If the study reported no attrition, (*i.e.*, no subjects were lost to follow-up, withdrew or were excluded) then reasons for withdrawals/dropouts is a "non-applicable" factor. In such a circumstance, please check "yes" so as to not unfairly lose a point.

[2] Specify the confounders considered in a footer to this table. Confounding could have occurred during subject selection (*e.g.,* inclusion/exclusion criteria), study conduct, or data analysis.

[3] Confounders related to subjects' demographics include age, sex and ethnicity.

[4] Confounders related to other risk factors of the health outcome include, but are not limited to, diet, physical activity, smoking, alcohol intake, body mass index (BMI), weight loss, health status, family history and medication/supplement use.

5.1.8 Step 8. Tabulate Study Findings per Health Outcome

Objective: To report the effect of the food exposure, per health outcome, in a consistent way across the studies and to summarize important elements of the studies.

Procedure:

- Complete Table 14a for intervention studies and Table 14b for prospective observational studies per health outcome.

- Refer to Excel spreadsheet (available upon request) to assist with the calculations of the magnitude of effect for intervention studies. Include the Excel spreadsheet of the calculations in an Appendix.

- *If possible*, provide a visual representation, or carry out a meta-analysis, of the findings by considering the quantity of exposure (*e.g.*, daily exposure) and the magnitude of effect. Include the visual plot and/or the methodology and results of the meta-analysis in an Appendix.

Table 14a. Summary of study findings from intervention studies per health outcome

Reference and Quality Score	Design	Sample Size	Outcome for which study was powered[1]	Study Duration	Food Matrix	Exposure (Food/Bioactive substance Intake Per Day)	Magnitude of Effect[2]		P-value[6]
							Number [3,4]	Percent [3,5]	
HEALTH OUTCOME – TOTAL CHOLESTEROL (mmol/L)									
Biorklund *et al.*, 2005 Quality:	R, C, SB, P	89	LDL cholesterol (6% decrease)	5 weeks	Beverage	5 or 10g beta-glucans from oats	5g: *-0.49* 10g: *-0.29*	5g: *-7.4%* 10g: *-4.5%*	p<0.01 (5g vs. control) p>0.05 (10g vs. control)

[1] If the study did not indicate an outcome for which it was powered, state N/A.
[2] Use Appendix B as a guide and include the Excel spreadsheet used to derive these calculations in an Appendix.
[3] Reporting the magnitude of effect as a number and as a percentage may require computations by the petitioner. Use a system to differentiate the computed values *versus* those taken directly from the study – *e.g.*, italicize all computed values.
[4] For studies with a control/comparison group, report the effect as: (Mean end-of-treatment – Mean baseline)$_{\text{treatment group}}$ – (Mean end-of-treatment – Mean baseline) $_{\text{control group}}$. For studies with a control/comparison group that do not report baseline values, report the effect as: Mean end-of-treatment$_{\text{treatment group}}$ – Mean end-of-treatment $_{\text{control group}}$.
[5] For studies with a control/comparison group, report the effect as: [(Mean end-of-treatment – Mean baseline)/Mean baseline]*100%$_{\text{treatment group}}$ – [(Mean end-of-treatment – Mean baseline)/Mean baseline] *100%$_{\text{control group}}$. For studies with a control/comparison group that do not report baseline values, report the effect as: [(Mean end-of-treatment$_{\text{treatment group}}$ – Mean end-of-treatment $_{\text{control group}}$)/Mean end-of-treatment $_{\text{control group}}$]*100%.
[6] Report between-group p-values. If between-group p-values are not reported in the study, report within-group values and indicate that values apply to within-group analyses.

Table 14b. Summary of study findings from prospective observational studies per health outcome									
Reference and Quality Score	**Design •Prospective cohort •Nested case-control**	**Study Population and Final Sample Size**	**Centile**	**Exposure (Dietary Intake/ Circulating Levels)**	**Incidence of Health Outcome**	**Multi-variate Adjusted Risk Ratios Between Different Centiles**			
						Hazards Ratio	**Relative Risk**	**95% CI**	**P_{trend}**
HEALTH OUTCOME – TOTAL CHD									
Wolk *et al.*, 1999 Quality	Prospective cohort; the Nurses' Health Study (10-year follow-up), FFQ administered at baseline and at 0, 2, and 6 years of follow-up	68 782 females ages 37 to 64 years at baseline (1984)	1st quintile of fibre intake	11.5 (median g fibre/day, energy-adjusted)	N/R	N/A	1	N/A	0.07
			2nd quintile of fibre intake	14.3	N/R	N/A	0.98	0.77, 1.24	
			3rd quintile of fibre intake	16.4	N/R	N/A	0.92	0.71, 1.18	
			4th quintile of fibre intake)	18.8	N/R	N/A	0.87	0.66, 1.15	
			5th quintile of fibre intake	22.9	N/R	N/A	0.77	0.57, 1.04	

Abbreviations: CHD, coronary heart disease; N/A, Not applicable; N/R, Not reported.

5.1.9 Step 9. Assess Causality

5.1.9 Step 9a. Rate Consistency

Objective: To rate the consistency of findings across studies, per health outcome with regard to the **direction of effect** of the food on the health outcome with consideration given to study quality.

Procedure:

- Complete Table 15a for intervention studies for each health outcome. This table requires you to consider all studies with regard to statistical significance, based on cut off of $p<0.05$, direction of effect (whether favourable, unfavourable or neutral), and study quality. Calculate the consistency rating according to direction of effect, alone [(C1 + C3) / A] and with regard to study quality [(D1 + D5) / (D1 + D3 + D5 + D7)].

- Complete Table 15b for observational studies for each health outcome. This table requires you to consider whether the trend was statistically significant ($p<0.05$) in each study, as well as the direction of effect (whether there was increased, decreased or no risk), and study quality.

- As indicated in Tables 15a and 15b, calculate the consistency ratings according to a favourable direction of effect alone, and with regard to a favourable direction of effect and study quality. Suggest plausible explanations for moderate or low consistency.

- Comment on the evidence related to study design; *e.g.*, do observational study designs tend to show an effect whereas intervention studies do not?

<table>
<tr><th colspan="8">Table 15a. Rating of consistency in direction of effect for intervention studies, considering study quality</th></tr>
<tr><td colspan="8">HEALTH OUTCOME 1</td></tr>
<tr><td colspan="8">A. Total number studies included: _____</td></tr>
<tr><td colspan="8">Statistical Significance (SS)</td></tr>
<tr><td colspan="4">B1. # studies with a SS effect of exposure ($p<0.05$): _____</td><td colspan="4">B2. # studies with a non-SS effect of exposure ($p>0.05$): _____</td></tr>
<tr><td colspan="8">Direction of Effect[1]</td></tr>
<tr><td colspan="2">C1. # studies from B1 with a SS favourable effect of the exposure: _____</td><td colspan="2">C2. # studies from B1 with a SS unfavourable effect of the exposure: _____</td><td colspan="2">C3. # studies from B2 with a non-SS favourable effect of the exposure: _____</td><td colspan="2">C4. # studies from B2 showing either a non-SS unfavourable effect or no distinguishable effect of the exposure: _____</td></tr>
<tr><td colspan="8">Study Quality</td></tr>
<tr><td>D1. # higher quality studies from C1:___</td><td>D2. # lower quality studies from C1:___</td><td>D3. # higher quality studies from C2:____</td><td>D4. # lower quality studies from C2:___</td><td>D5. # higher quality studies from C3:___</td><td>D6. # lower quality studies from C3:____</td><td>D7. # higher quality studies from C4:____</td><td>D8. # lower quality studies from C4:____</td></tr>
<tr><td colspan="8">Consistency Rating on Direction of Favourable Effect</td></tr>
<tr><td colspan="4">(C1 + C3) / A1 x 100 % =</td><td colspan="4">High (≥ 75%) □
Moderate (60-74%) □
Low (< 60%) □</td></tr>
<tr><td colspan="8">Consistency Rating on Direction of Favourable Effect in Higher Quality Studies</td></tr>
<tr><td colspan="4">(D1 + D5) / (D1 + D3 + D5 + D7) x 100% =</td><td colspan="4">High (≥ 75%) □
Moderate (60-74%) □
Low (< 60%) □</td></tr>
</table>

[1] Direction of effect assesses whether the health outcome is changing in a favourable (*i.e.*, beneficial) direction with exposure to the food, or in an unfavourable (non-beneficial) direction, without regard to statistical significance.

<table>
<tr><th colspan="6">Table 15b. Rating of consistency in direction of effect for prospective observational studies, considering study quality</th></tr>
<tr><td colspan="6">HEALTH OUTCOME 1</td></tr>
<tr><td colspan="6">A. Total Number of Studies Considered: _____</td></tr>
<tr><td colspan="6">Direction of Effect</td></tr>
<tr><td colspan="2">B1. # studies from A showing trend for risk reduction ($p < 0.05$)[1]: _____</td><td colspan="2">B2. # studies from A showing a trend for increase in risk ($p < 0.05$): _____</td><td colspan="2">B3. # studies from A showing no effect ($p > 0.05$): _____</td></tr>
<tr><td colspan="6">Study Quality</td></tr>
<tr><td>C1. # higher quality studies from B1: _____</td><td>C2. # lower quality studies from B1: _____</td><td>C3. # higher quality studies from B2: _____</td><td>C4. # lower quality studies from B2: _____</td><td>C5. # higher quality studies from B3: _____</td><td>C6. # lower quality studies from B3: _____</td></tr>
<tr><td colspan="2">Consistency Rating on Direction of Favourable Effect (Risk Reduction)</td><td colspan="2">Consistency Rating on Direction of Unfavourable Effect</td><td colspan="2">Consistency Rating on No Effect</td></tr>
<tr><td><u>B1</u> x 100% = A</td><td>High (≥ 75%) □
Moderate (60-74%) □
Low (< 60%) □</td><td><u>B2</u> x 100% = A</td><td>High (≥ 75%) □
Moderate (60-74%) □
Low (< 60%) □</td><td><u>B3</u> x 100% = A</td><td>High (≥ 75%) □
Moderate (60-74%) □
Low (< 60%) □</td></tr>
<tr><td colspan="6">Consistency Rating on Direction of Favourable Effect in Higher Quality Studies</td></tr>
<tr><td colspan="3">C1 / (C1 + C3 + C5) x 100% =</td><td colspan="3">High (≥ 75%) □
Moderate (60-74%) □
Low (< 60%) □</td></tr>
</table>

[1] Statistically significant associations may not be limited to trends. A rationale may be provided in a footer to this table that logically supports the consideration of statistically significant associations between the highest versus the lowest centiles of intake, or between intermediate centiles *versus* lowest centiles. In cohort studies, intakes distributions are normally grouped by tertiles, quartiles, quintiles or centiles of intake.

5.1.9 Step 9b. Rate the Strength of the Association

Objective: To assess the strength of the association between the food and health outcome by considering the proportion of studies that showed statistical significance at $p<0.05$ among all included studies.

Procedure:

- Consider studies of higher and lower quality from Table 15a [(D1 + D2) / A] and comment on whether all or most of the studies show a statistically significant favourable effect. Consider study features and discuss factors that may have contributed to statistical significance not being reached (e.g., power calculations, sample size, duration, etc.).

- Consider studies of higher quality from Table 15a [D1 / (D1 + D3 + D5 + D7)] and comment on whether all or most of the higher quality studies show a statistically significant favourable effect.

- Consider studies of higher and lower quality from Table 15b [B1/A] and comment on whether all or most of the studies show a statistically significant favourable effect. Consider study features and discuss factors that may have contributed to statistical significance not being reached (e.g., power calculations, sample size, duration, etc.).

- Consider studies of higher quality from Table 15b [C1 / (C1 + C3 + C5)] and comment on whether all or most of the higher quality studies showed a statistically significant favourable effect.

5.1.9 Step 9c. Discuss the Relationship between the Food Exposure and the Health Effect

Objective: To understand whether a dose-response relationship exists and /or the minimum effective dose.

Procedure:

- For intervention studies using Table 14a as a guide and visual plots (if conducted), discuss the range of effect sizes observed (number and percent) with different food exposures (doses). Discuss the relationship that exists between the food exposure and its effect: whether a greater effect is observed with a greater food exposure (dose-response), and/or whether the evidence indicates a minimum effective food dose/food intake.

- For the observational studies, using Table 14b and Table 15b (specifically B1/A) as guides, comment on whether a dose response relationship exists. Include discussion of whether statistical significance was achieved between the highest and lowest dietary intake groups, where a trend was also statistically significant.

5.1.10 Step 10. Discuss Generalizability of the Data to the Target Population

Objective: To demonstrate that the food/health relationship is relevant to the target population.

Procedure:

- Using all studies that support a favourable direction of effect, discuss the health status of the sample populations studied in the intervention/experimental and observational studies and whether the baseline health status of sample

populations was a factor in the effect of the food (*e.g.*, was a cholesterol-lowering effect only seen in hyperlipidemics?)

- Discuss whether the target population for the health claim was represented in the higher quality studies used to rate consistency with respect to background diets, health status, age, gender, study setting.

5.1.11 Step 11. Discuss the Physiological Meaningfulness of the Effect of the Food Exposure

Objective: To understand the impact of the food exposure on human health.

Procedure:

- Using Tables 14a and 14b as guides, discuss whether the effects (range of effects and/or a specific effect) observed with food exposure (range of exposures and/or a specific exposure) are physiologically meaningful/relevant to human health. Provide reasons to support your response. Based on the study durations, include discussion on the sustainability of the beneficial effect.

5.1.12 Step 12. Discuss the Feasibility of Consuming an Effective Amount of the Food

Objective: To discuss whether the food exposure required for a meaningful effect can be feasibly consumed as part of a healthy diet.

Procedure:

- Provide information on the feasibility of incorporating this effective amount of food into a healthy diet. Include information on the current intakes of the food in the target population (from Table 4).
- Provide information on the expected* intakes of the food/bioactive substance from all sources, if added to one or more foods, in the target population using Canadian intake data where possible.
- Estimate changes* in usual dietary patterns (*i.e.*, substitution or elimination of existing foods) with potential approval of the food for a health claim.
- State the subgroups of the population expected to have the greatest exposure to the food and subgroups at risk of exposure to the food.

*Clearly communicate the assumptions (and the evidence on which they were based) and statistical simulations used for these estimations

5.1.13 Step 13. Make Conclusions

Objective: To justify a health claim for a food based on the totality of evidence.

Procedure:

- Provide relevant information from the totality of evidence reviewed focusing on the outcome of Steps 9-12, and any other supporting evidence such as meta-analyses, systematic reviews and authoritative statements, to make concluding remarks on the food/health relationship and its relevance to public health.

- Propose claim wording.

- Propose and justify conditions for a food to qualify for the health claim such as:

    - The minimum amount of the food eligible to carry the claim, *e.g.*, minimum 1 g beta glucan per reference amount, minimum 3 servings per day required;
    - The maximum levels of food to be consumed, *e.g.*, no more than 3 grams plant sterols per day;
    - The proposed food matrix, *e.g.*, a fermented dairy matrix;
    - The minimum, maximum levels of nutrients in the food that are not the subject of the claim, *e.g.*, meets criterion for low in saturated fat.

- Comment on any adverse effects (*i.e.*, adverse direction of effect) observed in the evaluated human studies, and subgroups at risk of excessive intakes of the food.

- Propose risk management strategies (if necessary) to address adverse effect and/or restrictions on use of the food (*e.g.*, indicate wording of recommended warning statements).

6.0 CHECKLIST FOR SUBMISSION

Objective: To ensure that all requested information is included in the submission. Health Canada will use this same checklist when evaluating submissions for completeness. If deficiencies exist, petitioners may be asked to address them before the full evaluation can proceed.

Procedure:

- Please complete and submit the following checklist. If any items do not meet the requirements, please revise the application to include it before submitting it to Health Canada.

Table 16. Checklist for submission			
	Yes	**No**	**N/A**
Organization and Presentation of the Submission			
All required sections completed and properly identified			
Pagination sequential throughout submission			
Submission bound or organized in a binder			
Applicant identified on every page			
Language of submission in English or French			
References accurate and formatted			
Application signed by person responsible for it			
Two hardcopies of application provided			
All confidential/proprietary data is identified			
Content of the Submission			
Applicant information (Table 1)			
Details pertaining to proposed health claim (Table 2)			
Regulatory status of health claim in other jurisdictions (Table 3)			
Information requirements for characterization of the food (requirements in Table 4 met)			
Lab-certified specifications for the food/bioactive substance (added or inherent) included in an Appendix			
Characterization of biomarkers of the health effect			
Identification of databases and search parameters used for literature retrieval (Table 5)			
Keywords and their combinations used to retrieve literature on the food/health relationship from electronic databases (Table 6)			
Number of references retrieved from electronic and non-electronic sources (Table 7)			
A copy of the entire literature search, including the literature search strategy and the literature search results, by printing it directly from the electronic database in an Appendix			
Inclusion and exclusion criteria used for literature filtering (Table 8a)			
Results of literature filtering (Table 9)			
List of references that met the inclusion criteria at the full-text filtering stage (Table 10)			
List of references excluded at the full-text filtering stage and reason(s) for exclusion (Table 11)			

Table 16. Checklist for submission			
	Yes	**No**	**N/A**
Full-text copies of all publications that met the inclusion criteria at full-text filtering in an Appendix. If studies in languages other than English or French were included, then translations of the studies in either English or French provided.			
Tabulation of intervention studies (Table 12a) and/or prospective observational studies (Table 12b) grouped according to their research design			
Tabulation of study findings per health outcome for intervention studies (Table 14a) and/or prospective observational studies (Table 14b)			
A copy of each completed quality appraisal in an Appendix (Table 13a for intervention studies; Table 13b for prospective observational studies)			
Excel spreadsheet of calculations used to determine magnitude of effect of the food/bioactive substance for intervention studies in an Appendix			
A visual representation or a meta-analysis of the findings by considering the daily exposure and the magnitude of effect, in an Appendix (optional)			
Rating of consistency for intervention studies (Table 15a) and prospective observational studies (Table 15b)			
Discussion on whether a cause-and-effect relationship between the food and the health effect is supported (data requirements in Steps 9a, 9b, 9c met)			
Discussion on generalizability of the evidence to the target population (data requirements in Step 10 met)			
Discussion on physiological meaningfulness (data requirements in Step 11 met)			
Discussion on feasibility (data requirements in Step 12 met)			
Conclusions made (data requirements in Step 13 met)			
Appendices included			

7.0 REFERENCES

Aggett PJ, Antoine J-M, Asp N-G, Bellisle F, Contor L, Cummings JH, Howlett J, Müller DJG, Persin C, Pijls LTJ, Rechkemmer G, Tuijtelaars S, Vergen H. (2005). PASSCLAIM. Consensus on Criteria. *European Journal of Nutrition* 44 (Supplement 1): 1-30.

Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gotzsche PC, Lang T. (2001). The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 134: 663-694.

Biörklund, M, van Rees, A, Mensink, RP, Onning, G. (2005). Changes in serum lipids and postprandial glucose and insulin concentrations after consumption of beverages with beta-glucans from oats or barley: a randomised dose-controlled trial. *Eur J Clin Nutr* 59 (11):1272-1281.

Briss PA, Zaza S, Pappaioanou M, Fielding J, Wright-De Agüero L, Truman BI, Hopkins DP, Mullen PD, Thompson RS, Woolf SH, Carande-Kulis VG, Anderson L, Hinman AR, McQueen DV, Teutsch SM, Harris JR. (2000). Developing and Evidence-Based Guide to Community Preventive Services – Methods. *American Journal of Preventative Medicine* 18 (1S): 35-43.

Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008] www.cochrane-handbook org 2008; (4).

Codex Alimentarius Commission. (2008). *Proposed Draft Annex to the Codex Guidelines for Use of Nutrition and Health Claims: Recommendations on the Scientific Basis of Health Claims*. CX/NFSDU 06/28/7. Available at: ftp://ftp.fao.org/codex/ccnfsdu28/nf28_07e.pdf.

Codex Alimentarius Commission (1997) Guidelines for Use of Nutrition and Health Claims CAC/GL 23-1997. Available at: http://www.codexalimentarius.net/download/standards/351/CXG_023e_u.pdf

Downs SH, Black N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomized and non-randomized studies of healthcare interventions. *Journal of Epidemiology Community Health* 52: 377-384.

EFSA (European Food Safety Authority). (2007). *Scientific and Technical Guidance for the Preparation of the Application for Authorization of a Health Claim*. Available at: http://www.efsa.europa.eu/en/science/nda/nda_consultation/health_claim.html

FDA (US Food and Drug Administration). (2007, July). *Guidance for Industry. Evidence-Based Review System for the Scientific Evaluation of Health Claims*. Available at: http://www.cfsan.fda.gov/~dms/hclmgui5.html.

FDA (US Food and Drug Administration). (1999, November 2). *Guidance for Industry Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements*. Rockville, MD: Center for Food Safety and Applied Nutrition (CFSAN), Office of Special Nutritionals. Available at: http://www.cfsan.fda.gov/~dms/ssaguide.html.

FSANZ (Food Standards Australia New Zealand). (2008, April 11). *Proposal P293 – Nutrition, Health and Related Claims. Final Assessment Report*. Available at: http://www.foodstandards.gov.au/_srcfiles/P293%20Health%20Claims%20FAR%20and%20Att%201%20&%202%20FINAL.pdf.

Harris RP, Helfand M, Woolf SH, Lohr K.N., Mulrow CD, Teutsch SM, Atkins D, Methods Work Group, Third US Preventive Services Task Force. (2001). Current Methods of the U.S. Preventive Services Task Force: A Review of the Process. *American Journal of Preventative Medicine* 20 (Supplement 3): 21-35. (AHRQ [Agency for Healthcare Research and Quality])

Health Canada. (2002). *Interim Guidance Document – Preparing a Submission for Foods with Health Claims Incorporating Standards of Evidence for Evaluating Foods with Health Claims.* Available at: http://www.hc-sc.gc.ca/fn-an/alt_formats/hpfb-dgpsa/pdf/label-etiquet/abstract_guidance-orientation_resume-eng.pdf.

Higgins JPT, Green S, editors. (2008, February). *Cochrane Handbook for Systematic Reviews of Interventions 5.0.0.* Available at: http://www.cochrane-handbook.org/.

Hill, AB. (1965). The environment and disease: association or causation? *J R Soc Med* 58(5):295-300.

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. (1996). Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? *Controlled Clinical Trials* 17: 1-12.

Katrak P, Bialocerkowski AE, Massy-Westropp N, Kumar S, Grimmer KA. (2004). A systematic review of the content of critical appraisal tools. *BioMed Central Medical Research Methodology* 4: 22.

Moher D, Schultz KF, Altman D, for the CONSORT group (2001). The CONSORT statement: revised recommendations for improving the quality of report of parallet-group randomized trials. *Lancet* 351: 1191.

Wolk A, Manson JE, Stampfer MJ, Colditz GA, HU FB, Speizer FE, Hennekens CH, Willett WC. (1999). Long term intake of dietary fiber and decreased risk of coronary heart disease among women. *JAMA* 21: 1998-2004.

APPENDIX: Additional Definitions

- **Allocation Concealment:** A process to prevent selection bias by concealing the allocation sequence from those assigning participants to intervention and control groups (Altman *et al.*, 2001). The use of a third party is desirable; the third party assigns the participants without knowledge of which assignment is treatment or control. The allocation is concealed before random assignment takes place.

- **Biomarker/surrogate marker of a health effect:** Whenever possible, a claimed health benefit should measure the true endpoint. However, when it is not possible to measure in a practical way, a more easily measured surrogate, or biomarker, of the true endpoint may be used. Biomarkers can relate to health effect or to food intake. A biomarker of a health outcome is a proxy measure (an intermediate measure) of a true endpoint. It predicts development of a final health effect because it lies on the causal pathway between exposure to the food and development of the final health effect. For example, LDL cholesterol is a well accepted biomarker for heart disease because it can reasonably predict that individuals who have higher LDL cholesterol levels will have a higher probability of developing heart disease. A biomarker of intake or exposure to a food is a measure that supports that the food was consumed by study participants.

- **Blinding:** This refers to keeping study participants, health care providers and sometimes those collecting and analyzing clinical data unaware of the assigned intervention. This prevents bias at several stages in a controlled trial (Altman *et al.*, 2001).

- **Prospective Cohort Study:** This is a study design that follows a group of healthy/disease-free people for a period of time after which it can be assessed whether the development of a disease in this group is related to the presence of specific causes. The incidence of a health effect in those people who had a specific exposure (*e.g.*, to a food constituent such as long chain omega-3 fatty acids) is compared to those who did not receive the exposure. Cohort studies can yield relative estimates of risk. They are the most reliable observational study design since intake of the food of interest precedes development of the health effect; as such, temporality is supported.

- **Confounding:** This is a situation where the estimated effect of the intervention is biased because of some difference between the comparison groups apart from the planned interventions, such as baseline characteristics or concomitant intervention. For a factor to be a confounder, it must differ between the comparison groups and affect/predict the outcome of interest (Altman *et al.*, 2001).

- **Control group:** A control group is a group that has not received the exposure of interest and is being compared to the treatment or intervention group in the randomized trial. In a cross-over design, subjects serve as their own controls.

- **Intention-to-treat analysis:** A strategy for analyzing data in which all participants are included in the group to which they were assigned, regardless of whether they completed the intervention given to the group. This analysis prevents bias caused by loss of participants which may disrupt the baseline equivalence established by random assignment and may reflect nonadherence to the protocol (Altman *et al.*, 2001).

- **Intervention Studies:** In an intervention study, human subjects are administered the food of interest (intervention group) and the health outcome is subsequently measured. The gold standard intervention study includes randomization, a control group and double blinding. The composition and quantity of the food should be controlled for the intervention group and for the control group. Randomized, controlled studies offer the best assessment of cause and effect since a temporal relationship between the food and health effect – *i.e.*, administration of the food precedes observation of the effect – can be demonstrated. Randomized, controlled intervention studies have either a parallel or cross-over design. Parallel studies involve two groups of subjects, the test group and the control group, which simultaneously receive the test food or the control, respectively. In cross-over studies subjects from the intervention group cross over to the control group and vice versa.

- **Meta-Analysis:** A meta-analysis involves applying statistical methods that combine the quantitative research findings of several studies together allowing for their analysis and summary as if they were one unit.

- **Observational Studies:** Observational studies measure associations between a food and a health effect. These studies lack the controlled setting of intervention studies and are thus often susceptible to confounders. They are most reflective of free-living populations. Because the subjects are not randomized at the beginning of the study, known confounders of the health effect need to be collected and adjusted for to minimize bias. Evaluating the method of dietary assessment is critical to ensure the food of interest is reliably measured. Observational studies may be prospective or retrospective. In prospective studies, investigators recruit subjects and observe them prior to occurrence of a health effect. Prospective observational studies measure incidence of a health effect, and relative risk of developing the health effect associated with food or other risk factors of interest. In retrospective studies, investigators interview subjects after the health effect has occurred. Retrospective studies are vulnerable to measurement error and recall bias because they rely on subjects' recollections of what they consumed in the past.

- **Per Protocol Analysis:** This refers to a strategy for analyzing the set of data generated by the subset of subjects who complied with the protocol sufficiently to ensure that the data would be likely to exhibit the effects of the treatment according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurement and the absence of major protocol violations (European Medicines Agency, International Conference on

Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Used (ICH) Topic E9, *Statistical Principles for Clinical Trials*, September 1998) Codification as per November 2005.

- **Randomization:** The process of assigning participants to groups such that each participant has known and usually an equal chance of being assigned to a given group (Altman *et al.*, 2001). The random assignment of subjects to intervention and control groups avoids selection bias – that is the possibility that those subjects most likely to have a favorable effect, independent of the intervention, are preferentially selected to receive the intervention. Randomization also helps control for known and potential confounders (*e.g.*, factors that could affect risk of developing health effect).

- **Systematic Reviews:** Systematic reviews consist of a clearly formulated question and use systematic and explicit methods to identify, select, critically appraise, and extract and analyze data from relevant research (Cochrane Handbook, 2008).