Archived Content

INTERIM GUIDANCE DOCUMENT

Preparing a Submission for Foods with Health Claims: incorporating

STANDARDS OF EVIDENCE FOR EVALUATING FOODS WITH HEALTH CLAIMS

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

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PREFACE

1.1 In June 2000, Health Canada published a consultation document on Standards of Evidence for Evaluating Foods with Health Claims (http://www.hc-sc.gc.ca/food-aliment/english/ subjects/health_claims /Consultation_doc_en.pdf). The document outlined a proposal for ensuring that foods bearing health claims are supported by appropriate evidence with respect to product safety and claim validity, as well as quality assurance of the product and of the procedures and methods for testing the product.

1.2 No alternative suggestions to the proposal outlined in the June 2000 document were provided by respondents. Therefore, no major changes to the fundamental aspects of the standards proposed in June 2000 are being made in this document. However, based on the questions and concerns raised, there is the need to clarify certain terms and concepts and to simplify the communication of the proposed standards. In this document, we added "glossary of terms" and used a simplified format to present the core aspects of the principles and criteria proposed in the June 2000 publication. For detailed information on the rationale, the process and references used in the development of the evaluation framework, please refer to the June 2000 document.

1.3 Since the June 2000 publication of the proposed standards for evaluating foods with health claims, proposals on two approaches to regulating health claims on foods have been published. Briefly, the two approaches are: generic authorization (http://canada.gc.ca/gazette/part1/pdf/g1-13524.pdf, pp.68-235) and product-specific authorization. A comparison of the differences between the two approaches is provided in the proposed regulatory framework for Product-Specific Authorization of Health Claims).
(http://www.hc-sc.gc.ca/food-aliment/english/subjects/health_claims/index.html)
Accordingly, where there is a different emphasis on the type of evidence required in supporting claims to be approved under the generic and product-specific authorization processes, these differences will be identified in this interim guidance. Bear in mind however, that until the final regulatory framework for health claims for foods is put in place, changes to the proposed regulatory amendments will be unavoidable. This could have an impact on the requirements for product evaluation.

1.4 To ensure the usefulness and clarity of the Interim Guidance Document, we welcome questions and comments that would help us identify specific aspects of this document that require elaboration and clarification. These comments may be sent to:

Project Coordinator, Standards of Evidence for Foods with Health Claims
Nutrition Evaluation Division
Health Canada
Banting Research Centre, Ross Ave., PL 2203A
Ottawa, Ontario K1A 0L2

Fax: (613) 941-6636
E-mail: standards-evidence@hc-sc.gc.ca

PART I - EVALUATING THE EVIDENCE

1. Purpose of the Guidance Document

The purpose of this document is to provide:

1) guidance with respect to the principles and criteria by which health claims for foods offered or advertised for sale in Canada will be evaluated;

2) details on the types of information to be submitted for health claim approvals.

2. Glossary of Terms

The terms listed below are used in this and other related documents. Descriptions of these terms are provided here in response to public comments on the consultation document on Standards of Evidence for Evaluating Foods with Health Claims (June 2000). Respondents requested clarification of certain terms used in that document which are included below. **Except as established in the *Food and Drug Regulations* (i.e., "novel food" and "foods for special dietary use"), the descriptions for the other terms are for information only and should not be interpreted as definitions for regulatory purposes.**

(1) **Health claims**, for the purposes of this document and the regulatory proposal for product-specific authorization of health claims for foods, refer to claims that relate primarily to paragraphs (a) or (b) of the definition of "drug" found in section 2 of the *Food and Drugs Act* and include structure/function claims, risk reduction claims, and therapeutic claims (see below).

A claim is a statement or representation in product labelling or advertising regarding the character, value, quantity, composition, merit or safety of the product.

(2) **Structure/function claims** are claims that relate primarily to paragraph (b) of the definition of "drug" with respect to modifying, restoring, or correcting an organic function or body structure of human beings, beyond normal growth and development or maintenance of good health.[1]

(3) **Risk reduction claims** are claims that relate primarily to paragraph (a) of the definition of "drug" with respect to significantly altering a major risk factor(s) for a disease or adverse health condition. For diseases that have multiple risk factors, altering one of these risk factors may or may not have a demonstrable beneficial effect on prevention or timing of disease onset. The presentation of risk reduction claims should be such that consumers do not interpret them as prevention claims (e.g. by use of appropriate language and reference to other risk factors).

[1] As noted in the regulatory proposal for Product-specific Authorization of Health Claims for Foods, the current definition of "drug" set out in section 2 of the *Food and Drugs Act* includes "any substance or mixture of substances manufactured, sold or represented for use in ... restoring, correcting or modifying organic functions ...". By contrast, claims about "maintaining the functions of the body necessary to the maintenance of good health and normal growth and development" are considered as "biological role claims". These claims do not bring a food within the definition of a drug. For the purposes of developing a regulatory framework for health claims on foods, the focus will be on claims that relate to the "drug" definition as set out in the *Act*.

(4) **Therapeutic claims** are claims that relate primarily to paragraph (a) of the definition of "drug" with respect to treatment (management), mitigation or prevention of a disease, disorder, abnormal physical state, or its symptoms in humans.

We propose that therapeutic claims for foods be related to the role of the food in the *dietary management* of a disease, disorder, abnormal physical state, or the symptoms. The presentation of foods as an aid in dietary management should be such that consumers do not confuse them with drugs. It was also suggested in the regulatory proposal on Product-specific Authorization of Health Claims for Foods that foods bearing certain claims related to dietary management be identified as "foods for special dietary use" (see paragraph 9).

The following criteria are intended to provide guidance regarding "dietary management":

- the consumption of a diet with specific nutritional characteristics is generally recognized to be an integral part of the management of the disease or health condition
- the food bearing the claim is a source of energy and nutrients when consumed at the level recommended for the claimed effect as part of the diet
- the nutritional and other compositional characteristics of the food bearing the claim are compatible with the nutritional requirements generally recognized for the management of the disease or health condition
- where a biologically active substance has been added to or otherwise modified in the food bearing the claim, the food matrix and/or processing assists in or does not interfere with the absorption and the functioning of the substance
- the beneficial effect of the substance should be achieved through physiological processes that are generally recognized to be associated with foods[2]

(5) **Generic authorization of claims** applies to nutrients, other food components, a food or a group of foods that have compositional characteristic(s) that contribute to a dietary pattern associated with, for example, reducing the risk of a disease or health condition, as proposed in *Food and Drug Regulations* B.01.600. An authorized claim would be listed in the *Food and Drug Regulations* through a regulatory amendment process. The conditions for carrying a particular authorized claim in food labelling and advertising would be specified in the regulations, including product composition and labelling. Once a claim is authorized, any food that meets the specified conditions for composition and labelling may carry the claim without further assessment. The list of authorized claims in the regulations could be amended through submissions.

(6) **Product-specific authorization of claims**, as proposed in the corresponding regulatory proposal, applies to a food that is manufactured, sold or represented to have a direct, measurable effect on a body function or structure beyond normal growth and development or maintenance of good health. Submission of detailed information would be required to support such an effect before the food is advertised or offered for sale. The conditions which must be met before a food could be authorized to carry a claim or a representation conveying such an effect are outlined in the regulatory proposal. An authorized claim would be identified by a Claim Identification Number that would be displayed in product labelling. Authorization would be granted on a product-by-product basis without claim-specific regulatory amendments.

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[2] In the proposed regulatory framework for Product-specific Authorization of Health Claims for Foods, we propose that the claimed effects of foods be achieved through physiological processes that are generally recognized to be associated with foods, as opposed to pharmacological processes that are generally recognized to be associated with drugs.

(7) **Biological role claims** are claims related to "maintaining the functions of the body necessary to the maintenance of good health and normal growth and development". Under sections B.01.311, D.01.006 and D.02.004 of the *Food and Drug Regulations*, *generally recognized* "biological role claims" for *known* nutrients listed in the regulations are already permitted on foods and do not require premarket assessment under the existing or proposed regulations, nor are foods carrying such claims subject to drug regulations. "Calcium helps build strong bones" is an example of "biological role claim" that does not trigger the drug definition. Examples of acceptable "biological role claims" can be found in the *Guide to Food Labelling and Advertising*, Agriculture and Agri-Food Canada, section 7.5 (http://www.cfia-acia.agr.ca/english/bureau/labeti/labetie.shtml).

(8) **Novel foods** are regulated under Division 28 of Part B of the *Food and Drug Regulations* and consist of three categories:

(a) a substance, including a microorganism, that does not have a history of safe use as a food;

(b) a food that has been manufactured, prepared, preserved or packaged by a process that
  (i) has not been previously applied to that food, and
  (ii) causes the food to undergo a major change[3];

(c) a food that is derived from a plant, animal or microorganism that has been genetically modified such that
  (i) the plant, animal or microorganism exhibits characteristics that were not previously observed in that plant, animal or microorganism,
  (ii) the plant, animal or microorganism no longer exhibits characteristics that were previously observed in that plant, animal or microorganism, or
  (iii) one or more characteristics of the plant, animal or microorganism no longer fall within the anticipated range for that plant, animal or microorganism

(9) **Foods for special dietary use** are regulated under Division 24 of Part B of the *Food and Drug Regulations* and refer to foods that have been specially processed or formulated to meet the particular requirements of a person

(a) in whom a physical or physiological condition exists as a result of a disease, disorder or injury, or

(b) in whom a particular effect, including but not limited to weight loss, is to be obtained by a controlled intake of foods

(10) **Functional food** is a term originally coined to describe a food that, when consumed within daily dietary patterns, would provide health benefits over and above basic nutritional value in preventing or reducing the risk of developing a disease or in enhancing physiological functions. However, this term has also been used broadly (in marketing and in the media) to include foods that may or may not provide the claimed or implied health benefits. Health Canada is not pursuing a regulatory definition of functional food because a definition is not required under the current *Food and Drugs Act* to permit health claims for foods on a product-specific basis. However, foods that fall under the regulatory proposal for product-specific authorization of health claims for foods would fit with the technical concept of "functional food".

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[3] "Major change" means, in respect of a food, a change in the food that, based on the manufacturer's experience or generally accepted nutritional or food science theory, places the modified food outside the accepted limits of natural variations for that food with regard to (a) the composition, structure or nutritional quality of the food or its generally recognized physiological effects; (b) the manner in which the food is metabolized in the body; or (c) the microbiological safety, the chemical safety or the safe use of the food.

(11) Biologically active (bioactive) substance, for the purpose of this document, means a substance, including a microorganism, that occurs naturally in foods, or a similar substance that has physiologial effects comparable to a food constituent when consumed in equivalent quantities, which is added to or otherwise modified in a food to achieve a claimed or implied health benefit with respect to paragraphs (2) to (4) above.

3. Objectives, Scope and Application of Standards

3.1 The standards are developed to support a credible system of health claim review for foods with the primary objectives to prevent injury to health and to avoid misleading claims, while considering practicality, flexibility, and issues related to harmonization, industry innovation and competitiveness.

3.2 These standards will be applied to the evaluation of

(1) health claims to be authorized under the generic authorization process
(2) specific foods subject to the product-specific authorization process

4. Principles and Criteria

In addition to (1) general information about the product and the claim, three categories of information are required: (2) information on product safety, (3) claim validity, and (4) quality assurance.

4.1 General information

4.1.1 General information required as part of health claim review includes the following:

(1) the proposed health claim
(2) the type of authorization sought
(3) the characteristics of the food(s) to which the proposed health claim will be applied, including nutrient composition
(4) the effective intake of the food(s) and/or the biologically active substance in the food(s) that produce the intended effect

4.1.2 In addition, for foods subject to the product-specific authorization process, the following information will be required:

(5) detailed product information, including: ingredients and their sources, specifications, processing, product form
(6) intended use, target group(s), directions for preparation and/or use

4.2 Product safety

4.2.1 The evidence should provide reasonable assurance of no adverse **nutritional, toxicological or microbiological** effects from ingesting the product as intended.

4.2.2 The type and amount of data required to support safety will be proportional to the novelty of the product and the uncertainty regarding its safety.

Generic authorization

4.2.3 The safety requirements for health claims to be authorized under the generic authorization process will consist of first, a ***basic evaluation***, which will focus on assessing any changes in the consumption of the recommended food(s) to minimize the risk of:

(1) exceeding safe and tolerable intakes of any biologically active substance(s) of concern in the food(s), or
(2) dietary, nutritional or metabolic imbalance

With the generic authorization process, product safety is generally not a concern if:

(1) the food(s) carrying the claim have not been modified,
(2) the amount of the food(s) to be consumed falls within generally accepted or recommended dietary patterns, or
(3) the food(s) for which increased consumption is recommended do not contain known biologically active substance(s) that have the potential to have adverse health effects at higher levels of intakes, or the food(s) for which decreased consumption is recommended do not contain essential nutrients for which adequate intakes from the diet are a concern for some population groups

Product-specific authorization

4.2.4 Safety requirements for foods intended to have a direct effect on a function or structure of the body beyond normal growth and development or maintenance of good health will focus on the following:

(1) **Safety at high level of intake** - Foods carrying claims authorized under the product-specific route which may have effects indistinguishable from those of some drugs. These effects are most likely to be mediated through the addition of biologically active substance(s) present in food, or chemically-similar analogues to such substances, at levels higher than those naturally occurring in or currently consumed from the food supply. This could introduce the potential for adverse effects. It is important therefore to have an estimate of the total daily intake from all sources.
(2) **History of safe use** - The bioactive substances added to foods may include ones that either do not have a history of safe use as food or may have a long history of consumption in the human diet but have not been adequately tested for high dose toxicity or establishment of upper limit of safe intake. Concerns could arise because of the nature of the activity of the substance or because of groups that would be more susceptible to adverse effects from higher intakes.
(3) **Interactions** - Product safety means that the product must be safe in terms of intended use, and also in relation to its impact on the total diet including its effect on

other diet components. Interactions with drugs are also an important consideration particularly where a product is represented to have therapeutic uses.

4.2.5 In reviewing specific foods that are subject to the product-specific authorization process, product safety assessment will consist of:

(2) ***basic evaluation*** for all products to assess the potential for adverse nutritional or toxicological effects.

(3) ***further evaluation*** for some products to address any outstanding issues arising from the basic evaluation. The information required (e.g. the number and types of studies) will be determined on a case-by-case basis from the basic evaluation.

See Table 1 for the purpose of the basic evaluation and further evaluation and the information required.

Table 1
Product Safety Evaluation as part of Product-Specific Authorization of Health Claims for Foods

Basic evaluation:

Purpose of Evaluation	Information Required
To determine if the food is a novel food	- history of safe use as food - method or technology used in producing and processing the food as per requirements for novel foods under the *Food and Drug Regulations*
For a food that is not a novel food (e.g. a conventional food not appropriate for *ad libitum* consumption*;* other altered foods): basic evaluation will be undertaken to assess any potential changes in consumption of the food to minimize the risk of - exceeding safe and tolerable intakes of any biologically active substance(s) of concern in the food, and - dietary, nutritional or metabolic imbalance	- current and expected intakes of the food and/or the nutrient and/or the bioactive compound from all sources - potential replacement of existing foods - data indicating maximum intakes of those conventional foods which are not appropriate for *ad libitum* consumption
For a food containing an added or modified biologically active substance: to assess any potential for adverse health effects	- identification of susceptible and vulnerable group(s) potentially at risk of adverse effects from excessive intake of the biologically active substance - physiological role, metabolic fate, interactions of the biologically active substance with nutrients, other dietary components, or drugs, including potential adverse effects on meeting requirements of essential nutrients - safety assessment may be required on the isolated substance, as well as in the food matrix in which it is present, in order to assess any potential effects of interactions with other food components

Table 1 (cont'd)
Product Safety Evaluation as part of Product-Specific Authorization of Health Claims for Foods

Further evaluation:

Purpose of Evaluation	Information Required
To address any outstanding issues arising from the basic evaluation: - to support the absence of adverse health effects	- evidence from various sources (including human and animal experimental studies) of acceptable quality and relevance should be included - conflicting data suggesting the presence of adverse health effects must be explained - human data used to demonstrate health benefits for products with health claims will be assessed for their relevance for supporting product safety
- to assess the margin of safety in the expected exposure to the food and the bioactive substance in both the target and general populations - to guide the decision on whether or not the food product is acceptable as a food in providing a specific health benefit for the target population	- where available evidence suggests that adverse health effects may be expected in humans at a certain level of intake of the bioactive substance under evaluation, depending on the nature of the adverse health effects, information may be required to establish an upper safe limit of intake and the range of foods to which the bioactive substance may be added.
- to check against upper limit estimates for safe use derived from data from experimental studies	- data showing no adverse effects from relevant observational epidemiological data, where available, will be considered in conjunction with other data, since epidemiological evidence alone may not have sufficient power to detect a small increase in risk unless specifically designed for such a purpose
- to ensure long-term safety	- postmarket surveillance, in the form of adverse reaction reporting, may be required, in addition to meeting the above safety requirements. Consumption data may also need to be confirmed if there are concerns about displacement of other foods or concerns about exceeding upper safe levels of intake of the bioactive substance in the food
- to assess the safety of novel food products	- as per requirements for novel foods under the *Food and Drug Regulations*

4.3 Claim validity

4.3.1 The evaluation of claim validity is based on six underlying principles which can be summarized as follows:

(1) the totality of evidence relating to the claim will be considered and not just the evidence supporting the claim
(2) the evidence should support a causal relationship between the ingestion of the food and the claimed effect
(3) the evidence supporting the claim should be relevant and generalizable to the target population
(4) a systematic or structured approach should be used to ensure that all relevant evidence is considered and the conclusions are justified
(5) the level of certainty for claim validity should be high based on best practices in evaluating scientific evidence[4]
(6) the studies supporting the claim must be of acceptable design and quality and conducted in accordance with current best scientific practices

4.3.2 The adequacy of the evidence supporting a claim will be determined by considering the nature of the claim in its entirety on a case-by-case basis. The nature of a claim is the aggregate of such factors as:

(1) the type of health benefit
(2) how the benefit of the food is stated
(3) specificity of the substance or health benefit
(4) intended target of the claim
(5) potential impact of the claim
(6) novelty of the claimed relationship between the food/substance and health benefit

For example, the more specific the food/substance or the health benefit in the claim, the more emphasis would be placed on controlled human experimental studies. The assessment of a health claim for a specific food under the product-specific authorization process will require studies on the specific food being marketed. Systematic review of similar foods or the responsible biologically active substance in other food matrices or processed differently may provide supporting evidence, but this type of systematic review will not be adequate alone. On the other hand, claims related to dietary patterns or food groups and risk reduction of chronic diseases may be based largely on evidence from observational studies, given the constraints of our current analytical tools and the difficulty in conducting controlled dietary studies. Where experimental data are also available, these will be given appropriate weight.

4.3.3 The type and the quantity of evidence should be sufficient to support the claimed effect regardless of the type of claim (Table 2).

4.3.4 Two types of evidence (Type 1 and Type 2 evidence) will be considered acceptable, depending on which claim authorization is being sought (Table 3A).

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[4] High level of certainty of the validity of a claim provides reasonable assurance that the claim is unlikely to be reversed by new and evolving science and allows the knowledge characterizing the relationship between the food/substance and the health condition to be refined over time. High level of certainty does not mean absolute certainty.

Type 1 evidence consists mainly of controlled human experimental studies that are generally required for products reviewed under the product-specific authorization process. Type 2 evidence consists of a combination of experimental studies, observational studies and systematic reviews, generally required for claims applicable under the generic authorization process.

4.3.5 Regardless of the type of evidence, all studies included in the totality of evidence should be of acceptable quality. Study quality is related to both study design and conduct.

Certain designs are of inherent high quality in testing causality due to the nature of controls built into the design (Table 3B).

Quality related to study conduct refers to completeness in describing the study methodology; quantification of the food/substance; quantification of the health-related endpoint; sample size; and sample representativeness to the general or target population.

4.3.6 In assessing evidence from all available studies of acceptable quality, the totality of evidence should:

(1) support a causal relationship between the ingestion of a food/substance and the claimed effect, with respect to: consistency; magnitude of effect/strength of association; probability; temporality; opposing evidence; and dose response, where appropriate (Table 3A)

(2) be relevant and generalizable to the claim being made

(3) provide answers to specific questions in characterizing the relationship between the food/substance and the claimed effect, with respect to:

- product efficacy and effectiveness[5] - Available data should support that the claimed effect can be achieved under controlled conditions of use. However, if efficacy is demonstrated by a highly controlled metabolic study, additional evidence should be provided that the amount of food required for the claimed effect under defined conditions could reasonably be expected to be consumed under free living conditions without a negative effect on the diet.

- the magnitude of the effect - The size of the effect should be known and predictable, as part of examining the causal relationship between the ingestion of the food and the claimed benefit.

- effective intake - This refers to the level of intake required to achieve the claimed effect.

[5] One main aspect of the evidence supporting product effectiveness is whether, under average free-living conditions, the food carrying the claim will be consumed at levels similar to those observed under controlled experimental conditions. Such data should be confirmed after the product is on the market if they are not available as part of the premarket submission. As noted in Table 1, such data are also important when there are concerns about displacement of other foods or concerns about exceeding upper safe levels of intake of the bioactive substance in the food.

- who will benefit - Where the claimed effect has been studied in or is applicable only to limited population groups (i.e. gender, age and health condition of study subjects), such groups should be identified as part of the claim statement, and

- sustainability of the effect - The claimed effect should be sustainable and not due to a transient adaptive response with decreasing benefit over time.

4.3.7 Evidence will be considered inadequate when not all the essential criteria are met for all the required elements listed in 4.3.6.

4.3.8 Any biomarkers used in supporting a health claim must be validated and/or generally accepted. The biomarker used should be relevant to the health or disease outcome referred to in the claim.

Three types of biomarkers are particularly relevant in supporting health claims for foods: surrogate disease endpoints (for supporting risk reduction claims), biomarkers related to the effects on body function or structure, and biomarkers of food intake or exposure. General and specific criteria for the different types of biomarkers have been outlined in the consultation document on Standards of Evidence for Evaluating Foods with Health Claims published in June 2000.

Table 2
Study Design Types Required for Health Claims
for Generic or Product-Specific Authorization

		Product-Specific Studies			Published Literature		
		Expt	**Obs**	**Sys Rev**	**Expt**	**Obs**	**Sys Rev**
Generic authorization **Proposed applicable foods:** Dietary patterns, a group of foods or individual foods within the identified food groups meeting specified compositional requirements; also applicable to nutrients or other components in foods							
Proposed applicable claims:							
Reduction of risk of a disease or health-related condition					[✓]	✓	✓
Correcting, restoring or modifying organic functions or body structures beyond normal growth and development or maintenance of good health					[✓]	✓	✓
Dietary management of a disease or health-related condition					[✓]	✓	✓
Product-specific authorization **Proposed applicable foods:** A specific food or a biologically active substance(s) added to or otherwise modified in a food that can be consumed in a reasonable amount as part of a healthy diet to achieve the claimed effect							
Proposed applicable claims:							
Correcting, restoring or modifying organic functions or body structures beyond normal growth and development or maintenance of good health		✓					✓
Dietary management of a disease or health-related condition		✓					✓
Reduction of risk of a disease or health-related condition*		✓	✓				✓

Expt = Human experimental studies
Obs = Human observational (analytic) studies
Sys Rev = Systematic reviews (Human studies)

✓ - required
[✓] - strengthens the evidence but not always feasible or required

* In attributing disease risk reduction to a specific product, the claimed relationship between the ingestion of the product and disease risk reduction must be based on studies including the product and should demonstrate that the consumption of the food has a direct effect in reducing disease risks. Otherwise, the part of the claim related to disease risk reduction should be diet-based, subject to proposed regulations regarding permitted and prohibited disease claims in accordance with the product-specific authorization process.

Criteria for Evaluating the Nature of the Causal Relationship from Type 1 and Type 2 Evidence

Type 1 evidence is generally required for health claims approved under the product-specific authorization process and consists primarily of experimental studies. Type 2 evidence is generally required for health claims approved under the generic authorization process and consists of a combination of experimental studies, observational studies and systematic reviews, where applicable.

The following table (Table 3A) describes the differences in requirements between Type 1 and Type 2 evidence with respect to meeting essential criteria for causality, characterizing the relationship between the food and the claimed benefit, and assessing the relevance and generalizabiltiy of the evidence in relation to the proposed claim. An explanation of the causality criteria and the information required in characterizing the food-benefit relationship is provided at the end of Table 3A.

Table 3A

	Acceptable Evidence		**Inadequate Evidence / Opposing Evidence**
	Type 1 (mainly controlled human experimental studies)	**Type 2 (combination of different types of studies)**	
Demonstrating causal relationship - essential criteria			Not all essential criteria are met
Consistency	Criterion met when results are reproducible, preferably across study designs	Criterion met when results are reproducible, preferably across study designs	
Magnitude of effect/ strength of association	Significant physiological and statistical differences (experimental studies)	Relative risk (RR) or odds ratio different from and not overlapping 1 (observational studies)	
Probability	Demonstration of statistically significant relationship within studies	Small RR may be acceptable when number of affected people is large	
Temporality	Experimental design provides assurance that the intervention preceded the effect	Criterion is assumed to have been met where evidence is provided by prospective studies and is consistent with or provided by experimental studies	
Dose response	Estimates of intake required to achieve the claimed effect should be provided based on dose response, or other data where dose response data are not available	Not always feasible, but estimates of intake required to achieve the claimed effect should be provided using available data	
Opposing evidence	No equally strong opposing or neutral evidence		Moderate or strong evidence that is neutral or contrary to the claim

Table 3A (cont'd)

	Acceptable Evidence		Inadequate Evidence / Opposing Evidence
	Type 1 (mainly controlled human experimental studies)	**Type 2 (combination of different types of studies)**	
Characterizing causal relationship between the food and the benefit - essential information			
- efficacy - magnitude of effect - effective intake - who will benefit - sustainability of effect	Required as part of both types of evidence		Not all essential information is available
Relevance/ generalizability	May be limited if observational studies are lacking, or if results are extrapolated to populations beyond those studied	Combination of experimental and observational data strengthens the likelihood of meeting this criterion	Criterion not met: small sample and/or sample not representative of target group, short study; test conditions not relevant to typical use under free living conditions; health relevance of biomarkers questionable

Demonstrating causal relationship

Essential criteria

Consistency: replication of study findings in terms of the direction or pattern of results (i.e. positive or negative results) in different studies and by different investigators. Inconsistent findings should be explained.

Magnitude of an effect (in experimental studies) ***or strength of an association*** (in observational studies): The size of an effect should be both statistically and physiologically significant. The strength of the association is usually measured by the extent to which the relative risk or odds ratio (expressed with confidence limits) departs from unity. Weak relationships are susceptible to confounding and may reflect a poor measure of exposure or outcome.

Probability: demonstration of a statistically significant relationship between relevant variables within a study.

Temporal relationship: The exposure must precede the effect in demonstrating a causal relationship between the two variables.

Dose-response relationships: description of the gradient in the association between the magnitude or duration or both of the exposure and the size of the effect. The lack of experimental dose-response data should be explained in the testing of a specific product or bioactive substance (e.g. certain biologic relationships are dichotomous and reach a threshold level for observed effects) and other sources of information should be used to estimate the level of intake required to achieve the claimed effect.

Opposing or neutral evidence: Evidence for a causal effect is weakened or questionable when there is inconsistency in results and when the strength of equivocal or conflicting evidence is similar to that of corroborating evidence.

Supporting criteria

The following criteria are <u>not</u> considered essential for the purpose of demonstrating a causal relationship between the ingestion of a food/substance and the claimed effect. However, the more these criteria are met, the stronger the evidence.

Reversal or cessation of effects: If an agent has a beneficial effect, then the agent should reverse an existing risk factor or adverse condition or prevent the development of a risk factor. When it is removed, the benefit would be expected to cease (unless there is a carryover effect) or the risk factor would re-emerge. In some cases, long-term studies may be required to indicate that the beneficial effect is not transient.

Biological plausibility: The observed effect should fit into the current body of knowledge regarding a biologically plausible mechanism in explaining why an effect would be expected to occur.

Alternative explanations (confounding): The extent to which alternative explanations for the observed effect due to uncontrolled confounding or other methodological artifacts should be ruled out.

Specificity of effect **or cause**: the precision of the association between the exposure and the effect. (e.g. does X lead only to Y or does only X lead to Y?)

Coherence: concordance with other knowledge or data. The effect is seen in a variety of related endpoints.

<u>Study quality based on design and conduct</u>

Individual studies that are included as part of the totality of evidence should be categorized as described in Table 3B. The preponderance of studies should meet required criteria for study design, as outlined in this section.

Table 3B

	Acceptable Evidence		Inadequate Evidence
	Type 1 (mainly controlled human experimental studies)	**Type 2 (combination of different types of studies)**	
Study design - Evidence in support of health claims must be based on human studies of acceptable design, i.e. meeting required levels for the respective study categories [1, 2].			
Experimental - human	More weight given Meet levels A-C	Meet levels A-C	Primarily levels D-E
Observational - human (prospective or retrospective cohorts, case-controls)	Should be supportive if available	More weight on prospective studies Meet levels A-B	Level C
Systematic review	Should be supportive if available	Ideally meeting criteria 1-4	Unacceptable quality
Supportive data - Corroborating studies that do not meet the above criteria may be considered as part of the totality of evidence as supportive data.			
Animal/*in vitro*	Applicable to both as supportive data only		These types of data are considered inadequate on their own.
Other observational studies in humans			

Experimental Studies in Humans (Trials) (planned interventions with contemporaneous assignment of treatment and nontreatment)

(A) Randomized, double-blind, placebo-controlled trials, with sufficient power, appropriately analyzed
(B) Randomized, but blindness not achieved
(C) Non-randomized, but with good control of confounding variables and well conducted in other respects
(D) Randomized, but with deficiencies in execution or analysis (insufficient power, major losses to follow-up, suspect randomization, analysis with exclusions etc.)
(E) Non-randomized, with deficiencies in execution or analysis

Observational Studies in Humans (Prospective or Retrospective Cohorts or Case-controls)

(A) Hypothesis or objectives specified prior to analysis, with good data and confounders accounted for
(B) Hypothesis or objectives not specified prior to analysis, but with good data and confounders accounted for
(C) Hypothesis or objectives studied post-hoc, with problems(s) in the data or the analysis

Systematic Reviews

(1) Avoidance of bias in selection of studies (based on clearly stated inclusion and exclusion criteria)
(2) Conclusion supported by data and analysis presented
(3) Demonstration of comprehensive search for evidence
(4) Assessment of publication bias (including many small published studies with positive effects or ignoring known unpublished studies with negative effects)
(5) Assessment of the validity of each cited study

[1] Adapted from Gordis L, Kleinman JC, Klerman LV, Mullen PD, Paneth N. Criteria for evaluating evidence regarding the effectiveness of prenatal interventions. In: Merkats IR, Thompson JE, editors. New perspectives on prenatal care. New York (NY): Elsevier, 1990: 31-38.

[2] Adapted from Carruthers SG, Larochelle P, Haynes RB, Petrasovits A, Schiffrin E. Report to the Canadian Hypertension Society concensus conference: 1. Introduction. CMAJ 1993; 149(3): 289-293.

4.4 Quality assurance and practices

4.4.1 Quality assurance measures must be demonstrated and documented to ensure:

(1) product consistency such that the product contains the bioactive substance(s) in the right amount to deliver the claimed benefit without compromising product safety
(2) that acceptable procedures and methods are followed in product testing.

4.4.2 There are four elements of quality assurance:

(1) good manufacturing practices (GMPs)
(2) good laboratory (analytical) practices (GLPs)
(3) good practices concerning the collection and analysis of human data, including good clinical practices (GCPs), as relevant
(4) documentation

Good manufacturing practices

4.4.3 It is desirable to define the biologically active substance(s) in the food responsible for the claimed effect as it may relate to understanding the effects of food matrix and processing issues . Where this is not known or adequately defined, an appropriate proxy indicator that has a quantifiable relationship between its amount in the food and the claimed effect should be established for quality assurance purposes. Where a substance is added to or otherwise modified in a food to achieve the claimed effect, it should be characterized in sufficient detail to permit the development of adequate specifications and quality control.

4.4.4 Documentation on the consistency of the quantity of the biologically active substance(s) or appropriate proxy indicator(s) in the food bearing the claim should be provided, including stability data, where relevant. The data should be based on a validated method using a laboratory that is accredited to conduct the analysis (see 4.4.8 and 4.4.9 below).

4.4.5 Where the analysis of a biologically active substance in an ingredient added to the food originates from a third-party (i.e. ingredient supplier), it is the responsibility of the manufacturer of the finished food to ensure the accuracy and validity of the analytical data. A certificate of analysis from the third-party can be a supporting document for this purpose.

Generic authorization

4.4.6 In assessing health claims to be authorized under the generic authorization process for **unaltered** foods, no special concerns regarding good manufacturing practices are anticipated. The good manufacturing practices generally applicable to the food category in question should be observed. However, following acceptable procedures in analytical testing of product composition for the nutrient or other food component critical to the claimed effect will be important.

Product-specific authorization

4.4.7 In assessing claims as part of the product-specific authorization process, it is expected that in many cases, the food bearing the claim will have been modified, for example by adding a biologically active substance to the food, or by other means of modification including changing the bioavailability of a biologically active substance. It is also possible that the manufacturing of the food bearing the claim involves a unique process that relates to the product's beneficial effects. Therefore, detailed information on the manufacturing and processing of the product will be required. Such information includes:

(1) quality control procedures used throughout the process with respect to raw materials, manufacturing, processing, finished product, packaging and labelling, with documentation of procedures
(2) stability data on the final product, including shelf-life and a description of the methods used to obtain the data

Good laboratory (analytical) practices

4.4.8 All analyses relevant to supporting the claim should be performed using acceptable laboratory quality assurance and quality control procedures. Relevant analyses include measuring the level of biomarker(s) in experimental and observational studies and the amount of the nutrient, other biologically active substance/ingredient (or an appropriate proxy indicator) present in the finished food. Details of the methods of these analyses should be provided, as well as the sampling plan and the variability of the data.

4.4.9 If an analytical method is a new or modified method, data should be provided on the standardization and validation of the method. An acceptable standardization and validation procedure includes the analysis of the substance in question by at least three reputable analytical laboratories (preferably laboratories which have quality assurance and quality control systems in place) using standardized reference material.

In a formal validation process, laboratories that performed satisfactorily in the collaborative testing may be accredited to conduct the analysis being validated.

Good practices concerning the collection and analysis of human data

4.4.10 All experimental and observational studies conducted in support of the health claim should be conducted in accordance with applicable ethical standards and guidelines. This is particularly relevant for studies conducted or sponsored by the applicant for the purpose of health claim approval, in either generic or product-specific authorization. Under this circumstance, attestation to conformity with established ethical guidelines may be considered an acceptable form of compliance with this requirement. Ethical guidelines widely in use include the Ethical Conduct for Research Involving Humans-August 1998, (the Medical Research Council, Natural Sciences and Engineering Research Council and the Social Sciences and Humanities Research Council, all of Canada) and Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects, October 2000 (World. Medical Association).

Documentation

4.4.11 The quality assurance capability of the applicant will be judged based on submitted documentation which should include:

(1) identification of the critical control points
(2) specifications and an analysis plan based on statistical control principles for starting materials, processing, final products, packaging materials and labelling control
(3) record retention policy
(4) recall capability
(5) evidence of good manufacturing practices
(6) evidence of good practices in testing procedures, including laboratory (analytical) practices and practices concerning the collection and analysis of human data

4.4.12 The above requirements are applicable to products manufactured specifically to achieve the claimed effect by the addition or removal of biologically active ingredient(s) or other substance(s) to the food bearing the claim, or by other means of modification (such as those described in paragraph 4.4.7).

5. Evaluation Process

Preliminary evaluation

5.1 To assist timely evaluation, a submission for health claim approval will be screened:

(1) to assess the completeness of the submission in the required elements
(2) to ensure that the required information is provided in the required format
(3) to request clarification and/or further information
(4) to determine if detailed evaluation should proceed

In the case of product-specific authorization, preliminary evaluation will also:

(5) determine if the product submitted should be evaluated as a food

Detailed evaluation

5.2 Detailed evaluation includes assessing:

(1) whether the applicant has considered the totality of available data
(2) the adequacy of the data provided in supporting product safety, claim validity and quality assurance measures using the criteria described in section 4

Benefit-risk assessment and risk management

5.3 As a general principle, foods should be safe for *ad libitum* consumption for the general population. Where a food has been modified for a specified intended use or for a specified target population for the purpose of delivering a specific health benefit, it may be necessary to consider if the net health benefit of the food for the target users outweighs any potential health risk to the general population. It is expected that in approving such a food with any potential health risk, the severity of the potential adverse effect should be of a relatively small magnitude (with the exception of severe allergenic effects known to occur with some foods) and the probability or frequency of occurrence of the adverse effect in the general population should be low.

5.4 Where such a food may pose a nutritional or health risk to a user or non user group (e.g. intolerance or allergenicity, metabolic susceptibility among identifiable individuals), if there is a compelling reason for making such a food available to the target users, it would be necessary to apply risk management options to ensure that users and non users are not put at undue risk. Risk management options include:

(1) special labelling
(2) restricted product distribution and/or advertising
(3) postmarketing adverse reaction reporting

PART II - SUBMITTING THE EVIDENCE

1. Introduction

A submission for premarket review is required for foods that fall under *Food and Drug Regulations* [naming the sections] regarding product-specific authorization of health claims for foods. A submission for premarket review is also required where an applicant wishes to request changes to the Table to *Food and Drug Regulations* B.01.600 pertaining to the generic authorization of diet-related health claims.

This part of the Guidance Document is to assist applicants in providing the information required in a regular submission for premarket review of foods carrying health claims in a format that facilitates review (section 2.1 - Presentation of the Submission and and section 2.2 - Content of the Submission).

NOTE THAT IT IS THE INTENT OF HEALTH CANADA TO MAKE DECISION SUMMARIES OF APPROVED CLAIMS PUBLICLY AVAILABLE.

Potential applicants are encouraged to discuss their proposed claims and products well in advance of submitting a formal application with the appropriate regulatory authority within Health Canada.

2. Regular Submission

2.1 Presentation of the submission

(a) Accompanying letter and responsibility for the submission

The submission should be filed with an accompanying letter signed by a responsible officer of the firm, preferably the person with whom subsequent correspondence will be carried out.

(b) Language and translation

All data and information in the submission should be recorded in English or French. Material in other languages must be translated into English or French before it can be considered.

(c) Pagination and identification of different sections of the submission

Pagination may be sequential for the entire submission or by the individual segments of the technical information in the submission (i.e. Comprehensive Summary, General Information, Product Safety, Claim Validity, Quality Assurance). Include the applicant's identification and product/brand name (where applicable) on all pages.

Each section and sub-section of the submission should be identified using the numbering system and headings and sub-headings suggested in this guideline.

(d) Legibility and binding of the submission

All information should be legible and organized to fit on standard sized paper.

The paper copy of the submission should be bound for easy access to its information. If more than one binder is submitted, each volume should be sequentially numbered on the spine and front cover, starting at 1. This numbering will facilitate the reception, handling, transmission and storage of the submission by the Food Directorate.

(e) References

Avoid using abstracts as references. Include "personal communication" when it provides essential information not available from a public source. Applicants are responsible for the accuracy of all references cited, published or unpublished, and for obtaining permission from source to cite unpublished material, where appropriate.

Use an established style for citing references in the biomedical sciences (e.g. Uniform requirements for manuscripts submitted to biomedical journals - web site).

Identify on the reference list any publications for which paper copies have not been included in the submission.

(f) Number of copies and electronic submission

When hard copies are submitted, 2 copies of the submission should be included.

Where the submission is filed electronically, one paper copy of the submission should also be sent to ensure that the submission is complete and accurate without omissions, errors or ambiguities resulting from computer-related technical difficulties.

Two paper copies of references should be provided.

(g) Submission directions

The submission should be addressed to:

Mailing address:

Bureau of Nutritional Sciences
3rd Floor, Banting Building
Tunney's Pasture A.L. 2203A
Ottawa, Ontario K1A 0L2

Electronic address:

Healthclaims_submissions/hc-sc.gc.ca

Applicants may wish to send a copy of the cover letter to the above contact point under separate cover advising that the submission has been mailed. It is advisable to enclose a copy of this letter with the submission.

2.2 Content of the submission

2.2.1 Application form and checklist

Explanation for the italicized terms can be found at the end of the application form and checklist, by following the corresponding identification numbers listed on the form (e.g., for an explanation regarding *product-specific* and *generic authorizations* listed as item #2 under section II on this form, look up item II-2 in the "Guidelines" section).

Health Claims for Foods - Application Form and Checklist	**Ref. No.** (to be assigned by Health Canada)
I. Applicant Information - provide the information requested in sections I & II on this form	
Name of Company/Organization	❒ Manufacturer ❒ Distributor ❒ Importer
Mailing Address	
Responsible Officer	Name:
	Position:
	E-mail:
	Phone: Fax:
	Date of submission:
Contact Person (if different from above)	Name:
	Position:
	E-mail:
	Phone: Fax:
II. General Information on the Health Claim and the Product	
1. Proposed health claim	
2. Type of authorization sought (refer to Part I, section 2 of this document for definitions)	❒ Product-specific ❒ Generic
3. Product *(common name* and brand name - see II-4 in 2.2.2)	
4. Manufacturing location (also provide name of manufacturer if different from the applicant)	
5. Ingredient list	

6. *Reference amount, serving of stated size, recommended serving and reasonable daily intake* - see II-7 in 2.2.2	
7. Nutrient information (as sold, as consumed, per 100g, per serving of stated size)	
8. Target group(s) for the product carrying the claim	

The following information is required of products subject to the product-specific authorization process	
9. *Product form* - as sold, as consumed - see II-10 in 2.2.2	
10. *Intended use* of product - see II-11 in 2.2.2	
11. If applicable a. Directions for preparation b. Directions for use	

III. Supplementary Information - Identify any supplementary information provided in addition to the topics suggested in the section 2.2.3 (Outline of Technical Information), and where the information is included in the submission. Supplementary information may include official meeting minutes, regulatory guidance or advice from other jurisdictions. All information known to the applicant, whether it is positive or negative with respect to the product or the proposed claim must be disclosed. Provide information on whether the product claim has been submitted elsewhere and the outcome of that submission.

2.2.2 Guidelines on specific items on the application form and checklist

II-4 Common name - the common name of a food is
- the name prescribed by the *Food and Drug Regulations* [B.01.001, B.01.006]
- the name prescribed by other federal regulation [*Consumer Packaging and Labelling Act* 10]
- if not prescribed by regulation, the name by which the food is commonly known

II-7 Reference amount - in respect of a food set out in column 1 of Schedule M, means the amount of that food set out column 2 [proposed *Food and Drug Regulations* B.01.001]

Serving of stated size - the serving size declared on label

Recommended serving - the recommended amount of a food to be consumed daily

Reasonably daily intake - in respect of a food set out in column 1 of Schedule K, means the amount of that food set out column 2 [*Food and Drug Regulations* B.01.001]

II-10 Product form - refers to the form of a product as sold and as consumed (e.g. powder, liquid)

II-11 Intended use - the purpose and target population(s) for which the product was developed and marketed.

2.2.3 Outline of technical information

The guidelines provided here **(pp 29-39)** and outlined below are intended to ensure that the content of all submissions is factual, relevant and complete and that the manner of presentation is uniform and logical. A submission that follows the organization and content suggested here will facilitate the review process. However, this outline may not cover all the issues that may be pertinent in a particular submission. Applicants should include all pertinent information and add specific headings or subheadings in their submissions as necessary.

Deviations from these guidelines may be acceptable following prior discussion with the specific Bureau of the Food Directorate responsible for reviewing the specific segment of the submission. Deviations, additions, or omissions, authorized or not, must be explained, either by introductory remarks or within each relevant section of the submission, whichever is more appropriate.

A submission that deviates from the suggested outline that follow without prior discussion with the Food Directorate or explanation will be returned to the applicant without review.

Please start each segment of the submission (I-V) on a new page and include the applicant's identification on all pages of the submission which should be numbered.

Applicant's Identification: Name of Company/Organization Product/Brand Name
I Comprehensive Summary
II General Information-Manufacturing, Specifications, Consumption **IF FOOD IS ALTERED/NOVEL:** **1. Manufacturing of finished food** **2. Manufacturing and properties of bioactive substance** **3. Specifications of other raw materials** **FOR ALL FOODS AND CLAIMS:** **4. Consumption data** **5. Estimated consumption vs recommendations** **6. References re (4) and (5) above**
III Product Safety **1. INDICATE PRODUCT SAFETY CATEGORY.** **IF APPLICABLE, PROVIDE:** **2. History of safe use** **3. Identify susceptble and vulnerable groups** **4. Identify interactions and nutritional adverse effects** **5. Microbial ecology** **6. Safety information** **7. References re (2) to (6) above**

IV CLAIM VALIDITY
- **Part A-Background information**
- **Part B-Literature review**
- **Part C-Primary evidence**
- **Part D-Assessment of totality of evidence**
- **Part E-References**
- **Part F-Detailed description of primary evidence**

V QUALITY ASSURANCE (FOR PRODUCT-SPECIFIC HEALTH CLAIMS)
- **Part A-Bioactive substance-analysis and control**
- **Part B-Food bearing the claim-manufacturing and analysis**
- **Part C-Stability of finished product**
- **Part D-Methods of analysis used in testing bioactive substance and finished food**
- **Part E-References**
- **Part F-Supporting documents**

I. Comprehensive Summary

The Comprehensive Summary should be based on information, data or justification that was included in segments II - V of the submission and should indicate where such information is provided in the submission. The Comprehensive Summary should not include information, data or justification that was not already included in segments II - V of the submission.

1. **Summary of the evidence**

   Where the claim involves an altered food, the evidence provided in the submission with respect to product safety, claim validity and quality assurance should be summarized.

   Where the claim does not involve an altered food, the emphasis should be on how the evidence supports the proposed claim by assessing the totality of evidence with respect to the required elements, including a) the extent to which essential criteria supporting a causality relationship between the ingestion of the food/substance and the claimed benefit has been met, b) essential information characterizing the relationship, c) the relevance and generalizability of the evidence to the claim.

2. **Limitation of the evidence** - identify any limitations in the evidence assessed and how the limitations have been addressed.

3. **Proposed claim** - state the proposed claim.

4. **Method of authorization** - based on the evidence presented in the submission, justify the method of authorization requested (i.e. generic or product-specific authorization).

5. **Considerations in the use of the claim** - identify the conditions and qualifications for the use of the claim with respect to: food composition criteria, target group(s), safe use of the food (directions for use, upper limit of intake, advisory or cautionary statements).

II. General Information - Manufacturing, Specifications, Consumption

The following information is relevant to more than one area of the review with respect to product safety, claim validity and quality assurance. It is important to provide the information requested as fully as possible to facilitate Health Canada in completing the review. Attach flow diagrams and manufacturing documents as necessary. Information on quality control aspects of manufacturing and raw material testing is to be provided under segment V.

Information requested under paragraphs 1-3 below will help assess if the food is subject to the requirements of novel foods under Division 28 of Part B of the *Food and Drug Regulations.* This information does not apply to unaltered foods intended to carry claims reviewed under the generic authorization process. This information is also not required when reviewing a health claim that is applicable to a dietary pattern or a class of foods (e.g. fruits and vegetables).

Note: Refer to Glossary of Terms, section 2, Part I of this document for the meaning of "biologically active" or "bioactive" substance for the purpose of health claim authorization.

1. **Manufacturing of the finished food** - describe in details the method by which the product (the finished food that is being offered or advertised for sale) is manufactured, prepared, preserved, packaged and stored. Identify any relevant issues related to "major change" as defined in Division 28, Part B of the *Food and Drug Regulations* pertaining to novel foods, e.g., where a bioactive substance naturally present in the food is intentionally or unintentionally modified.

2. **Manufacturing and properties of added bioactive substance**
   If a biologically active ingredient is added to the product, describe:
   a) its method of fractionation, purification, concentration
   b) its physical and chemical properties, source and biological activity and specifications, including any critical stability/storage/preparation information.

3. **Specifications of other raw materials** - provide a list of ingredients specifying quantity and their specifications (chemical, microbiological, physical, purity, contaminants, processing methods).

Information requested under paragraphs 4-5 below is applicable to all foods and claims to be reviewed under either the generic or product-specific authorization process.

4. **Consumption data** - estimate current and expected levels of consumption by target groups and susceptible/vulnerable groups of :
   a) the product and similar foods which have a similar role in the diet, and
   b) the bioactive substance in the food responsible for the claimed health benefit, where known.
   c) projected total daily intake of the bioactive substance from all sources.

   Include all anticipated sources of intake, and any potential use of the product as replacement of existing foods. Also provide the sources of the information.

5. **Estimated consumption vs. recommendations** - compare current and expected exposures to current dietary recommendations (or targets) and safe (or tolerable) intakes of the bioactive substance in the food responsible for the claimed health benefit, where known, including relevant references.

6. **Complete list of references** - attach a list of the references used for information requested in paragraphs (4) and (5) and two copies of each..

III. Product Safety

The completion of this segment is not required for a health claim that is applicable to a dietary pattern or a class of foods (e.g. fruits and vegetables).

The information requested below is applicable to an altered food, including a novel food, as defined in Division 28, Part B of the *Food and Drug Regulations*. For the purpose of product safety evaluation, "altered food" means: the addition of a bioactive substance to the food, or other modification in the food, including modifying the level and/or bioavailability of a bioactive substance naturally occurring in the food in order to achieve the claimed effect, that is not already regulated in the *Food and Drug Regulations*. [Where regulations and/or guidelines for product safety for a specific food category are already in effect, they will apply.]

1. **Indicate which of the following product safety categories applies:**

❒ (a) The food bearing the proposed claim is not an altered food and no information on product safety is provided in this submission

❒ (b) The food bearing the proposed claim is an altered food or novel food; product safety has previously been reviewed and no information on product safety is provided in this submission

❒ (c) The food bearing the proposed claim is an altered food or novel food; product safety has not previously been reviewed and information on product safety is provided in this submission

If (c) applies provide information on 2 to 7 as follows:

2. **History of safe use** - provide information respecting the product's history of safe use as a food, or previous human consumption, including that in a country other than Canada, if applicable. Describe the form, preparation and range of intake of the food.

3. **Susceptible and vulnerable groups** - identify susceptible and vulnerable group(s) potentially at risk of adverse effects from ad libitum consumption of the product, including children, pregnant and lactating women and the elderly. This should include effects of the substance related and unrelated to the intended desirable effects of the product. For

example, allergenicity is an effect unrelated to the intended use of the product; cholesterol lowering (an intended use of the product for the general or target population) may have adverse health effects on some susceptible groups.

4. **Interactions and nutritional adverse effects -** identify any issues related to potential interactions with nutrients, other dietary components, or drugs, bioavailability and nutritional quality.

5. **Microbial ecology** - microbiological organisms in the food that have an effect on the gastrointestinal tract. If a product contains microorganisms as the bioactive substance, then appropriate data (experimental or literature) should be provided to ensure the safety of the product.

6. **Information relied on to establish that the food is safe for consumption as intended.**

   Organize the information based on a) the type of evidence, b) the endpoint(s) evaluated based on organ/system or function, and c) the doses tested (high doses vs. doses comparable to those required to achieve the claimed effect):

   Animal (justify use of animal species re relevance to safety for humans)
   - Experimental assessment of metabolic disposition
   - Experimental demonstration of key element of mechanism
   - Experimental assessment of in vivo toxicity

   In vitro (as needed)
   - Experimental demonstration of in vitro toxicity
   - Experimental demonstration of key element of mechanism

   Human
   - Evidence from experimental studies (including studies conducted to evaluate product efficacy)
   - Direct epidemiological evidence of causality (analytic studies)
   - Epidemiological evidence of association (cross-sectional studies, case series)

7. **Complete list of references -**attach a list of reference used for information requested in paragraphs 2 to 6 above and two copies of each.

IV. Claim Validity

Part A - Background Information

1. Indicate which of the following applies:

Original research was conducted on the product for which a claim is sought: complete Parts A, B, C*, D, E, F

Only a review of existing literature is submitted : complete Parts A, B, D, and E

The following parts are included:
❒ Part B: Literature review
❒ Part C*: Primary evidence - information on the product for which a claim is sought (product research)
❒ Part D: Assessment of the totality of evidence
❒ Part E: Reference list
❒ Part F: Detailed description of primary evidence

* Part C is required for products with health claims to be reviewed under the product-specific authorization process

1.1 If original research on the product was done, list the following information for each study:
(a) Principal Investigator(s) and Affiliation(s)
(b) Centre(s) where research was conducted
(c) Funding source
(d) Publication, if applicable

1.2 If an independent review of the data included this submission was conducted, provide the following information:
(a) Reviewers and Affiliations
(b) Conflict of interest declaration
(c) Other acknowledgements

1.3 If the product and the claim have been approved or rejected in other jurisdictions, provide the following information:
(a) Name of country for which approval or rejection was given. If the product was rejected elsewhere, reasons for rejection should be provided.
(b) Date of approval
(c) Claim statement approved
(d) Any conditions for the use of the claim: food composition criteria, target group(s), safe use of the food (directions for use, upper limit of intake, advisory or cautionary statements)
(e) Relevant postmarketing information (e.g. adverse response)
(f) Attach information on the formulation, processing and nutrient composition of the product sold in the country for which claim approval was obtained
(g) Are product formulation, processing and composition identical to the product to be sold in Canada? Yes ❒ No ❒

2. Background (explain what prompted your original research and/or literature review)
3. Objectives of your original research and/or literature review

Part B - Literature Review

1. Identifying relevant studies

(a) Describe the search strategy
(b) Describe the selection (inclusion and exclusion) criteria

2. Summary of the studies reviewed

In a table format, summarize each study within each of the following study design categories
(a) Experimental Studies in humans
(b) Observational Studies in humans
(c) Systematic Reviews, and

Under the following headings (use the table attached to this segment as a guide):
(a) Study identification (author, year)
(b) Study design and level (refer to Table 3B), Part I of this Guidance Document regarding categories of study design and levels)
(c) Description of participants in control and intervention groups, including sample size
(d) Description of treatment and control and duration
(e) Amount of food and bioactive substance consumed, method of collecting intake data
(f) Identification of baseline (background) diet and/or use of control diet
(g) Main results - provide actual data and statistical significance, include graphs where appropriate
(h) Comments - statistical analysis, other factors affecting interpretation of results, methods of analysis of intake of food and bioactive substance, and outcome measures*, general comment about study quality

* Provide additional information on the rationale for the endpoint(s) chosen and its relevance to the proposed claim (e.g. if bone density was chosen as a surrogate marker for osteoporosis risk, provide justification for using this endpoint and include the conditions under which this marker may or may not be valid).

Part C - Primary Evidence - information on the product for which a claim is sought (product research)

1. Summary of the studies conducted

Using a systematic approach similar to that for literature review in Part B, for each study conducted on the product for which the health claim is sought, categorize the study into one of 3 categories
(a) Experimental Studies in humans
(b) Observational Studies in humans
(c) Meta-analysis, if applicable

In a table format, summarize each study by study design under the following headings (use attached table to this section as a guide):
(a) Study identification (author, year)
(b) Study design and level (refer to Table 3B, Part I of this Guidance Document regarding categories of study design and levels)
(c) Description of participants in control and intervention groups, including sample size
(d) Description of treatment and control and duration
(e) Amount of food and bioactive substance consumed
(f) Identification of baseline (background) diet and/or use of control diet
(g) Main results - provide actual data and statistical significance, include graphs where appropriate
(h) Comments - statistical analysis (justify the types of statistics used), other factors affecting interpretation of results, methods of analysis of intake of food and bioactive substance, and outcome measures, general comment about study quality, deviations from protocol, adverse or side effects

2. Health relevance of the outcome measures or endpoints chosen

Provide additional information on the rationale for the endpoint(s) chosen and its relevance to the proposed claim (e.g. if bone density was chosen as a surrogate marker for osteoporosis risk, provide justification for using this endpoint and include the conditions under which this marker may or may not be valid).

3. Validation of the analytical method(s) for the endpoint(s) chosen

Describe the process for validating the analytical method(s) for the endpoint(s) chosen for any new or modified methods.

Part D - Assessment of Totality of Evidence

The assessment should be made by *integrating and synthesizing* the literature review as summarized in Part B, and the primary evidence as summarized in Part C, where applicable. Refer to section 4.3, Part I of this Guidance Document regarding the criteria against which the assessment of totality of evidence is to be conducted.

1. **Causality criteria -** assess the extent to which the following causality criteria have been met:

   Essential causality criteria
   (a) consistency
   (b) magnitude of effect
   (c) statistical probability
   (d) temporal relationship
   (e) no equally strong opposing/neutral evidence
   (f) dose response or relevant data in support of an effective dose

   Supporting causality criteria (information from animal studies, *in vitro* studies, human studies that do not meet essential study design and quality criteria may be discussed here)
   (g) reversal / cessation of effects
   (h) biological plausibility
   (i) alternative explanations
   (j) specificity of effect or cause
   (k) coherence

2. **Characterization of the relationship -** characterize the relationship between the food/bioactive substance and the claimed health effect using information provided in previous sections.

   Essential information
   (a) is the beneficial effect achieved under controlled conditions?
   (b) is the beneficial effect achieved under free-living conditions?
   (c) is the magnitude of effect physiologically meaningful?
   (d) is the beneficial effect sustainable?
   (e) what is the amount of food and bioactive substance required to achieve the claimed effect? can the amount be reasonably consumed from foods as part of a healthy diet?
   (f) what are the usual intakes of the food and bioactive substance?
   (g) who will benefit?

3. **Relevance and generalizability -** assess the relevance / generalizability of the evidence to the claimed effect and target group, including any limitations of the data.

4. Other Considerations - Regulatory Requirements, Benefit-Risk Assessment and Risk Management (revise as necessary when regulatory amendments are finalized)

Provide information to support the following:

(a) where a substance is added to the food or otherwise modified in the food to achieve the claimed effect, the composition of the food bearing the claim does not counteract the beneficial effect of the added or otherwise modified substance

(b) safe use of the product - are directions for use, cautionary statements, restricted advertising to health professionals, restricted channels of distribution and/or postmarket surveillance warranted?(such as confirming consumption data, developing a proactive system of reporting adverse reactions). Integrate information from segment III (Product Safety) in justifying your assessment. Where any of these measures are warranted, indicate your proposed course of action.

Part E - Complete Reference List

List the references cited in Parts B, C and D
Provide one copy of all references cited.

Part F - Detailed Description of Primary Evidence

For each original study conducted or sponsored by the applicant, include protocol and data.

<table>
<tr><th>Study</th><th>Design</th><th>Diet component</th><th>Subjects</th><th>Duration</th><th>Diet method</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Zino et al., 1997
New Zealand</td>
<td>RCT
(B)</td>
<td>Fruit and vegetables</td>
<td>90 healthy volunteers (26 men aged 19-69 yrs, and 64 women aged 18-61 yrs).

Subjects had to be consuming 3 or fewer servings of fruit and vegetables daily.</td>
<td>2 week run-in period;
8 week treatment period.</td>
<td>Subjects were randomly assigned to control (habitual diet) or intervention groups;
intervention group instructed to increase consumption of fruit and vegetables to 8 servings/day and not to alter intake of nuts, oil, butter or margarine.

Four day diet records completed during run in and week 4.

Unannounced 24 hr recalls were taken in week 6 as an additional measure of compliance.</td>
<td>Reported consumption of fruit, vegetables and other nutrients (means ± SD):
<table>
<tr><th>Intake</th><th>Baseline Control</th><th>Baseline Treatment</th><th>Week 4 Control</th><th>Week 4 Treatment</th><th>Adjusted Difference (95% CI)*</th></tr>
<tr><td>Fruit (g)</td><td>37 ± 51</td><td>93 ± 118</td><td>55 ± 84</td><td>256 ± 132</td><td>177 (125- 228)</td></tr>
<tr><td>Juice (g)</td><td>25 ± 68</td><td>56 ± 96</td><td>46 ± 104</td><td>413 ±283</td><td>341 (243- 438)</td></tr>
<tr><td>Vegetable (g)</td><td>196 ± 87</td><td>228 ± 127</td><td>218 ± 104</td><td>332 ± 149</td><td>104 (47-162)</td></tr>
<tr><td>Total (g)</td><td>258 ± 131</td><td>377 ± 210</td><td>319 ± 183</td><td>1001 ± 313</td><td>630 (510-751)</td></tr>
<tr><td>No. of servings/d</td><td>1.9 ± 0.7</td><td>2.4 ± 0.9</td><td>2.1 ± 1.0</td><td>7.1 ± 1.4</td><td>4.7 (4.2-5.2)</td></tr>
<tr><td>Total fat (% MJ)</td><td>36</td><td>35</td><td>36</td><td>32</td><td>-3.5 (-6.1 to -1.0)</td></tr>
<tr><td>Fibre (g)</td><td>17</td><td>19</td><td>19</td><td>25</td><td>6.2 (2.4- 10.0)</td></tr>
</table>
* Between treatment and control groups at week 4 adjusted for age, sex and baseline value.

Plasma lipid concentrations (mmol/L) during study period (mean ± SD):
<table>
<tr><th>Lipid</th><th>Baseline Control</th><th>Baseline Treatment</th><th>Week 8 Control</th><th>Week 8 Treatment</th><th>Adjusted Difference (95% CI)[§]</th></tr>
<tr><td>TC</td><td>5.13 ± 0.97</td><td>4.72 ± 0.98</td><td>4.94 ± 1.05</td><td>4.64 ± 0.94</td><td>-0.02 (-0.29- 0.25)</td></tr>
<tr><td>LDL</td><td>3.18 ± 0.85</td><td>2.96 ± 0.92</td><td>2.98 ± 0.92</td><td>2.83 ± 0.85</td><td>0.02 (-0.23- 0.27)</td></tr>
<tr><td>HDL</td><td>1.28 ± 0.38</td><td>1.19 ± 0.38</td><td>1.36 ± 0.41</td><td>1.24 ± 0.41</td><td>-0.08 (-0.15- 0.001)</td></tr>
<tr><td>TG</td><td>1.48 ± 0.55</td><td>1.26 ± 0.81</td><td>1.34 ± 0.50</td><td>1.26 ± 0.68</td><td>0.06 (-0.12- 0.24)</td></tr>
</table></td>
<td>Concentrations of lipids and lipoproteins remained unchanged throughout the study.

The percentage of energy from total and saturated fat was lower in the intervention group.

- healthy volunteers
-good study- does not support</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Design</th><th>Diet component</th><th>Subjects</th><th>Duration</th><th>Diet method</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>Joshipura et al, 2001</td>
<td>Prospective cohort

Nurses'Health Study and Health Professionals' Follow-up Study

(A)</td>
<td>Whole diet based on repeated FFQ

including 15 fruit items and 28 vegetable items plus potatoes

Did not include potatoes, tofu and soybeans, dried beans, lentils as vegetables</td>
<td>84 251 women age 34-59 years, beginning in 1976 to 1994

42 148 men age 40-75 years beginning in 1986 to 1994</td>
<td>Women followed for 14 years
Men followed for 8 years

Primary endpoints_nonfatal MI or fatal CHD</td>
<td>Repeated FFQ in 1980, 1984, 1986 and 1990 for women;

1986 and 1990 for men using similar FFQ

126 item questionnaire

Average daily intake of each fruit and vegetable item for each participant was determined, then average daily intake of individual food items was used to compute total fruit and veg intake, and composite groups.</td>
<td>Multivariate Relative Risk for CHD, by Fruit and Vegetable Intake
<table>
<tr><th>Composite item</th><th colspan="5">Relative Risk for CHD per Quintile of Intake (95% CI)
1 2 3 4 5</th><th>1-srv/d increase in f&v</th></tr>
<tr><td>All fr &veg
-f
-m
-pool</td><td>
1.0
1.0
1.0</td><td>
0.91
1.01
.95
(0.84-1.08)</td><td>
0.88
0.95
0.92
(0.80-1.05)</td><td>
0.86
0.87
0.86
(0.75-0.99)</td><td>
0.80
0.80
0.80
(0.69-0.93)</td><td>
0.97
0.96
0.96
(0.94-0.99)</td></tr>
<tr><td>All fr
-f
-m
-pool</td><td>
1.0
1.0
1.0</td><td>
0.84
0.91
0.87
(0.76-0.99)</td><td>
0.95
0.94
0.94
(0.83-1.08)</td><td>
0.76
0.86
0.81
(0.70-0.93)</td><td>
0.85
0.74
0.80
(0.69-0.92)</td><td>
0.95
0.92
0.94
(0.90-0.98)</td></tr>
<tr><td>All veg
-f
-m
-pool</td><td>
1.0
1.0
1.0</td><td>
0.89
0.96
0.92
(0.81-1.04)</td><td>
0.92
1.00
0.96
(0.84-1.09)</td><td>
0.80
0.94
0.86
(0.73-1.02)</td><td>
0.77
0.87
0.82
(0.71-0.94)</td><td>
0.93
0.97
0.95
(0.92-0.99)</td></tr>
<tr><td>Green leafy vg
-f
-m
-pool</td><td>
1.0
1.0
1.0</td><td>
0.92
0.89
0.90
(0.79-1.03)</td><td>
0.89
0.93
0.91
(0.80-1.03)</td><td>
0.74
0.89
0.81
(0.68-0.97)</td><td>
0.69-0.76
0.72
(0.63-0.83)</td><td>0.70
0.84
0.77
(0.64-0.93)</td></tr>
</table>
Adjusted for age, smoking, alcohol, family history of MI, BMI, vitamin supplement use, vitamin E use, physical activity, aspirin use, 2-yr follow up period, presence of hypertension, kcal intake, HRT</td>
<td>Strong suppport for modest but significant risk reduction associated with highest quintile of intake for all fruit and veg, vs lowest and particularly for green leafy vegetables and vitamin C-rich fruits and vegetables (not shown in this table).</td>
</tr>
</table>

V. Quality Assurance

The completion of this segment is <u>not</u> required for a health claim that is applicable to a dietary pattern or a class of foods (e.g. fruits and vegetables).

If the product is an "altered food" for the purpose of health claim authorization, i.e., the processing of the product involves the addition to the food or other modification in the food of a bioactive substance to achieve the claimed effect not regulated in the *Food and Drug Regulations*, complete:
Parts A-F

Otherwise, complete:
Parts B-F

The following parts are included:
❒ Part A: Bioactive substance added to or otherwise modified in the food - analysis and control
❒ Part B: The food bearing the claim - manufacturing and analysis
❒ Part C: Stability of finished food
❒ Part D: Methods of analysis used in testing bioactive substance and finished food
❒ Part E: References
❒ Part F: Supporting documents

<u>Part A - Bioactive Substance Added to or Otherwise Modified in the Food - Analysis and Control</u>

Refer to Glossary of Terms, section 2, Part I of this document for the meaning of "bioactive substance" for the purpose of health claim authorization.

1. Indicate which of the following applies:

❒ The bioactive substance is purchased from a supplier; information requested under paragraphs (2)-(3) is provided.

❒ The bioactive substance is produced by the manufacturer of the finished food or a contract third-party; information requested under paragraphs (2)-(4) is provided.

2. Justifications for the specifications - provide a brief summary of the justifications for the specifications of raw materials, including bioactive substances described in segment II.

3. Identity verification - outline how the identity and property of the bioactive substance is verified.
(a) provide analytical data collected on the substance and the statistical analysis conducted to indicate compliance with specifications; include certificate of analysis from supplier where applicable
(b) the analytical data should include all types of analysis to verify the identity, critical specifications and biological activity (where applicable) of the bioactive substance
(c) include sampling plan, frequency of analysis for the analytical data provided
(d) where outside laboratory services were used in the analyses, provide the name(s) of the laboratory services

4. **Quality control procedures in the manufacturing of the bioactive substance** - describe the quality control procedures used throughout the processing of the bioactive substance.
(a) identify the critical control points and justify their selection and the acceptance criteria used
(b) describe any process validation and/or evaluation conducted
(c) attach relevant manufacturing documentation as necessary

Part B - The Food Bearing the Claim - Manufacturing and Analysis

1. **Indicate which of the following applies:**

❒ The food is not an altered food and the bioactive substance responsible for the claimed effect is known or adequately defined; information requested in paragraphs (2) is provided.

❒ This applies to a nutrient or other food component that is the subject of a claim (e.g. calcium in a calcium-osteoporosis claim for a dairy product)

❒ The food is not an altered food and the bioactive substance responsible for the claimed effect is not known or adequately defined; an appropriate proxy indicator has been used; information requested in paragraphs (2) - (4) is provided.

❒ The food has been modified by the addition of a bioactive substance or the alteration of a bioactive substance naturally occurring in the food; information requested in paragraphs (2), (4)-(5) is provided.

2. **Analysis of bioactive substance in the finished food** - outline how the level of the bioactive substance in the finished food is verified.
(a) provide analytical data collected on the levels of the bioactive substance in the finished food and the statistical analysis conducted to indicate compliance within specifications or acceptable variability
(b) where applicable, the analytical data should include biological activity of the bioactive substance as found in the food matrix
(c) include sampling plan, frequency of analysis for the analytical data provided
(d) where outside laboratory services were used, provide the name(s) of the laboratory services

3. **Justification of proxy indicator** - summarize the justification for the proxy indicator used. There should be a quantifiable relationship between the amount of the proxy indicator in the food and the claimed effect.

4. **Quality control procedures in the manufacturing of the finished food** - describe the quality control procedures used throughout the processing of the finished food with respect to ensuring consistent levels of the bioactive substance in the finished food, including quality control procedures for the application of packaging and labelling.
(a) identify the critical control points and justify their selection and the acceptance criteria used
(b) describe any process validation and/or evaluation conducted
(c) attach relevant manufacturing documentation as necessary

Part C - Stability Studies on the Finished Food

Include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed packaging, shipping and storage conditions, retest date or shelf-life, where relevant. Stability data should support product safety and claimed effect for the entire duration of the product's shelf-life.

Part D - Methods of Analysis

1. Indicate which of the following applies:

❒ Established analytical method(s) were used in measuring the level of the bioactive substance or proxy indicator in the finished food, references are provided in Part E.

❒ Established analytical methods were used in assessing the identity and conformity with critical specifications of the bioactive substance, references are provided in Part E.

❒ New or modified analytical method(s) were used in measuring the level of the bioactive substance or proxy indicator in the finished food, information requested in paragraphs (2) and (3) is provided.

❒ New or modified analytical method(s) were used in assessing the identity and conformity with critical specifications of the bioactive substance, information requested in paragraphs (2) and (3) is provided.

2. Analytical procedure - describe the analytical procedure, including reference(s) if published.

3. Validation process - describe the validation process, including the use of reference materials.

Part E - Complete Reference list

List the references cited in Parts A, B, C and D
Provide two copies of all references cited.

Part F - Supporting Documents

If not already included as part of the submission, the following documents may be requested as part of the health claim review process or during an inspection. Indicate which of the following documents are available when requested for verification purposes.

	Included	Available
Good manufacturing practices guidelines	❒	❒
Quality assurance manual	❒	❒
Record retention policy	❒	❒
Recall procedures	❒	❒
Ethical guidelines for research involving human subjects	❒	❒
Other, specify _____	❒	❒
_____	❒	❒

The undersigned hereby certifies that the manufacturing and all aspects of testing of the finished food, and of the bioactive substance where applicable, are conducted in accordance with the documentation/guidelines provided in this submission or available upon request.

Senior executive officer

Name: _____

Signature: _____

Date: _____

Medical or scientific director

Name: _____

Signature: _____

Date: _____