Health Canada Santé Canada

CONSULTATION DOCUMENT

Standards of Evidence for Evaluating Foods with Health Claims:

A Proposed Framework

Bureau of Nutritional Sciences
Food Directorate
Health Protection Branch
Health Canada

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Canada

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PREFACE

The growing scientific support for, and consumer and industry interest in, the role of diet in health and disease has prompted Health Canada to review its policy on health claims for foods. After a two-year consultation, Health Canada published a policy decision on the subject in November 1998. Subsequently, the Food Directorate of Health Canada initiated a project to develop standards of evidence and a framework for evaluating food products with health claims.

While the protection of public health interests and consumer confidence in health claims on foods must be the primary objectives in developing standards of evidence, other implementation issues such as feasibility and practicality also have to be considered. This Consultation Document outlines general requirements for the type and quality of evidence required for new health claims for foods and a framework for evaluating such evidence. The principles and the rationale for the proposed standards are described. This paper will form the basis of a subsequent Guidance Document which will provide more detailed information pertinent to the preparation of submissions for health claims for foods.

To assist us in our next steps in developing a credible system of health claim review in Canada, we are particularly interested in receiving comments on two key areas outlined below. Respondents are asked to provide a rationale for any changes they would like to suggest for the proposed framework. Questions provided here are intended to facilitate comments regarding these key areas.

1. The proposed Standards of Evidence and Evaluation Framework

General

- Are there elements missing from the proposed framework?
- Keeping in mind the primary objectives of developing standards of evidence and the practical considerations, how can the proposed framework be improved?

Specific to Claim Validity

- Are there other considerations we should give to classifying the strength of evidence?
- Are there ways we could improve the application of the strength-of-evidence approach to claim validity?

2. Guidance Document

- What elements of the evaluation framework require clarification and elaboration in the Guidance Document?
- What types of guidelines would you find helpful to be included in the Guidance Document?

Other areas for which we are seeking input are noted in the respective sections of this document (sections 5.1.3, 7.3 and 8.1). Individuals and organizations wishing to comment on these and other aspects of the document are asked to respond **by August 31, 2000** to:

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Please include in your response the following identification information:
Respondent Name:
Organization (where applicable):
Address:
Affiliation: ❍ Academia/Education
❍ Industry/Consulting
❍ Government
❍ Non governmental organization
❍ Consumer
❍ Health/Disease
❍ Professional
❍ Other (please specify)

Indicate if comments represent those of ❍ an individual or ❍ an association/group

Please note that in keeping with our commitments to an open and transparent process, comments made to Health Canada as part of this consultation will not be considered confidential. However, the names of the individuals sending comments will be protected pursuant to the *Access to Information Act*.

EXECUTIVE SUMMARY

The Health Canada policy released in November 1998, allowing a broader range of health claims for foods than what is permitted currently, has the potential to enhance public health. It is intended to provide more opportunities for communicating to consumers the role of diet in health and disease risk reduction. It also provides incentives to industry for formulating functional food products to achieve specific health benefits. For functional foods to realize their potential, they must be safe and their health benefits must be substantiated. A reliable system of health claim review will assure Canadians that only credible, evidence-based claims about the health benefits of diets, foods or food substances will be permitted in Canada. Clear guidelines on evidence requirements are also important in facilitating the development and testing of functional foods with *bona fide* health benefits by researchers and industry.

To achieve these objectives, it is essential that foods with health claims be supported by appropriate evidence with respect to *product safety* and *efficacy*, as well as by *quality assurance* of the product and testing methods.

The standards of evidence and framework for evaluating foods with health claims outlined in this Consultation Document and (summarized in Figure 1 (page 8) will form the basis of a subsequent Guidance Document that will provide more detailed information pertinent to the preparation of submissions for health claims for foods.

This Consultation Document includes an overview of:

1) **Considerations in the development of an evaluation framework for foods with health claims**. Foods are a complex matrix of nutrients and other bioactive substances that may influence health. Because of the potential of health claims on foods to change food consumption patterns and exposure to bioactive substances, the evaluation of foods with health claims must be based on a high standard of evidence. Assessing the safety of whole foods and the validity of health claims is a challenge. In developing a framework for evaluating foods with health claims, the protection of public health interests and consumer confidence must be the primary objectives. Other considerations include economic factors, trade issues and fairness among different product categories with respect to the evidence requirements for similar claims.

2) **The three types of evidence required.**

- ***Product safety***. Foods are generally intended for *ad libitum* consumption by the general public, therefore, a high standard for product safety should provide a reasonable assurance of no adverse health effects. All foods with health claims will be subject to at least a basic evaluation to assess the potential for nutritional and toxicological impacts in the context of the intended form and use of the product. A basic assessment takes into account the fact that a health claim is intended to promote increased consumption of the food carrying the claim. This evaluation is particularly pertinent to those foods that have been modified with respect to the level or bioavailability of bioactive substances. The basic evaluation will take into consideration anticipated exposure to the food and bioactive substance from all sources. Further safety evaluation, where required, will be proportional to the novelty and the

uncertainty regarding the safety of the product.

- ***Claim validity***. The validity of a health claim is determined by demonstration of product efficacy and effectiveness. These depend on establishing an etiologic link between the desired effect and the consumption of the food or bioactive substance, at the recommended level of intake in the target population that will most likely benefit. A 3-part evidence-based evaluation framework is proposed, that considers totality of evidence, causality, study quality, relevance and generalizablity, systematic evaluation and level of certainty by:

    1) evaluating the strength of evidence supporting a causal relationship between the food or the bioactive substance and the claimed benefit using a systematic approach;
    2) determining if the strength of evidence is at the required level to support the claim, taking into consideration the nature of the claim; and by
    3) determining if the total evidence provides the required information for characterizing the relationship between the claimed benefit and the food or the bioactive substance.

Special considerations are given to the measurement of beneficial health effects and food intake, with an emphasis on the criteria for validating surrogate disease endpoints and biomarkers of food intake.

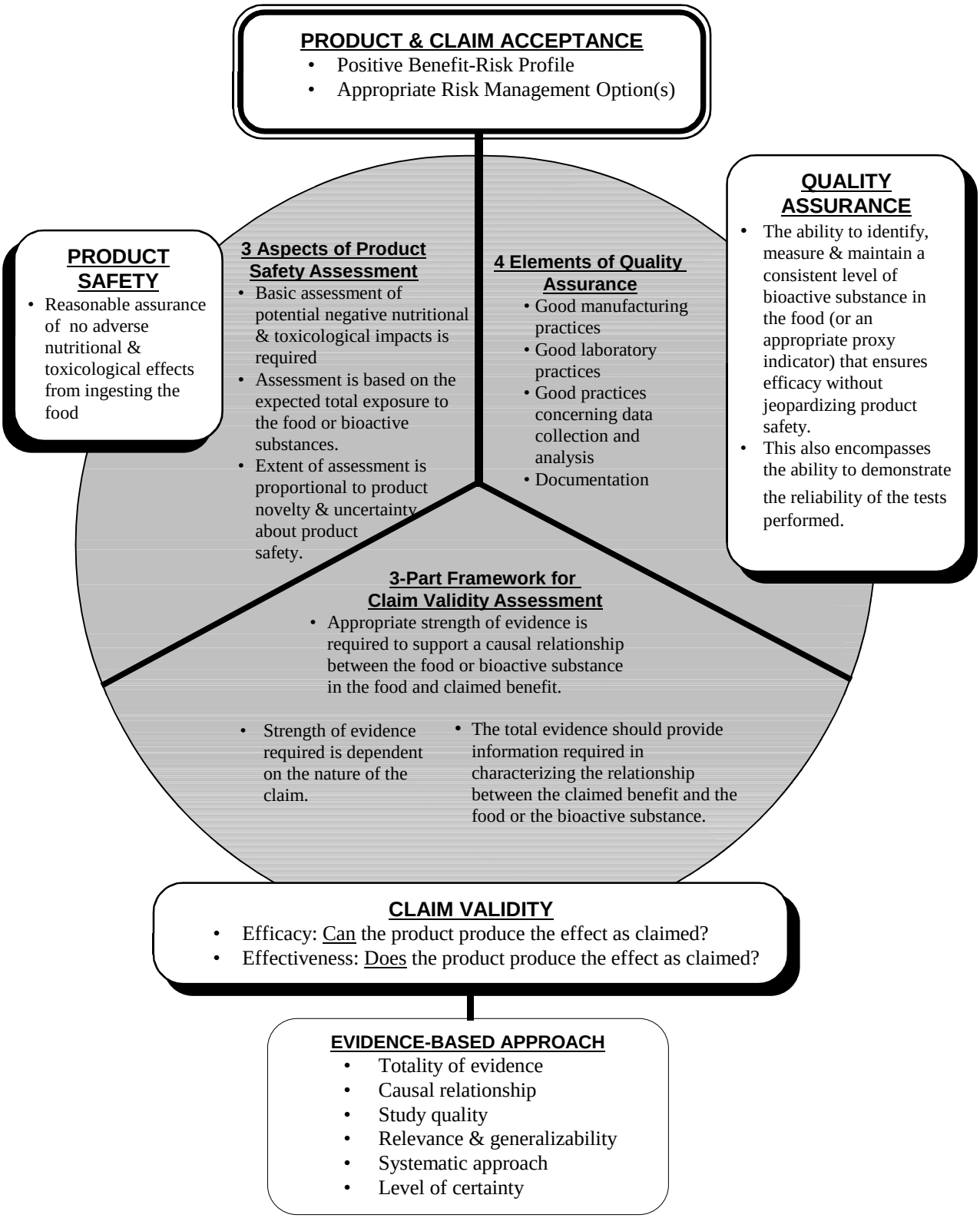
- ***Quality assurance***. For foods bearing health claims, quality assurance relates to the ability to identify, measure and maintain a consistent level of the bioactive substance (or an appropriate proxy indicator) in the product that ensures efficacy without jeopardizing product safety. Quality assurance also encompasses the ability to demonstrate the reliability of the tests performed. In evaluating foods bearing health claims, there are four main elements of quality assurance:

    1) Good manufacturing practices (GMPs)
    2) Good laboratory practices (GLPs)
    3) Good practices concerning the collection and analysis of human data - clinical and/or epidemiological practices (GCPs/GEPs)
    4) Documentation

3) Evaluation process. The evaluation process includes screening, detailed evaluation, benefit-risk assessment and consideration of risk management options. Considering the complexities in evaluating foods with health claims, Health Canada proposes that, at least initially, only claims (regardless of type) with the potential for major public health benefit and for which there is sufficient acceptable scientific evidence, be given priority for evaluation.

4) Issues related to the implementation of the new policy on health claims for foods. These include: developing criteria for health claim prioritization, developing guidelines for evaluating specific health outcomes, keeping claims current, validating claims approved in other jurisdictions and establishing mechanisms for evaluating and approving claims.

Figure 1
Standards of Evidence for Evaluating Foods with Health Claims: A Proposed Framework



1. OBJECTIVES AND BACKGROUND

1.1 Purpose of Consultation Document

The purpose of this Consultation Document is to provide a common basis for input from interested parties on the standards of evidence and a framework for evaluating food products with health claims to be marketed in Canada. This document proposes general requirements for the type and quality of evidence required for new health claims for foods and outlines the background, principles and rationale used in their development. The input from the consultation will be used in the development of a subsequent Guidance Document which will detail the evidence requirements and provide guidelines for preparing submissions supporting new health claims on foods.

The standards of evidence and evaluation framework in this Consultation Document are intended to apply to all food products represented explicitly or implicitly as having specific health benefits (other than as a source of nutrients). In other words, this applies to products sold in food form (as whole foods and drinks), including those to which bioactive substances have been added to enhance the health attributes of the food and those that have been modified by other means.

Biological role claims for recognized nutrients currently permitted by sections B.01.311, D.01.006 and D.02.004 of the *Food and Drug Regulations* are excluded from the scope of health claims covered in this document.

1.2 Background

1.2.1 Policy Development

The scientific understanding of the relationships between diet and disease risk reduction and development has progressed tremendously in the past decades. With the growing scientific evidence supporting the important role of diet in modifying the risks of some chronic diseases, there is increasing consumer and marketing interest in nutrition and health. However, the current *Food and Drugs Act* restricts the nature and extent of health information that may be communicated on the food label and in advertising. In the Fall of 1996, the Therapeutic Products Programme and Food Directorate of Health Canada initiated a joint project to develop a policy framework for health claims on foods. The policy decision was released in November 1998 in the *Policy Paper on Nutraceuticals/Functional Foods and Health Claims on Foods* [http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/ffn.html].

The policy decision is stated in the 1998 Policy Paper as follows:

> *"Structure/function and risk reduction claims for foods should be permitted while all other products claiming to cure, treat, mitigate or prevent illness should continue to be regulated as drugs."*

1.2.2 Policy Implementation

In implementing the policy decision for health claims on foods, the Food Directorate is taking a three-part approach:

- ❑ Adoption, where applicable, of certain diet-based disease risk reduction claims currently approved in the U.S. under the *Nutrition Labeling and Education Act*[a].

- ❑ Development of standards of evidence for evaluating foods with new health claims and a Guidance Document which will provide more detailed information regarding the preparation of submissions for health claim review.

- ❑ Development of a regulatory framework for foods with new health claims.

The focus of this Consultation Document will be on the development of standards of evidence for evaluating foods with new health claims.

1.3 Objectives of Developing Standards of Evidence

The 1998 Health Canada policy on health claims for foods is intended to provide more opportunities for communicating to consumers, the role of diet in health and disease risk reduction, thus enhancing public health. It also provides incentive for industry to formulate food products to achieve health benefits. Research is increasingly identifying bioactive substances and other conventional nutrients in foods which have beneficial effects on health. This has led to the term "functional foods", a short form for conventional or modified foods that are represented or demonstrated to have specific or special health benefits, in addition to providing basic nutrients and nutritional benefits.

For functional foods to realize their potential in benefiting human health, certain challenges must be met.

- Functional foods must be safe in terms of intended use and their impact on the total diet.
- Claims must be well substantiated. If the industry is to flourish, health claims must be valid. If the claims are discredited, the industry will suffer.
- Food- or substance-specific health claims linked to specific diseases or adverse health conditions should not undermine the importance of the total diet, the interrelationships among dietary factors and effects on other health conditions or outcomes.

Therefore, the objectives of developing standards of evidence for foods with health claims are:

- to ensure that claims regarding the specific health benefits of foods are based on the best scientific evidence that is likely to stand the test of time;

[a] An update on the progress regarding the adoption of certain U.S. health claims is available on the Health Canada website: http://www.hc.sc.gc.ca/food-aliment/english/subjects/health_claims.

- to provide reasonable assurance that foods with health claims do not have negative nutritional and health impacts at recommended levels of intake; and
- to contribute to a credible system of managing the use of health claims on foods in Canada.

2. GUIDING PRINCIPLES FOR MAKING A HEALTH CLAIM ON FOODS

Given the challenges noted above, it is important that the use of health claims on foods be guided by sound principles in order to balance the interests of public health, consumer protection and consumer choice. In developing the guiding principles for health claims for foods, rules established by regulatory agencies and codes of practice proposed by non-governmental organizations in several jurisdictions were compiled and common features are outlined below. These principles will guide the development of regulations and guidelines for health claims for foods in Canada in accordance with the health and safety provisions in applicable legislation. They will also provide guidance regarding the approval of products with health claims and the prioritization of public resources for their review.

Health Claim Statements

- Must be supported by acceptable scientific evidence.
- Must be truthful and not misleading, consistent with the scope and the nature of the scientific evidence.
- Must not conflict with national health and nutrition policies and guidelines.
- Must not imply cure, treatment or prevention of diseases or adverse health conditions.

Foods Bearing Health Claims

- Must be safe for consumption as intended.
- Must have appropriate nutrient composition to avoid promoting consumption of foods that might increase risk factors for certain diseases or that have little nutritional value.
- Must provide the claimed benefit in amounts that can reasonably be consumed as part of a normal diet.

Context and Labelling

- Health claims, and risk reduction claims in particular, should be made in the context of the total diet to help consumers make informed choices in adopting a healthy diet.
- When a health claim is made, the label must also provide adequate information to allow users to assess the product for themselves and to facilitate safe use of the product, including standardized nutrition labelling.

Health Relevance

- The health benefit of the product should be meaningful and relevant to the target population, and sustainable under typical or intended conditions of use.
- Priority may be given to products intended to address conditions of public health significance.

3. DEVELOPMENT OF AN EVALUATION FRAMEWORK

3.1 Key Components

Three types of evidence are required in evaluating foods with health claims: product safety, claim validity, and quality assurance. Details on these three types of evidence are discussed in sections 4 to 6.

3.2 Considerations

3.2.1 Complexities of Foods

Foods are complex and present challenges in evaluating their effects on health.

- The exact nature and quantity of the bioactive substance in food responsible for the beneficial health effect of the food is not always known.
- The same food constituents in an extracted or purified form may have different physiological effects.
- As a biological entity, foods are subject to genetic and other natural variations affecting nutrient composition and other physico-chemical properties that may influence their effects on health.
- Foods are consumed as part of a diet and the consumption of certain foods may affect other aspects of the diet. Controlling the composition of the control and test diets is not always feasible for testing placebo vs. study effect.
- In identifying the specific food substance responsible for a given physiological effect, the use of a strictly controlled diet is required. However, such a testing method also raises the question of whether the health benefits observed under controlled dietary conditions can be maintained outside an experimental regimen.

This complexity makes it impossible to state *a priori* that the evidence required for foods with health claims will be lower or higher than that prescribed and predetermined for the approval of a new drug or a supplement product. However, the standards of evidence for evaluating foods with health claims must be high because of the potential of health claims to change food consumption patterns and exposure to bioactive substances that influence health.

3.2.2 Other Considerations

In developing an evaluation framework for health claims for foods, the protection of public health interests and consumer confidence must be the primary objectives. However, other factors are

also taken into consideration. Standards of evidence should:

- be practical and flexible enough for industry to develop useful products at reasonable costs;
- not be more trade-restrictive than necessary to fulfill legitimate national objectives, including the protection and promotion of human health;
- ensure a level-playing field across competing product categories and prevent the situation whereby manufacturers could bypass the more rigorous review process for one product category in favour of another that has less rigorous requirements.

4. PRODUCT SAFETY

4.1 Terms of Reference

For the purposes of evaluating food products with health claims, product safety will refer to the reasonable assurance that no adverse nutritional and toxicological effects would result from the ingestion of such products. This relates to adverse effects on the structure or function of the human body due to: a direct toxic effect of substances in the foods; adverse nutritional and metabolic effects resulting from component interactions or increased intake; or toxic effects of metabolic imbalance with respect to enzyme substrate depletion and accumulation.

For food products and ingredients that require premarket assessment of safety under applicable regulations (i.e., infant formulas, novel foods and food additives), current regulations will apply regardless of whether health claims are made. This means that for food products that are subject to control under these regulations, premarket safety assessment will precede any evaluation of their potential health benefits, if health claims are made for these products.

This discussion will focus on the assessment of those aspects of product safety that apply particularly to food products represented to have specific health benefits. These products are likely to fall into several broad categories: conventional foods containing bioactive substances; modified foods to which a substance has been added or removed; modified foods with one or more constituents whose nature or bioavailability has been altered; and new foods produced from *de novo* synthesis.

This discussion will not include safety concerns resulting from quality assurance issues (i.e., microbiological hazards, contaminants and other concerns related to product specifications, manufacturing and food handling practices).

4.2 Guiding Principles

1) All products for which health claims are made will be subject to at least a basic evaluation to assess the potential for nutritional and toxicological impacts in the context of the intended form and use of the product containing the bioactive substance. This will take into consideration anticipated exposure to the food and the bioactive substance from all sources.

- Although safety may be presumed for food products, including conventional foods and bioactive substances that have been consumed in Western diets as foods for extended periods of time, based on long usage and experience, the use of a health claim may promote increased consumption of the food or bioactive substance and may warrant a reassessment of exposure level.

- For functional foods to impart health benefits beyond basic nutrition, they must contain sufficient levels of bioactive substances. Some bioactive substances may also have adverse effects at high levels of intake.

- When there is increased consumption of bioactive substances from multiple sources, aggregate and cumulative effects could pose new health concerns related to dose and previously unknown interactions. Where warranted by safety concerns, there will be a need to establish a toxic level or upper safe limit on the level of addition of bioactive substances and the range of foods to which such substances may be added.

2) Because foods are generally intended for *ad libitum* consumption by the general public, a high standard for product safety should provide a reasonable assurance of no adverse health effects.

- This differs from the situation with pharmaceuticals, where some adverse effects may be tolerated because the therapeutic benefits in an unwell group of individuals are considered to outweigh the risks associated with the product.

- However, special benefit-risk considerations may be given to a food product that may not be appropriate for *ad libitum* consumption by the general public, but will provide specific health benefit to an identifiable target population based on compelling evidence.

3) Many modified foods for which health claims are being sought, will meet the description for novel foods (*Food and Drug Regulations* Part B, Division 28). Such foods will be treated in the same manner as novel foods for the purposes of establishing product safety.

- Novel foods include: foods resulting from a process that has not been previously used for foods and that causes the food to undergo a major change[b]; foods without a history of safe use as a food; and foods derived from organisms which have been genetically-modified to add, remove or alter expression of characteristics.

4.3 Data Requirements

The information that will be required of all foods with health claims to assess the potential for safety concerns will include: a) the characterization of the product, including composition, source, effects of processing, directions for preparation and description of the modification from a traditional

[b] Major change has been defined as placing "the modified food outside the accepted limits of natural variations for that food in regard to the composition, structure or nutritional quality of the food or its generally recognized physiological effects ..."

reference product, if applicable; b) proposed target groups; c) history of safe use or previous human exposure; d) dietary significance and physiological role, including the identification of susceptible groups and potential interactions with nutrients and other food components; e) current exposure, anticipated use and exposure from different sources; f) relation of current and expected exposures to current dietary recommendations or targets; g) metabolic fate of the bioactive substance, including a microorganism; h) relevant safety issues based on the foregoing information.

The above information will be used to determine what further data will be required to complete a product safety assessment. The types of data required will be established on a case-by-case basis according to the safety issues identified for the particular product. Information on metabolic disposition, physiological role, susceptible groups, and possibly upper safety limits, may be generated in the process of conducting studies to establish health claims, and can be used as part of the product safety assessment. Epidemiological data, where applicable, will also be included as part of the assessment.

For foods which have been modified by the addition of a bioactive substance, a 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. It is recognized that challenges exist in testing whole foods at high doses.

Difficulties in the interpretation of the data may be encountered due to nutritional imbalance. For example, high doses of long chain polyunsaturated fatty acids are associated with adverse effects when administered in the absence of adequate intake of antioxidant vitamins, in particular, vitamin E. Therefore, information on the physiological role of a bioactive substance will be useful in contributing to an understanding of nutritional interactions, in interpreting the results of safety studies, and in establishing conditions under which the bioactive substance might be used.

When more experience is gained in performing safety assessments of modified foods, it may be possible to establish criteria for categorizing these foods into a safety assessment scheme. Such a scheme would standardize the kinds of data required to establish safety for a particular category.

4.4 Proposed Framework for Evaluating Evidence Supporting Product Safety

To provide reasonable assurance that no adverse health effects will result from the ingestion of food products promoted for specific health benefits, the type and amount of data required to support product safety will be proportional to the novelty and the uncertainty regarding the safety of the product.

1) For a conventional food with a history of presumed safety, data will be required to demonstrate that such a food can be incorporated at the recommended level in the diet by the target population under typical conditions of use. Their inclusion in the overall diet should satisfy nutrient and nutrition recommendations without causing dietary and nutritional imbalance.

2) For modified foods (such as those described under Terms of Reference), evidence should also

demonstrate that their inclusion in the diet at the recommended level will not induce dietary and nutritional imbalance. In addition, the following information will be required:

- Evidence from various sources (including human and animal experimental studies) of acceptable quality and relevance should support the absence of adverse health effects (negative data). Conflicting positive data suggesting the presence of adverse health effects must be explained.

- Since human data will be required to demonstrate health benefits for products with health claims, available human data will also be assessed for their relevance for supporting product safety. Where new human studies are required to confirm the absence of adverse health effects, such data will be given the most weight.

- Relevant epidemiological data, where available, will also be considered as part of the safety assessment. Since epidemiological evidence may not have sufficient power to detect a small increase in risk unless specifically designed for such a purpose, negative data from epidemiologic studies may be used to derive upper limit estimates for safe use as a check against the estimates derived from positive data from experimental studies.

- Where available evidence suggests that adverse health effects in humans may be expected at a certain level of intake of the product under evaluation, depending on the nature of the adverse health effects, it may be appropriate to establish an upper safe limit of intake. This limit will be used in assessing the margin of safety in the expected exposure to the food and the bioactive substance in both the target and general populations. This will also 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.

3) For novel food products produced from *de novo* synthesis or without history of safe use as a food, *in vitro* and animal studies can be used to screen and assess the acceptability of testing the product in humans and to provide supporting evidence to human data with respect to mechanism of action. Postmarket surveillance may be required to ensure long-term safety, in addition to meeting the above safety requirements.

5. CLAIM VALIDITY

5.1 Terms of Reference

The November 1998 policy on health claims recommended that structure/function claims and risk reduction claims be permitted for foods. These claims may be generic or product-specific. The following sub-sections (5.1.1 and 5.1.2) will outline the relevance of these terms with respect to evidence requirements.

5.1.1 Structure/Function and Risk Reduction Claims

The following descriptions of structure/function and risk reduction claims in the context of

food products are based on those provided in the November 1998 Policy Paper:

A ***structure/function health claim*** describes the effect of a food or a diet on a structure or physiological function in the human body[c].

A ***risk reduction health claim*** describes the relationship between the consumption of a food or a diet and the reduction in the risk of developing a chronic disease or abnormal physiological state, by significantly altering a major risk factor or factors recognized to be involved in its development.

From a scientific perspective, maintaining normal physiological functions and reducing the risk of disease development may be considered as a continuum. With respect to the key elements of an evidence-based approach to evaluating health claims, such as causality, relevance and generalizability, there is little justification for distinguishing the evidence required for these claims on a global basis. Therefore, evidence requirements will be determined, in part, by the nature of the claim on a case-by-case basis (details in section 5.4).

5.1.2 Generic and Product-Specific Claims

The November 1998 Policy Paper described generic and product-specific claims as follows:

A ***generic health claim*** is a claim that may be applied to any food or food product, provided that it meets the criteria for the claim.

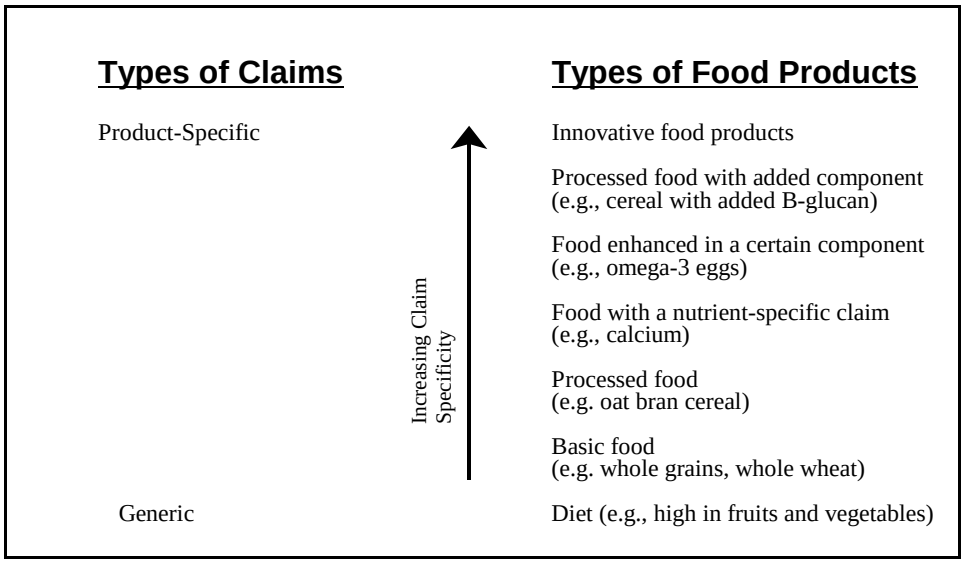
A ***product-specific health claim*** is a claim that is made for a proprietary product. The claim cannot be generalized to other similar products unless acceptable supporting evidence is provided.

While these two terms delineate two categories of claims, they in fact portray a broader spectrum of products that form a continuum, increasing in specificity from food groups or dietary patterns, to innovative proprietary products by virtue of unique formulation and/or processing (Figure 2).

With respect to evidence requirements, the specificity of the product in the claim will be considered in determining the type of evidence required (section 5.4).

[c] A therapeutic claim pertaining to the cure, treatment, mitigation or prevention of illness is not permitted as a structure/function claim for foods.

Figure 2
Types of Claims and Types of Food Products



The issue of product-specific claims has been raised as a means of encouraging industry research and development in generating the required evidence for health claims. In this regard, a 3-tier classification has been suggested:

- Claims based on diet or food groups
- Food- or substance-specific claims based on a specific food or substance, including a generic commodity, an ingredient or a nutrient
- Product-specific claims (i.e., a claim specific to a proprietary product)

Table 1 and the explanatory notes below are intended to clarify the distinctions and the relationships among the type of claim, requirement for product-specific studies and the basis for health claim authorization.

Table 1
Relationships between the Type of Claim, Requirement for Product-Specific Studies and the Basis for Claim Authorization

	Claims based on Diet or Food Groups	Food- or Substance-Specific Claims	Product-Specific Claims[a]
Requirement for Product-Specific Studies[b]	Not applicable	Generally required	Required in all cases
Basis for Claim Authorization	Meet pre-established criteria[c]	Meet pre-established criteria, or product-specific authorization	Product-specific authorization

[a] Product-specific claims do not imply health claim exclusivity (i.e., preventing other manufacturers to use a similar claim for a period of time), which is an issue beyond the scope of this document. However, it is envisioned that the requirement for product-specific studies in all cases of product-specific claims will provide appropriate substantiation for claim validity as well as the prevention of similar claims being used on untested products.

[b] It is expected that original product-specific studies will be required to support health claims on foods in most cases. This means that manufacturers will be required to provide product-specific data to support health claims, except under the following situations:

- When the claim is based on diet or a food group (such claims can be based on generic evidence, i.e., publicly available literature), or
- When the manufacturer can provide a rationale why the health benefit (efficacy) of the ingredient or the bioactive substance in the food is not affected by the food matrix and/or processing (e.g., minor formulation difference from a previously approved product).

Product-specific studies may also be required when the claim is based on a known nutrient (e.g., vitamin and mineral). In this case, the manufacturer will be required to provide evidence on nutrient bioavailability. The extent of the data required would depend on the nature and the form of the food or the nutrient and estimated total daily intake from all sources.

All data from product-specific studies will be subject to applicable laws regarding the protection of proprietary information.

The inclusion of product brand name as part of a health claim may be acceptable provided that it does not mislead consumers with respect to unique product benefit. Product-specific studies supporting the claim will be required and the evidence should also demonstrate that the product benefit is specific to the product specially formulated by the company.

[c] It would not be appropriate to restrict the use of diet- or food group-based health claims. These claims will be allowed on any food that meets the criteria established for the claim.

5.1.3 Product Efficacy and Effectiveness

There are two aspects to the validity of health claims:

- Can the product produce the effect as claimed (efficacy)?
- Does the product produce the effect as claimed (effectiveness)?

Efficacy measures the desired effect of a product under ideal conditions (such as those reproducible in short-term controlled diet trials with participants meeting study criteria), whereas effectiveness measures the actual effect of a product under average conditions among the population at large. Efficacy is likely to over-estimate effectiveness. For example, a macronutrient replacer may have a reduced energy value, however, it does not necessarily follow that the total energy intake will be reduced in the diet. When the macronutrient replacer also has adverse nutritional or health effects, this latter aspect of effectiveness becomes critical in balancing benefits and risks.[1-5]

It may be difficult to assess the effectiveness of a food product given the multitude of components and interactions in the diet. Depending on the nature and history of use of the product, the availability of existing data on the long-term health effects of a product may vary. For conventional foods or food ingredients with a long history of use, data on the product may be available from observational epidemiologic studies. For new products, uncontrolled trials simulating typical conditions of use may be appropriate for assessing product effectiveness. Models may be useful in estimating the effectiveness of an intervention strategy in disease risk reduction.[2] *We welcome suggestions on how flexibility in the evidence requirement for product effectiveness may be achieved.*

5.2 Process of Developing Standards of Evidence for Claim Validity

In order to gauge the level of evidence that would be appropriate for health claims for foods, we reviewed a selection of standards and classifications of level of evidence used in regulatory, preventive and clinical applications. The review of regulatory applications consisted of compiling and assessing the criteria and evidence requirements in other jurisdictions for health claims for foods,[6-15] drugs[16,17] and herbs and botanicals.[18-20]

We also reviewed the evidence-based approach to developing policy and guidelines for preventive health, clinical practice and health technology assessment.[4,21-25] The application of the evidence-based approach has evolved in the last decade. When combined with more recent refinements,[4,24,25] the application of systematic review[26-28] and explicit rules for decision making,[29,30] the evidence-based approach developed by the Canadian Task Force on the Periodic Health Examination can provide a basis for developing a framework for evaluating health claims for foods.

The following section (5.3) describes in brief the key elements that form the foundation of the evidence-based evaluation framework proposed in this document which is based in part on the model developed by the Canadian Task Force and modified by others. Section 5.4 describes the proposed 3-part framework for standards of evidence for evaluating the validity of health claims on foods [adapted from Gordis et al., Carruthers et al., Weed, CEPA/FPAC Working Group on Air Quality Objectives and Guidelines[24,31-33] and others assessed in the literature review[4,21-30]].

5.3 Evidence-Based Approach

5.3.1 Totality of Evidence

A health claim should be based on the totality of available scientific evidence pertinent to the subject of the claim. This ensures that all evidence relating to the claim is considered and not just the evidence that supports the claim. Scientific evidence includes evidence from well designed studies conducted in a manner which is consistent with generally recognized scientific procedures and principles.

No single study can be considered definitive in the understanding of diet-disease relationships.[34] Scientific evidence is built on the collective strength of different approaches, including chemical analysis, *in vitro* testing, animal studies, human experimental and observational studies.[35] Each approach contributes different types of information. Understanding and complementing the strengths and limitations of individual approaches will be key to developing strong evidence in support of a health claim.

5.3.2 Causality

A health claim, by linking a beneficial effect to a specific product or bioactive substance, implies that the beneficial effect is attributable to (caused by) the product or the bioactive substance. This requires evidence that supports a causative or etiologic link between the product or the bioactive substance and the health benefit, independent of other associated (confounding) factors.

Study designs vary in their ability to support a causal relationship between an agent or an intervention and a health outcome, with controlled experimental studies being the strongest. Observational studies (prospective cohort or case control) are more limited in demonstrating causal links because of the lack of random assignment to an intervention and lack of control for confounding variables.

To enhance the utility of observational epidemiologic data, Bradford Hill[36] developed criteria for supporting causal relationships at the population level from this type of evidence. The criteria, subsequently revised by others, have been widely accepted.[37] Coupled with expert judgement, conclusion about a causal relationship between a risk factor or an intervention and a health outcome can be made on the basis of the extent of adherence to the Hill criteria.

5.3.3 Study Quality

Study quality is complex and difficult to define. It could encompass the design, conduct, analysis, and external validity, as well as the reporting of a study.[38] When reviewing the evidence, consideration should be given to the completeness of the description of the measurement methods and their appropriateness, the intervention being evaluated, and the adequacy of the sample size and the characteristics of the sample studied.

5.3.4 Relevance and Generalizability

Relevance of the evidence refers to the applicability of the evidence to the purpose for which the evidence is used. For claims related to reducing the risk of certain diet-related diseases, or adverse health conditions in particular, the results from well conducted observational studies in humans of sufficient duration, including an adequate sample size, may be more relevant and generalizable than extremely well controlled metabolic studies of small sample size with highly selected individuals. Also, one cannot automatically extrapolate the results of a study involving subjects at a high risk of a disease to those at a low risk, and vice versa.[39] In the dietary context, the amounts of the food that must be consumed to achieve the health benefit claimed should be within the range of what is feasible and practical in the daily diet.

5.3.5 Systematic Approach

Given that health claims should be based on the totality of scientific evidence related to the subject of the claim, a systematic or organized approach to evaluating evidence similar to that used for other purposes has been advocated.[40] A systematic approach aims to ensure that all evidence relating to the research question is considered and that conclusions drawn from the best quality evidence are justified.[27-29,40]

The systematic approach to assessing scientific data consists of the following major steps:

- systematic review and/or meta-analysis of available data;
- applying rules or hierarchy of scientific evidence based on study design and types of data;
- applying criteria and weight for assessing causation.

In evaluating scientific evidence, it is important to define explicitly, at the outset, the specific questions to be answered and the outcomes to be assessed.[26,29] In making a decision on the evidence, assumptions based on theory, experience, or opinion, should be clearly articulated.[29]

A systematic approach can be applied to the evaluation of pre-existing evidence for supporting a health claim based on diet, a specific food, or a bioactive substance, which has been consumed for a sufficient length of time and by large population groups. However, even for an innovative or novel product, a systematic review of existing literature that guided the development of the new product for the targeted health effect will also be helpful in evaluating the validity of the product claim.

5.3.6 Level of Certainty

To ensure the credibility of health claims, the level of certainty regarding the validity of the claim should be high. This means that the evidence should be such that the validity of the claim is not likely to be reversed by new and evolving science, although the knowledge regarding the exact nature of the relationship between a substance or a product and a disease or a health condition may be refined over time.[15] Strong evidence is also needed to ensure that the claimed beneficial effect is meaningful, specific and relevant for the health of the intended population. This requires the health benefit to be measured using validated methodology.

It has been suggested that the strength of evidence required for structure/function or disease risk reduction claims could be lower or more flexible than that required for disease treatment claims with respect to the level of certainty of the desired health outcome. However, since the impact of these claims on population health could be potentially larger than that involving the use of therapeutic products by individuals, lower standards of evidence for the former cannot be justified. Moreover, unlike therapeutic products, which may be used for a limited period of time for a specific condition (often under medical supervision), products claimed to promote health or reduce disease risk will be used for a long duration (likely without professional guidance).

Health claims on foods can serve as a vehicle for conveying important health messages. Public confidence in health messages must not be undermined by health claims that are discredited because of inadequate evidence. Health claims are generally more specific with respect to the food, or the bioactive substance in the food and the health benefit than general nutrition recommendations. General nutrition recommendations aim at promoting general health through change in the overall dietary pattern whereas health claims assert specific health benefits resulting from the consumption of specific diets, foods or food substances. When linked to individual food products in labelling or advertising, the claims are intended to promote the consumption of the particular food carrying the claim. Therefore, the specificity of health claims would demand a higher level of evidence than general nutrition or diet messages.

5.4 Proposed 3-Part Framework for Evaluating Evidence Supporting Claim Validity

For assessing the validity of health claims for foods, Health Canada proposes a 3-part framework as follows:

I Evaluate the strength of evidence supporting a causal relationship between the food or the bioactive substance (agent) and the claimed benefit (outcome) using a systematic approach:

Step 1 Categorize the evidence by study design and study quality

Step 2 Assess the causal relationship between an agent and a health outcome

Step 3 Rate the strength of the evidence based on:
- study category (design) and study quality (from Step 1)
- the extent to which causality criteria are met (from Step 2);

II Determine if the strength of evidence is at the required level to support the claim, taking into consideration the nature of the claim;

III Determine if the total evidence provides the required information for characterizing the relationship between the claimed benefit and the food or the bioactive substance.

Part 1 Evaluate the Strength of Evidence Using a Systematic Approach

Step 1 Categorize the Evidence by Study Design and Study Quality

The following categorization of studies reflects, in general, the weight of evidence in descending order that will be given when assessing their strength in supporting a health claim, subject to the considerations explained in section 5.3 above. Within each category of study design, studies are listed in descending order of quality. Other essential criteria for study quality are listed at the end of this Step.

Essential Study Quality Criteria Based on Study Category

Experimental Studies in Humans: Trials

(Planned interventions with contemporaneous assignment of treatment and non-treatment.)

A Randomized, double-blind, placebo-controlled trials with sufficient power appropriately analysed

B. Randomized trials, but blindness not achieved

C. Non-randomized trials with good control of confounding variables, that are well conducted in other respects

D. Randomized trials, but with deficiencies in execution or analysis (insufficient power, major losses to follow-up, suspect randomization, analysis with exclusions)

E. Non-randomized trials with deficiencies in execution or analysis

Observational Studies in Humans: Prospective Cohort or Case-Control

A. Hypothesis specified prior to analysis, good data, confounders accounted for

B. As above, but hypothesis not specified prior to analysis

C. Post hoc, with problem(s) in the data or the analysis

Prospective cohort is generally considered a stronger design for supporting causality than case-control. The acceptability of evidence consisting primarily of case-control studies will be determined by the strength of the totality of evidence as judged by the extent to which the criteria listed in Step 2 are met.

Systematic Reviews

A. Avoidance of bias in the selection of studies (based on clearly stated inclusion and exclusion criteria)

B. Conclusion supported by the data and analysis presented

C. Comprehensive search for evidence

D. Assessment of publication bias (e.g., many small studies with positive effect)

E. Assessment of the validity of each cited study

A meta-analysis, if conducted, should also meet the criteria for systematic review listed above, in addition to ensuring that the rationale for combining data is justified.

Where opinions of experts or reports of expert committees are used in support of health claims, such reports should also meet the criteria for systematic review listed above. Where reports on a similar topic are available from more than one group of experts, there should be consistency in their conclusions and recommendations. Opinions of expert groups and published reports carry more weight than those of individual experts.

Other Experimental Studies

Animal and *in vitro* studies may be considered as providing supporting data. In some cases, where human data are limited, a well-accepted or validated animal model may be accorded appropriate weight. However, under no circumstances will animal or *in vitro* studies on their own be considered sufficient to support a relevant causal relationship between an agent and a beneficial health outcome in humans.

Other Observational Studies in Humans

Historical (retrospective) cohort, cross-sectional and ecological studies are generally inadequate in establishing a temporal relationship between an agent and a health outcome. Case reports, lacking proper control, are also inadequate as evidence for supporting health claims.

Other Essential Study Quality Criteria

Study quality issues that must be considered in reviewing the evidence are:

- the validity and appropriateness of the method for measuring the agent and outcome (including the validity of any biomarkers used),
- the completeness of the description of the study methodology,
- adequacy of the sample size,
- the degree to which the characteristics of the sample studied and of the intervention being evaluated have been described, and
- the representativeness of the study sample with respect to the larger target population

A study can be well designed and carried out in an exemplary fashion (internal validity), but if the sample studied is an unusual or highly selected one, the results may not be generalizable (external validity). This factor will be considered in determining whether the evidence supports the use of a health claim on a food product for a particular target population.

Step 2 Assess the Causal Relationship Between an Agent and a Health Outcome

These criteria can be applied within a study category and across study categories - the higher the congruence both within and across study categories, the stronger the total evidence.

Essential Causality Criteria

All essential criteria must be met for supporting health claims.

A. ***Consistency***: Single studies are rarely definitive. Study findings that are replicated in different populations and by different investigators carry more weight than those that are not. If the findings of studies are inconsistent, the inconsistency must be explained.

B. ***Magnitude of an effect*** (in experimental studies) ***or strength of an association*** (in observational studies): The magnitude of an effect is reflected in the change in the effect relative to the control (size of the effect) and the statistical and physiological significance of the difference between intervention and control. The strength of the association is usually measured by the extent to which the relative risk or odds ratio departs from unity. In the case of preventive interventions, relative risk or odds ratio below one and confidence interval not overlapping one (or a high level of statistical significance) would be indicative of a meaningful strength of association. Weak relationships are susceptible to confounding and may reflect a poor measure of exposure or outcome.

C. ***Probability***: There should be a demonstration of a statistical relationship.

D. ***Temporal relationship***: An agent can be considered to have a causal effect on body function/structure, or reducing the risk of a disease or abnormality, only if the agent was applied prior to the observation of the effect on body function/structure, or prior to the time the disease or abnormality would have developed.

E. There should be ***no equally strong opposing evidence***.

Supporting Causality Criteria

Not all supporting criteria have to be met; however, the more these criteria are met, the stronger the evidence.

F. ***Dose-response relationships***: If an agent is beneficial or if a factor is indeed the cause of a disease, usually (but not invariably) the greater the dose of the agent or the exposure, the greater the beneficial effect or risk of the disease. Such a dose-response relationship may not always be seen because many important biologic relationships are dichotomous, and reach a threshold level for observed effects.

G. ***Reversal or cessation of effects***: If an agent has a beneficial effect, then the agent should reverse a risk factor or adverse condition (if preventing the occurrence of the risk factor or adverse condition cannot be shown in humans for ethical reasons). Similarly, if an agent has a beneficial effect, then the benefit is expected to cease when it is removed from a population (unless there is a carryover effect). In some cases, long-term studies may be required to indicate that the effect is not transient.

H. ***Biological plausibility***: A biologically plausible mechanism should be able to explain why such an effect or relationship would be expected to occur.

I. ***Alternative explanations*** (confounding): The extent to which alternative explanations (due to uncontrolled confounding or other methodological artifacts) have been explored is an important criterion in judging causality.

J. ***Specificity of effect***: The extent to which the precision of the association between the exposure and the agent can be demonstrated - does X lead only to Y?

K. ***Specificity of cause***: Does only X lead to Y?

L. ***Coherence***: Is the effect seen in a variety of related endpoints as could be expected?

Step 3 Rate the Strength of Evidence

For the purpose of linking the strength of the evidence and the validity of a claim, we propose that the strength of the evidence be rated as acceptable, or inadequate. Table 2 summarizes the two types of acceptable evidence (Type 1 and Type 2) based on: study category (design) and study quality (from Step 1), and the extent to which causality criteria are met (from Step 2). A summary of what is considered inadequate evidence is also outlined in Table 2.

Table 2
Acceptable and Inadequate Evidence

	Acceptable Evidence	Inadequate Evidence
Study Category and Quality (described in Step 1)	Human studies must be used to support health claims. Depending on the type of health claim, two types of evidence based on human studies will be considered. ▸ **Type 1**: defined as primarily experimental studies in humans ▸ **Type 2**: defined as a combination of experimental and observational studies in humans and reported systematic review(s) of acceptable quality (ideally meeting criteria A-D) Product-specific studies should meet the following level of quality: ▸ Experimental studies in humans: levels A-C ▸ Observational studies in humans (prospective and case control): level A Both generic and product-specific studies should meet other essential study quality criteria	Evidence consisting primarily of: ▸ Human experimental studies at levels D-E ▸ Observational studies at levels B-C ▸ Systematic reviews of unacceptable quality ▸ Animal studies or *in vitro* studies alone ▸ Historical (retrospective) cohort, cross-sectional, ecological studies or case reports alone

Table 2 (continued)
Acceptable and Inadequate Evidence

	Acceptable Evidence	Inadequate Evidence
Causality Criteria (described in Step 2)	Evidence meets all essential causality criteria	Evidence of any category of acceptable quality without meeting all essential causality criteria
Other		Studies of any category of acceptable quality without meeting the criterion for relevance and generalizability Moderate or strong evidence that the agent has an effect that is opposite to what is asserted in the claim

Part II Determine if the Strength of Evidence is at the Level Required to Support the Claim

In determining the validity of a claim, the strength of the total evidence required (including the number of studies) will be considered in relation to the nature of the claim. The nature of the claim includes the following elements:

- the stated health benefit of the food or bioactive substance;
- the type of health benefit (Is the emphasis on maintaining and promoting health, or on risk reduction of disease or adverse health condition? Is the effect discernable by consumers?);
- the specificity of the claim with respect to the bioactive substance or the health benefit (e.g., ß-carotene is more specific than fruits and vegetables; brand X is more specific than nutrient/substance Y; reduction of risk of osteoporosis is more specific than bone health);
- the intended target of the claim (general population or specific groups);
- the potential impact of the claim (Does the claim have the potential to mislead consumers to self-diagnosis or self-treatment? What is the likely impact if the claim is not valid?);
- the novelty of the claimed relationship between the agent and the health benefit (e.g., a claim about the benefit of dietary fibre in enhanced immune function will be considered more "novel" than a claim about its benefit in promoting regularity).

All health claims will be evaluated on a case-by-case basis according to the general guidelines described above. As the food or bioactive substance becomes more specific, there is the need for increased control in the study design, and thus more weight will be put on human experimental studies.

The following standard is provided as general guidance only.

- For ***product-specific claims***, Type 1 evidence will be required.
- For ***food- or substance-specific claims***, Type 1 evidence will generally be required.
- For ***claims based on diet or food groups***, Type 1 or Type 2 evidence will be required. Flexibility will be exercised in evaluating the adequacy of evidence.

The explanations for Type 1 and Type 2 evidence are given in Table 2.

Part III Determine if the Total Evidence Provides the Required Information for Characterizing the Relationship Between the Claimed Benefit and the Food or the Bioactive Substance

A health claim for a food will be considered valid if it meets the required standard for acceptable evidence for a causal relationship between the food or the bioactive substance and the health benefit and if the total evidence provides the required information for characterizing the relationship.

The totality of the evidence should address the following specific questions in characterizing the causal relationship:

- Can the product produce the beneficial effect as claimed under ideal (controlled) conditions?
- Does the product produce the beneficial effect as claimed under average conditions of use, or at the minimum, is the food or bioactive substance likely to be consumed in amounts required for the beneficial effect under free living conditions without a negative impact on the diet?
- What is the magnitude of the beneficial effect or reduction in risk?
- Is the beneficial effect sustainable? (i.e., not a transient adaptive response with decreasing benefit over time.)
- What is the recommended intake for the food or bioactive substance to achieve the beneficial effect?
- How is the intake of the food or the bioactive substance that is the subject of the claim measured?
- Who will benefit?

Optional information

- What is the potential impact on population health?
- How does it work? (A biologically plausible mechanism helps strengthen the evidence and the use of biomarkers although the exact mechanism may not be known.)
- What is the lag time between the consumption of the food or the bioactive substance and the beneficial effect? (This information helps to assess if a study is of sufficient duration to detect the desired effect.)

In addition to the validity of the claim on the health benefit of a food or a bioactive substance, the acceptability of a food product represented as having a health benefit will be determined based on compliance with applicable legislation, regulations and guidelines and adherence to guiding principles for making a health claim (section 2), product safety assessment (section 4) and the quality assurance capability of the manufacturer (section 6). The final decision on the acceptability of the food product with a health claim will be made in concert with risk management considerations (section 7.3).

5.5 Measuring Health Benefits and Food Intake: Use of Biomarkers

5.5.1 Terms of Reference

A key factor in substantiating a health claim is the reliable measurements of both the health benefits claimed and the consumption of a product, or bioactive substance responsible for the health benefit, by using appropriate biomarkers. A biomarker, or biological marker, has been defined broadly as "a measured structure or process at any level of biologic reality, including molecules, cells, tissues, organs, organ systems, or whole organisms".[41] For the purpose of supporting health claims for foods, three types of biomarkers are particularly relevant:

1) Surrogate disease endpoints (for supporting risk reduction claims)
2) Biomarkers related to the achievement of optimal health and normal growth and development (for structure/function claims)
3) Biomarkers of food intake or exposure

The development, validation and acceptance of appropriate biomarkers, particularly surrogate disease endpoints, are seen as crucial in advancing the science of functional foods and in supporting health claims.[41-43] Surrogate disease endpoints can shorten the time required to detect an effect, help identify the timing of intervention to reduce disease risk, and permit the conduct of intervention trials where the measurement of disease endpoints may be unethical or impractical. Biological measures of food intake have the potential to be more reliable than traditional dietary assessments, which are based primarily on self-reporting methods that rely on subjects' ability to recall or record information accurately and completely.

This paper will focus on the use of surrogate disease endpoints and biomarkers of food intake for the purpose of substantiating health claims. Further development is needed on the use of biomarkers relating to optimal health and normal growth and development for substantiating structure/function claims.

Other types of biological markers, including genetic and molecular biomarkers, may also be useful when designing studies by identifying individuals who are susceptible to disease risk and who could benefit from an intervention.

Given the current understanding of the relationships between diet and health, it is expected in the near future, that major areas of health claims with strong evidence will likely be based on biological endpoints. While valid methodologies for behavioural and psychological markers exist, behavioural and psychological outcomes are not generally well established for foods at present.

5.5.2 General Criteria for All Biomarkers

All markers must meet certain criteria.[43-45] The markers should:

- be clearly linked to the phenomena involved in the biological process being studied;
- represent relatively immediate outcomes, which can be used to assess interventions in a reasonable time;
- preferably be dynamic responses (e.g., changes during clearance studies) rather than static measurements;
- be measurable in easily accessible material, or obtainable using methodology that is minimally invasive and ethically acceptable;
- be rigorously validated. The analytical method
  - meet standards for sensitivity and specificity (through single-centre studies) and reproducibility (through multi-centre validation),
  - is subject to interlaboratory standardization and quality control.

Other researchers included feasibility and logistics in the considerations for criteria.[45,46] Some biomarkers may not meet all criteria in all circumstances. In some cases, multiple markers may be needed to create a "decision tree" from multiple tests.[43]

Certain factors may affect the application of the proposed criteria in determining appropriate biomarkers to be used in studies examining the relationship between diet and disease. Knowledge of the main causal pathway relevant to disease etiology and the mechanistic relationship between the bioactive substance and its effect will be important in determining the usefulness of a particular biomarker.

5.5.3 Surrogate Disease Endpoints

Traditionally, clear clinical events, or endpoints, are used to determine whether a treatment was successful in preventing an adverse clinical outcome or modifying a health condition in a manner that has clear benefits for the patient. Surrogate disease endpoints may be acceptable in place of clear clinical events if they can be expected to reasonably predict clinical benefit. Surrogate disease endpoints may also be useful in assessing the efficacy of an intervention in reducing disease risk.

Criteria

A biomarker can be classified as an intermediate endpoint and serve as a surrogate marker for a disease if:[41,47]

- it is on the causal pathway between exposure and disease;
- it can be expected to reasonably predict clinical benefit [*Food and Drug Administration Modernization Act* §112(b) (1)];
- it is differentially expressed in normal vs. high risk tissues;
- it has short latency compared to disease expression;
- it is modulated by preventive agents in a dose-response manner.

To determine the strength of evidence required for surrogacy, the following considerations were noted at the International Conference on Harmonization:[47]

- the biological plausibility of the relationship between the surrogate variable and clinical outcome;
- the demonstration of the prognostic value of the surrogate for the clinical outcome in epidemiological studies; and
- evidence from clinical trials that treatment effects on the surrogate marker correspond to effects on the clinical outcome.

Currently, there are only a few examples of well accepted surrogate markers for disease development, including serum lipids for heart disease, adenomatous polyps for colon cancer, and oral leukoplakia as a surrogate for oral cancer. In the U.S., the only biomarkers currently accepted by the Food and Drug Administration in assessing health claims are serum cholesterol levels (total, LDL and HDL).[41] Serum cholesterol level is an accepted surrogate marker for heart disease because it can reasonably predict that patients who have higher cholesterol levels will have a higher probability of developing coronary heart disease (CHD). In other words, CHD is more frequent among patients who have elevated cholesterol levels than among patients who do not.

The criteria listed above can form the basis for accepting new surrogate disease endpoints in the future. For risk reduction claims, surrogate disease endpoints that have been validated or generally accepted by qualified experts may be considered as part of the evidence to support a claim.

Limitations

Despite some obvious benefits of using surrogate disease endpoints, concerns have been raised regarding their use in clinical and preventive practice.[5,47-49] Surrogate variables may reflect only an effect associated with one specific biological mechanism and not the full range of actions and ultimate effects, thus not truly predictive of the health outcome of interest. Therefore, focussing only on the target condition based on the intermediate endpoint may lead to neglect of adverse effects from other unrelated conditions. Also, surrogate variables may not yield a quantitative measure of clinical benefit that can be weighed directly against adverse effects. The beneficial effect of a product on a surrogate variable dependent on one mechanism may not apply to another product with a different mode of action.

5.5.4 Biomarkers of Food Intake

There is a great need for objective methods of assessing the food intake of individuals in diet studies. While biomarkers may give some indication of nutrient bioavailability, their main purpose is to estimate the level of bioactive food substances entering the body. Because biomarkers can provide much more objective measures of diet intake compared to traditional methods, their use is encouraged to increase the validity of food intake data.[50]

Criteria

Appropriate biomarkers of food intake should:

- discriminate between past (long-term) and present (short-term) intakes;[45,51]
- measure intake with precision;[52]
- reflect changes in the consumption of the food substance in question;[52]
- be applicable across different population groups with different dietary intakes, physiologic characteristics, health status and lifestyles.[45,53,54]

Another important consideration for biomarkers of food intake is their ability to reflect intakes of nutrients even at doses in the pharmacological range. This would be an advantage over traditional methods of dietary assessment which often overlook the intake of supplements.[51]

Limitations

Despite the benefits of using biomarkers for estimating dietary intake over traditional dietary assessment methods, this area is presently at an early stage and there is great need for progress.[51] Many issues complicate the measurement of dietary exposures.[50] As a tool of dietary assessment, biomarkers are subject to the same sources of intra-and inter-individual variability as traditional dietary intake methods. The extent to which biomarkers reflect the amounts present in the diet would depend on factors affecting absorption and other aspects of metabolism, distribution, excretion, storage, exchange etc.[51] The usefulness of biomarkers of food intake also depends on study design and the health status of the study subjects.

5.5.5 Research Needs

There is a need for research in these areas in order to develop more effective approaches in estimating food intakes and investigating the relationships between consumption of foods or bioactive substances, effects on body functions and disease risk reduction. Progress in this area will be important in order to form the scientific basis for supporting some types of structure/function and risk reduction claims.

5.5.6 Validation and Acceptance of New Biomarkers

The use of new biomarkers in supporting a health claim will require a validation process [adapted from Zeiger[55]]. Validation is the scientific process for establishing the reliability and relevance of a biomarker in identifying a biological effect of interest. Where the mechanisms in a biological process are understood, the relevance of a biomarker to the biological effect would likely be easier to establish. Therefore, the validation process for biomarkers should be flexible and adapted to the biomarker in question on a case-by-case basis. Despite the need for flexibility, some basic components of a validation process should be required, including:

- scientific basis supporting the biological relationship and relevance of the biomarker to the effect of interest;
- formal detailed protocol for assessing the biomarker with appropriate reference materials;
- reliability (intra- and interlaboratory reproducibility);
- identification of limitations;
- data quality (ideally performed under Good Laboratory Practices);
- all data available for review;
- independent scientific peer review.

For the purposes of gaining product approval for health claims on foods, regulatory acceptance that a given biomarker is considered suitable for the intended purpose may be required. The biomarker should adequately predict the end point of interest. The method for analyzing the biomarker should be robust and transferable across laboratories. Validation is a prerequisite for regulatory acceptance.

Other acceptance criteria will depend on the significance of the biomarker. A high level of validation will be required for a biomarker that forms a pivotal or definitive part of the evidence in establishing a health benefit; in assessing the intake or the activity of a specific bioactive substance; or in replacing a generally accepted biomarker.

6. QUALITY ASSURANCE

6.1 Terms of Reference

Quality assurance is the capability to ensure quality consistency. Consistency refers to meeting required specifications within a defined range of variation and frequency. For foods bearing health claims, quality assurance relates to the ability to identify, measure and maintain a consistent level of the bioactive substance in the product (or an appropriate proxy indicator) that ensures efficacy without jeopardizing product safety. Quality assurance also encompasses the ability to demonstrate the reliability of the tests performed. The final product must also be free from harmful contaminants.

In evaluating foods bearing health claims, there are four main elements of quality assurance:

1) Good manufacturing practices (GMPs)
2) Good laboratory practices (GLPs)
3) Good practices concerning the collection and analysis of human data - clinical and/or epidemiological practices (GCPs/GEPs)
4) Documentation

Where national or international guidelines have been established in any of these elements, for any commodity or food category, such guidelines should be followed.

6.2 Good Manufacturing Practices

6.2.1 Starting Materials, Manufacturing and Processing

One of the most important areas of quality assurance in the food industry is the maintenance of the integrity of raw materials and of their properties which are desired in the finished product. This is particularly important in the case of foods represented to have specific health benefits. For these foods, it is critical to use raw materials possessing the ability to elicit the desired effect and processes which do not lead to a deterioration of that effect (either during manufacturing or subsequent storage of the product).[56] Quality specifications routinely include:

- identification
- physical characteristics
- purity
- microbiological quality
- pesticides and fumigant residues
- toxic chemicals
- likely contaminants
- source, where applicable (e.g., site of origin of the plant, time of harvesting and stage of growth, part of plant harvested, drying and storage conditions)
- stability

Acceptable analytical procedures should be used to evaluate and confirm the functionality of the ingredients containing bioactive substances before being used in manufacturing. Similarly, there should be appropriate processing, monitoring and control systems in place to ensure quality and functionality in the final product, as well as to minimize adverse effects in the event of manufacturing malfunction.

6.2.2 Finished Product, Packaging and Labelling

A shelf-life evaluation program, which may be ongoing depending on the type of product, will be necessary to ensure that the bioactive substance is present in sufficient quantities in the product to exert the desired biological effect throughout its shelf-life (i.e., up to the point at which it is consumed by the end-user).

The choice of packaging material and format can also have an impact on the stability of the finished product. Where the packaging material is in direct contact with the food, regulations governing their use may apply.

The term "labelling" applies to all text including symbols, on both inner and outer packaging. Products bearing health claims must meet all general labelling requirements as well as specific requirements regarding nutrition and other information (e.g., usage directions).

6.3 Good Laboratory Practices

6.3.1 Identity of Product and Bioactive Substance

For a product bearing a health claim, the bioactive substance(s) can either be a naturally occurring constituent of the product, an added ingredient or a component of an ingredient, or the entire product *per se* by virtue of its formulation and/or processing (particularly in the case of a product-specific claim). It would be desirable to identify the bioactive substance(s) responsible for the desired health benefit. For many foods represented to have specific health benefits, the bioactive substance(s) is usually well known.[57] Where the bioactive substance is not known, it would be essential to identify a product characteristic by which quality assurance can be established. Measurements of the known characteristics of the bioactive substance (such as the physico-chemical properties of the active substance) may serve as proxy indicators of the ability of the product to deliver the desired physiological effect.

Regardless of the source of the bioactive substance, it would be essential to monitor its quantity and stability in a given product as part of quality assurance. Where the bioactive substance is added, it is essential to ensure that the specifications for the active substance can be met consistently. Analysis of the product and the bioactive substance, if known, must be ongoing and carried out at regular intervals.

In cases where the activity of the bioactive substance may be dependent on its physico-chemical properties that are subject to change by processing or other conditions, it would also be critical to characterize those properties as part of the specifications of the substance.

In some cases, the bioactive agent is produced by a substance in the product. For example, the beneficial effects of bifidobacteria are likely due to their interaction with other bacteria, production of short-chain fatty acids, or reduced pH in the colonic environment, or some other action that is the true "protective" agent. In this example, counts of bifidobacteria would give an indication of the likely production of the real protective agent.[57]

6.3.2 Use of Reference Material and Validated Methodology

There should be standardization or specification of bioactive materials in studies, given the inherent variability in natural products. Reference materials should be included as part of the standardization process.

6.3.3 Interlaboratory Standardization

New methods under development (e.g., for analyzing new biomarkers) should be validated using an acceptable interlaboratory standardization process.

The competence of the analytical services of a laboratory should be demonstrated through the participation in an interlaboratory testing program.

6.4 Good Practices Concerning the Collection and Analysis of Human Data

There is the need to develop appropriate Standard Operating Procedures (SOPs) appropriate for the conduct of human studies involving assessments of food intakes and health outcomes.

Until such guidelines are in place, studies conducted using acceptable procedures, including validated dietary assessment methodology, will be considered. Acceptable procedures include those comparable to Good Clinical Practice and Guidelines for Good Epidemiology Practices used in therapeutic products research.[16,58]

6.5 Documentation

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

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

IMPLEMENTATION

7. EVALUATION PROCESS

Applications for health claims for foods will be subject to the 5-step evaluation process proposed below. The process is based on the evaluation framework outlined in this paper. All applications will be screened before a detailed evaluation is undertaken. The purpose of screening is to help reduce unnecessary delays and increase the efficiency of the evaluation process. Regular consultation between applicant and review agency prior to and after submission will also help facilitate the evaluation process.

7.1 Preliminary Evaluation (Screening)

I-A. Determine the appropriateness of the product being reviewed as a food product, as necessary.

I-B. Assess the completeness of required elements in the application dossier.

- Does the dossier contain the required elements to support product efficacy, safety and quality assurance?
- All claims: systematic review in required format and references.
- Claims requiring product-specific testing: original studies on the product being evaluated, and certification where required.

I-C. Assess if detailed evaluation should proceed; notify applicant if clarification is needed.

7.2 Detailed Evaluation

II. Assess the quality of the data in the application dossier, including whether the applicant has considered the totality of available data.

III. Assess the adequacy of the data in supporting product safety, claim validity and quality assurance capability.

The above 3 types of assessment (product safety, claim validity and quality assurance) will occur in parallel, except in the case of a novel food, for which product safety will

be evaluated first; if unsatisfactory, the application will be rejected without assessment of the other data.

IV. Identify if further data are required and request more data from applicant where appropriate.

V. Make decision regarding product approval status after all required data are evaluated.
A. Assess the overall benefit-risk profile of the product.
B. Where applicable, assess if appropriate risk management options are available.

7.3 Risk Management

In Canada, as in many other Western countries with a well established health protection system, foods have a presumption of safety, and are typically not subject to benefit-risk analysis. However, the move towards emphasizing specific foods and food substances in addition to the total diet in health promotion and disease risk reduction[59-61] raises new concerns about the introduction of new health risks (section 4). Similarly, the shift in dietary guidelines from targeting the general population, to subpopulations with specific risk factors[60,61] also poses new challenges in health communication. Not all individuals will benefit equally from the increased intake of specific foods or bioactive substances.[62] It will be equally important that there is no increased risk for those individuals for whom the health claim is not intended.

Therefore, in evaluating food products designed to achieve specific health benefits, there is a greater need today to consider an appropriate benefit-risk balance for the general population and population subgroups with special dietary and health needs. A broader range of risk management options other than product prohibition will need to be considered. In addition to regulatory options, consumer education will be essential to enhance credibility and proper interpretation of the claim, and prudent consumption of the product carrying the claim. Information provision, in the form of labelling, may assume a more important role in the risk management of foods represented to provide specific health benefits for specific groups. This approach potentially could allow more food products to enter the market while minimizing risk. This requires the cooperation of manufacturers to provide adequate information while expecting consumers to also assume more responsibility to make informed and balanced choices for themselves. *Comments are welcome on the targeting of foods to specific population groups and risk management options*.

After determining the overall benefit-risk profile of the product and an appropriate risk management option, one of three types of decisions is possible:

1) The product is safe as food and the claimed benefit is supported: the product and the health claim will be approved without change or with a modified claim (taking into consideration consistency with nutrition recommendations in Canada and consistency with the scope and nature of the scientific evidence).
2) Both claimed benefit and safe use as food under special conditions cannot be supported: the product and the claim will be rejected.

3) Claimed benefit is supported but the use of the product as food should be limited due to safety concerns: the product may be sold as a food with special labelling, through special distribution channels, or both. Special labelling options are outlined in Table 3.

Table 3
Indications for Special Labelling Options

Labelling Options	Indications
Caution statement	May be required when the product contains an uncommon or unusual allergenic substance not typically associated with food product.
Recommended usage level	Statement may be required concerning the maximum intake level above which there is an increased risk of adverse health effects or possible interactions with other foods or drugs.
For special dietary use only; not to be used without professional supervision	Product has demonstrated benefits for indicated use, but its safe use by the general public without professional supervision has not been established. The marketing of such a product as food may require postmarket surveillance among target users as well as demonstrating the effectiveness of the special label instruction regarding restricted use.

8. IMPLEMENTATION ISSUES

Health Canada will give priority to addressing the following issues related to the development of standards of evidence.

8.1 Developing Criteria for Health Claim Prioritization

To realize the potential for public health benefits in permitting health claims for foods, it is important that claims with the potential for major public health benefit be given priority in evaluation, at least during the initial stages of the implementation of the health claims policy. *We welcome comments on the development of criteria for setting priorities.*

8.2 Developing Specific Guidelines for Evaluating Specific Health Outcomes

One important aspect of evaluating the validity of a health claim is to identify an acceptable biological marker for a claimed effect and an acceptable protocol for studying the effect. It may be necessary to develop specific guidance regarding protocols for studying specific effects. For example, guidelines outlining acceptable protocols for demonstrating the biological effects of dietary fibre were developed[63] and may serve as a model.

8.3 Establishing a Process for Keeping Claims Current

Ensuring that health claims are based on a rigorous standard will result in health claims that are likely to be enduring.[64] However, new data and advances in scientific developments may necessitate a review of the health claims already approved. It would be important that this type of review be done efficiently and on a regular basis, perhaps every five years.

8.4 Establishing a Process for Validating Claims Approved in Other Jurisdictions

In considering the adoption of a health claim approved in another jurisdiction, the compatibility of scientific standards, the consistency of the claim with current science, and the process for validating the science supporting the claims must be assessed. In this regard, Health Canada is currently considering adopting certain U.S. generic health claims in the Canadian context. The scientific standards used in the approval of existing U.S. health claims under the *Nutrition Labeling and Education Act* may be considered compatible with those proposed for Canada and serve as a basis for their consideration. The recommendations from an update of the scientific evidence and broad consultation on the policy aspects of the claims will be considered in the final decision.

8.5 Establishing Mechanisms for Evaluating and Approving Claims

The implementation of an appropriate mechanism that will ensure a comprehensive and timely evaluation of health claims is vital to the establishment of a credible health claim review system in Canada. It has been suggested that a third party system of review outside a regulatory agency should be considered. In addition, interest has been expressed regarding the use of a logo or identification number to clearly identify products for which health claims have been approved and to assure consumers of product quality and efficacy. These administrative aspects of product evaluation and approval will be assessed as part of the regulatory development process.

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