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## PASSCLAIM<sup>1</sup> – Synthesis and review of existing processes

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■ **Summary** Several approaches to the use of health claims on foods have been made around the world, and the common theme is that any health claim will require scientific validation and substantiation. There is also broad consensus that any regulatory framework should protect the consumer, promote fair trade and encourage innovation in the food industry.

This paper is based on a critical evaluation of existing international approaches to the scientific substantiation of health claims, with a view to identifying common new ideas, definitions, best practice and a methodology to underpin current and future developments.

There is a clear need to have uniform understanding, terminology and description of types of nutrition and health claims. Two broad categories were defined: *Nutrition Claims*, i. e. what the product contains, and *Health Claims*, i. e. relating to health, well-being and/or performance, including well-established nutrient function claims, enhanced function claims and disease risk reduction claims. Such health claims relate to what the food or food components *does or do*. The categories of health claims are closely and progressively related and are, in practice, part of a continuum. Provision is also made for “generic” or well-established, generally accepted claims and for “innovative” or

“product-specific” claims. Special attention was paid to reflect the health-promoting properties of a food or food component in such a way as to facilitate the making of risk reduction claims outside the medical scope of the term prevention.

The paper sets out basic principles and guidelines for communication of health claims and principles of nutritional safety. The main body of the work examines the process for the assessment of scientific support for health claims on food and emphasises an evidence-based approach consisting of:

- Identification of all relevant studies exploring the collection of evidence, data searches, the nature of the scientific evidence, sources of scientific data (including human intervention studies, human observational studies, animal studies and *in vitro* studies, and the use of biomarkers in human studies)
- Evaluation of the quality of individual studies to ensure good experimental design and interpretation
- Interpretation of the totality of evidence to apply scientific judgement to interpret the weight of evidence as a whole
- Assessment of significant scientific agreement on a case-by-

<sup>1</sup> Process for the Assessment of Scientific Support for Claims on Foods

case basis to agree within the relevant scientific community that an association between a food or a food component and a health benefit is valid. Annexes include an interna-

tional comparison of regulatory approaches to health claims, suggestions for the documentation and presentation of evidence, and a procedure for reviewing the evidence.

■ **Key words** health claims – definitions – scientific substantiation

## Introduction

The primary roles of diet are to provide sufficient nutrients to meet the metabolic requirements of an individual and to give the consumer a feeling of satisfaction and well-being through the pleasure of eating. In addition, particular diets, foods and food components can provide additional physiological, cognitive and psychological benefits and biological activities beyond their widely accepted nutritional effects. In fact, diet not only helps to achieve optimal health and development but can also play an important role in reducing the risk of specific diseases.

Much attention is now being paid to health claims for foods, especially those related to the newly discovered functions of diet. Several approaches to the use of health claims on foods have been made around the world, and the common theme is that any health claim will require scientific validation and substantiation. There is also broad consensus that any regulatory framework should protect the consumer, promote fair trade and encourage innovation in the food industry [1].

A main impetus in the European Union (EU) was the Consensus Document on Scientific Concepts of Functional Foods in Europe (FUFOSE) produced from the EU DG XII Concerted Action Project, whose objective was to suggest a scheme to link “enhanced function” claims and “reduced risk of disease” claims to solid scientific evidence [2, 3]. The FUFOSE conclusions are now being developed in the current project to establish a Process for the Assessment of Scientific Support for Claims on Foods (PASSCLAIM).

The objectives of PASSCLAIM are the following:

- Produce a generic tool with principles for assessing the scientific support for health-related claims for foods and food components
- Evaluate critically the existing schemes that assess the scientific substantiation of claims
- Select common criteria for how markers should be identified, validated and used in well-designed studies to explore links between diet and health.

The following commentary is based on a critical evaluation of existing international approaches to the scientific substantiation of health claims, with a view to identifying common new ideas and definitions, best practice and a methodology to underpin current and future developments.

Several European countries are already developing guidelines on what to do with health claims [4]. Many of these codes are still evolving, and although there is an underlying consistency of approach, there are differences – sometimes in minor, and sometimes in major, aspects. Similarly, international comparisons of regulatory approaches indicate the need for promoting harmonisation (see Table 1). Difficulties arise in the analysis of the different codes to determine how important they are, what kind of supporting information and substantiating evidence is required, who is going to evaluate the application, what are the associated costs and timescales involved. This lack of a harmonised approach to health claims, the lack of a unified system for authorisation and the increasing number of local regulations, guidelines or codes of practice can create major inefficiencies. For example, in some countries lists have been compiled with defined wording for health claims, e.g. the USA, whereas in others, such as the UK, the wording of the scientific linkage between a health benefit and a food or food component is carefully formulated by an expert panel of scientists to reflect the evidence on which the claim is approved. However, the wording of the claim for labelling and advertising itself may be altered after consultation with the code administrators, provided that the claim does not imply health benefits beyond the scope of the evidence, change the meaning or confuse consumers [5].

It is clear that the various initiatives on health claims around Europe and beyond could lead to divergent and inconsistent interpretations and enforcement of the existing European legal provisions, and, potentially, a different regulatory status for a given product with the same composition between Member States. Nutrition and medical sciences now recognise the contributions that diet and individual foods may make to the promotion and maintenance of health. Currently, however, EU law prevents the communication of these benefits to consumers, whilst law on medicinal products is established on a very broad basis that also encompasses foods making preventive, therapeutic or curative claims. The concept “disease risk reduction” as proposed by FUFOSE and other international bodies has been developed to reflect the “health-promoting” properties of a food or food components in such a way as to facilitate such health claims for “risk reduction” to be made outside the medical scope of the term “prevention” [6, 7]. The new concepts of health claims, including disease risk reduction

**Table 1** International comparison of regulatory approaches to health claims (✓ = yes sometimes still under development, X = no, – = not applicable)

	e. g. (UK) JHCI (5)	Sweden (10, 21, 32)	Canada (33)	CIAA (34)	Japan (34, 35)
Website	www.jhci.co.uk	www.snf.ideon.se	www.hc-sc.gc.ca/food-aliment/english/subjects/health_claims/	www.ciaa.be	Available in Japanese
Voluntary/mandatory	Voluntary	Voluntary	Mandatory	Voluntary	Mandatory
Origin	Industry, consumers, enforcement partnerships	Industry (from primary production to retail organisations). Supported by main consumer organisations	Government	Food manufacturing industry guidelines	Government
Definitions	✓	✓	✓	✓	✓
Health claims	✓	✓	✓	✓	✓
Enhanced function	✓	✓		✓	✓
Disease risk reduction	X	✓, for generic claims in two steps	✓	✓	X
Generic claims	✓	✓	✓	X	✓
Product specific	✓	✓	✓	X	✓
Communication guidelines	✓	✓		✓	✓
Nutrition principles	✓	✓		✓	✓
Amount and frequency specified	✓	✓		✓	✓
Safety	Refers to existing law	Refers to existing law	✓	Refers to existing law	✓ data required
Quality assurance	Refers to existing law	In general terms	✓	Refers to existing law	✓
Guidelines for dossier	✓	X	✓	✓	✓
Process for substantiation	✓	✓	✓	X	✓
Approval procedure	Level of data required	✓	outlined	X	✓
Administrative procedures	✓	✓		X	✓
Use of independent expert panel	✓ (7 experts)	At least 3 experts appointed case by case		X	✓ (Ministry)
Defined wording of health claims	X	X		X	✓ (6 months)
Start date of code	2000	12 years generic < 1 year product specific	still evolving	–	Since 1991 (revised 2001)
Health claims approved (to Sept. 2002)	6	8 generic since 1990. 1 product specific		–	302 product specific claims
Financial support	Mainly industry funding/project grants from FSA, moving to membership scheme in 2002	Principals of code basic funding. Fees for evaluation of product-specific claims		–	Fees to be paid for evaluation
Timescale for approval	X	✓ (4 months)		–	✓ (6 months minimum)

claims, reflect the fact that foods with health claims are aimed either at the healthy population or healthy individuals, i.e. recognising that the disease is not present; the cause of the disease is multifactorial, including dietary, behavioural, environmental and genetic factors, and that the modification of certain dietary components alone cannot ensure that a disease will not develop, since it does not affect the other confounding factors. Nevertheless, the food or food component may help significantly to reduce the likelihood of developing the disease.

The purpose of this review is, therefore, to develop the process for the assessment of scientific support for health claims on foods. Once the scientific validity of a link between a food or a food component and a health benefit has been established, health claims, including reduction of disease risk claims, should be permitted in food labelling and advertising to express clearly, and more directly, the beneficial relationship between either a diet, a food or a food component and human health.

**Table 1** *Continued*

	USA (18, 36)	Codex (9)	Council of Europe (16)	The Netherlands (22)	Belgium (37)
Website	<a href="http://www.cfsan.fda.gov/~dms/hclaims.html">www.cfsan.fda.gov/~dms/hclaims.html</a>	<a href="http://www.codexalimentarius.net/reports.asp">http://www.codexalimentarius.net/reports.asp</a>	<a href="http://www.coe.fr/soc-sp">www.coe.fr/soc-sp</a>	<a href="http://www.voedingscentrum.nl">www.voedingscentrum.nl</a>	
Voluntary/mandatory	Voluntary	Voluntary	Voluntary	Voluntary	Voluntary
Origin	Manufacturers, federal scientific bodies, e. g. NAS, NIH etc.	Codex members	Council of Europe	Industry, consumers, scientists	Industry
Definitions	✓	✓	✓	✓	✓
Health claims	✓	✓	✓	✓	✓
Enhanced function	✓	✓	✓	✓	✓
Disease risk reduction	✓	✓	✓	✓	✓
Generic claims	✓	✓	(X)	X	✓
Product specific	✓	✓	✓	X	✓
Communication guidelines	✓		✓	✓	✓
Nutrition principles	✓	✓	✓	✓	✓
Amount and frequency guidelines	✓		✓	X	X
Safety	Refers to existing law	✓	Refers to existing law	Refers to existing law	X
Quality assurance		✓	✓	X	X
Guidelines for dossier	✓	✓	X	X	X
Process for substantiation	✓	✓	✓	✓	✓
Approval procedure	✓ (except medical foods)	–	–	✓	X
Administrative procedures	✓		X	✓	X
Use of independent expert panel	FDA, federal scientific bodies	–	–	✓	X
Defined wording of health claims	✓	X	X	X	X
Start date of code	1990 (NLEA authorised health claims) 1997 (FDAMA, based on authoritative statement) 2000 (Qualified health claims)	At step 5 of the Codex procedure	–	1998	Draft 1998
Health claims approved (to May 2002)	12 generic since 1993 2 generic health claims based on authoritative statements since 1997		–	2	X
Financial support			–	Fees for evaluation	X
Timescale for approval	Yes (more than 1 year under NLEA) FDAMA gives FDA 120 days to respond the health claim notification		–	3 months	X

## Definitions

### ■ Background

There is a clear need to have uniform understanding, terminology and descriptions of the types of nutrition and health claims in order to provide clarity in commu-

nication and presentation of the concepts, particularly with regard to the nature and extent of the scientific substantiation that will ultimately be required. Descriptions that are likely to be most appropriate are those based on the experience developed internationally through Codex. The concepts set out by the European Commission Concerted Action on Functional Food Science in Europe (FUFOSE) project can also provide guidance as

well as the guidelines concerning scientific substantiation of health-related claims for functional foods recently issued by The Council of Europe.

*Claim* means any representation that states, suggests or implies that a food has particular characteristics relating to its origin, nutritional properties, function, nature, production, processing, composition or any other quality.

There are two broad categories of claims relevant to food:

- **Nutrition claim**, i.e. what the product *contains* (see Nutrition claim section)
- **Health claim**, i.e. a *claim related to health, well-being and/or performance, including* nutrient function claims, enhanced function claims and disease risk reduction claims. Such claims relate to what the food or food components of the products *does or do* (see Health claim section).

### ■ Nutrition claim

Nutrition claim means any representation that states, suggests or implies that a food has particular nutritional properties including, but not limited to, the energy value and the content of protein, fat and carbohydrates, as well as the content of vitamins and minerals.

■ **Nutrient content claim** is a nutrition claim that describes the level of a nutrient contained in a food. Nutrient means any substance normally consumed as a constituent of food: a) which provides energy; or b) which is needed for growth, development and maintenance of life; or c) a deficit of which will cause characteristic biochemical or physiological changes to occur [8].

■ **Comparative claim** is a claim that compares the nutrient levels and/or energy value of two or more foods (examples: “reduced”, “less than”, “fewer”, “increased”, “more than”).

These are factual statements that draw consumers’ attention to an aspect of the product’s nutrient content that may be of interest and benefit to them, e.g. low fat, high fibre, source of calcium. These claims may signal a change from the manufacturers’ standard product or from the standard product of a competitor; or it may be that the product is particularly high or low in a specific nutrient, which would make that product of interest to groups of consumers seeking to increase or reduce their intake of that nutrient.

### ■ Health claim

Health claim means any representation that states, suggests or implies that a relationship exists between a food

or a constituent of that food and health [9]. Health claims include the following:

■ **A nutrient function claim** promotes the role of a nutrient in its broadest understanding in growth, development and normal physiological functions of the body, e.g. calcium aids in the development of strong bones and teeth. These claims are generally based on well-established and generally accepted scientific knowledge.

■ **An enhanced function claim** refers to specific beneficial effects of foods and food components on physiological and psychological, cognitive functions or biological activities, but does not include nutrient function claims. Beneficial health effects of nutrients (where an additional function is identified or claimed, i.e. beyond its generally accepted nutritional effect), ingredients and non-nutritive substances are included under the definition of food component. Diseases or disorders are not named. Such claims have recently been referred to as “(other) function claims” [9] and relate to FUFOSE Type A claims (Fig. 1).

For example, enhanced function could apply to the following:

- An additional function of a listed nutrient (usually at a higher level of intake)
- A function of a food component (e.g. an ingredient that has cholesterol-lowering, calcium-absorption-stimulating, prebiotic effects etc.)
- A specific physical or chemical property of the food or food components (e.g. low glycaemic index due to specific structural or starch properties).

■ **A reduction of disease risk claim** refers to the fact that the consumption of a food may help to reduce the risk of a disease. The disease or disorder is named and the risk reduction is explicitly stated. These claims relate to FUFOSE Type B claims. “Reduction of disease risk claims” may currently often be regarded as illegal under the interpretation of food labelling legislation. However, risk

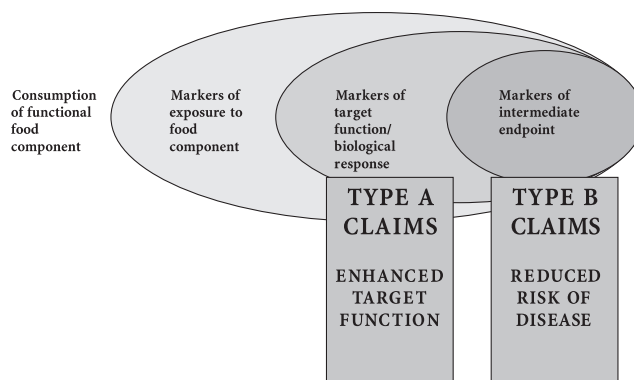


Fig. 1 Functional foods; a proposal for a scientific basis for claims



reduction means significantly altering a major risk factor for a disease or health-related condition. Diseases have multiple risk factors and altering one of these risk factors may or may not have a beneficial effect. The presentation of risk reduction claims must ensure, for example by use of appropriate language and reference to other risk factors, that consumers do not interpret them as prevention claims [7, 9].

## Continuum

The categories of health claims set out above are closely and progressively related and are, in practice, part of a continuum. The use of health claims relating a food or a food component, in the context of the total diet, to the reduced risk of developing a disease, has made it necessary to clarify in the EU regulatory framework that such claims do not fall under the prohibition of preventive claims. In addition, the prohibition deriving from the ability “to modify a particular physiological function” needs to be re-considered in the light of the recognition that physiological effects of foods and food components are normal and commonplace. Developments in the nutrition and medical sciences now recognise many important contributions that diet, individual foods and food components can make to the promotion and maintenance of health. In particular, the concept that foods can reduce the risk of disease over and above the provision of nutrients that they contain is now generally accepted.

## Generic versus product-specific claims

Two approaches, which have been developed in the Swedish, UK, Canadian and Australia New Zealand codes, include Generic Health Claims and Product-specific Health Claims.

Claims may relate to diets, broad food categories, food components including nutrients (“generic”), or relate to particular food products (“product specific”). The degree of substantiation required may relate to this distinction. The scientific standard for the substantiation of generic and product-specific health claims should be the same, although the sources and nature of the supporting evidence for health claims may be different. Product-specific health claims are likely to be based primarily on human intervention studies showing the claimed effect when the product is consumed as part of a normal diet.

■ **A generic claim** is based on well-established, generally accepted evidence in the scientific literature and/or to recommendations from national or international public health bodies, e. g. EU SCF and US FDA and national scientific advisory committees.

Based on this definition, the scientific linkages for

generic health claims, including nutrient function claims, should be pronounced once the totality of the evidence that supports the claim has been assessed (see the Sources of scientific data section). A generic health claim may be relevant for complying diets, foods or food components including nutrients. A “complying” food comprises or contains the components in sufficient quantity to produce the effect claimed, or falls within the category of foods to which the generic claim applies.

“Two-step” health claims are based on the establishment of a diet and health relationship and linkage of the health claim to a nutrition claim about what the product contains. The principle for these claims is similar to that used in the USA. In Sweden, the so-called “two-step principle” has been used since 1997 to ensure compatibility with the general prohibition on medicinal claims in the EU. The National Food Administration in Sweden considers the “two-step claims” to be compatible with existing EU law. A good example is the link of a generic health claim “saturated fatty acids increase the level of cholesterol in the blood” and a nutrient content claim that the product contains low levels of saturated fat. Within CODEX, the two-step principle is now suggested for both nutrient function claims and reduction of disease risk claims.

■ **A product-specific claim** is one other than a generic claim. It means that in the marketing of a product, there is a claim concerning the health-promoting effect of the product itself. The food product must have been designed to provide a specific and documented effect [10].

It is very important that the distinction is made between generic claims made in two steps, and product-specific claims. For the former, there is no requirement to document the effect(s) of a particular product in human studies where the composition of the product fulfils the nutrient content claim condition, e. g. a product low in saturated fatty acids may have a claim relating to a cholesterol-lowering effect.

## ■ Medicinal claims and human disease

A medicinal claim is a claim that states or implies that a food or a food component (including any nutrient) has the property of treating, preventing or curing human disease or makes any reference to such a property. “Human disease” means any injury, ailment or adverse condition, whether of body or mind. These claims are prohibited absolutely in the labelling or advertising of food in current EU legislation [7, 11].

## ■ Claims relating to foods for particular nutritional uses (PARNUTS)

There is a basic difference between foodstuffs qualifying for health claims and PARNUTS/Foods for special dietary uses. The former products are intended for basically healthy individuals, who want to stay healthy, while the latter are intended for individuals with a particular physical or physiological condition and/or a specific disease or disorder.

The present Codex definition of Foods for special dietary uses is as follows:

Foods which are specially processed or formulated to satisfy particular dietary requirements which exist because of a particular physical or physiological condition and/or specific diseases or disorders and which are presented as such. The composition of these foodstuffs must differ significantly from the composition of ordinary foods of comparable nature, if such ordinary foods exist [12].

Foodstuffs intended for particular nutritional uses [13, 13 with later amendments] are products that, owing to their special composition or manufacturing process, are:

- Clearly distinguishable from foodstuffs of normal composition;
- Suitable for their claimed nutritional purposes and
- Marketed in such a way as to indicate such suitability.

The particular nutritional nature of these products means that they must fulfil the particular nutritional requirement of:

- Certain categories of persons whose digestive processes of metabolism are disturbed or
- Certain categories of persons who are in a special physiological condition and who are therefore able to obtain special benefit from controlled consumption of certain substances in foodstuffs.

Within the category of PARNUT products there are also infant and baby foods and foods intended for use in energy-restricted diets for weight reduction.

A new category is:

- Dietetic foods for special medical purposes [14].

Moreover, special provisions regarding 'foods intended to meet the expenditure of intense muscular effort, especially for sportsmen' will be laid down by specific directives.

The different categories of health claims should be considered as parts of a health continuum, however, and in practice it may not be clear where an enhanced function, disease risk reduction or dietetic (medicinal) claim begins and ends. It is important to clarify these aspects in the near future.

## Communication aspects

Communication of the health benefits to the consumer is an important challenge in the development and marketing of health-promoting foods. Communication should not only aim at informing about the quality of a particular food but it should also play, where appropriate, an education role in addition to existing nutrition education programmes. The importance of adequate nutrition and the relationships between diet and health and between diet and disease risk should be emphasised.

The claim must be communicated in such a way as to assist consumer understanding of the basis of the claim.

### ■ Basic principles

Health claims must be truthful and must not mislead, exaggerate or deceive either directly or by implication. The claim must not suggest or imply health benefits beyond the scope of the evidence.

### ■ Guidelines for communication of health claims

The claims may suggest that consuming a food or a food component with a health claim may contribute to the improvement of the diet or well-being but it should not suggest or imply that intake of that food alone can correct otherwise unhealthy lifestyles and/or dietary habits or is the only way to enhance a particular physiological effect or to reduce the risk of a given disease, unless true.

Communication of health-related claims to the consumer may include all means of communication, e.g. package label, advertisements, product information sheets, recipe brochure, marketing brochure, spoken and textual content of video, film and TV commercials and Website.

Communication of health-related claims should trigger nutrition labelling in accordance with relevant EU laws; this should be in the form of Group 2, i.e. energy, protein, carbohydrate, sugars, fat, saturates, fibre and sodium, in accordance with Council directive 90/496/EEC. In addition any further information relevant to the claim must be given.

It must be truthful, unambiguous and understandable for the intended consumer; make clear that the health-related claim applies only to the food consumed in the context of a total dietary pattern; not encourage over consumption of a given food to the detriment of others unless justifiable; include information on the intended consumer or potentially vulnerable segment of the population; include information on how to consume or use the functional food to obtain the claimed effect, and finally, the likely consumer perception of the health-

related claims should be taken into consideration. Special care should be taken in the case of advertising directed at children.

The labelling and the labelling methods used, the presentation and the advertising of foods must not suggest or imply the prevention, treatment or cure of human disease. With regard to PARNUTS, this fact should not prevent the dissemination of any useful information or recommendations exclusively intended for persons having qualifications in medicine, nutrition or pharmacy.

## Principles of nutritional safety

Food safety is already covered by general rules of existing legislation. However, the development of foods and food components with health claims must take into account basic nutritional principles and nutritional safety considerations. As such, nutritional safety is an important issue related to a claim but is NOT part of a claim.

Across the codes there is great variation in the use of the word “safety” or “safe”. Some codes do mention “safety” or “safe” but state that their code does not concern safety. The absence of “safety” or “safe” from the codes does not mean that this is not a concern of the originator. Rather food safety is subject to extensive regulations throughout the world. Several codes have therefore not made mention thereof or have just indicated that this is taken care of elsewhere.

### ■ Basic principles

All foods, including those for which health claims are made, should as a matter of routine comply with the general requirements as laid down in applicable food laws and take into account basic principles of nutrition and safety. In all circumstances food should be safe. Where appropriate, foods should conform to the requirements of the European Novel Food Regulation [15]. The Council of Europe paper on the guidelines of health claims for food and food components has considered these safety aspects in detail [16].

### ■ Dietary significance

Foods with health claims have the potential to influence dietary habits, and hence it is essential that their composition should contribute positively to a nutritionally adequate diet. Food should be consumed in realistic amounts in the normal daily diet and the claim must be made in the context of the total diet. Health claims that relate to dietary guidelines must be consistent with the pattern of eating described in the dietary guidelines.

Health claims should not unfairly denigrate other foods or imply that normal foods cannot provide a healthy diet. The benefit must be fulfilled by the amount of the food or food component and the frequency of consumption as recommended on the label, and the marketing information should give the consumer good insight into the connection between good diet and health. The extent of use of a product is important and health claims that could encourage high levels of consumption must not be made for any substance where there is evidence that high intakes of the food or food component could be harmful, or be unlikely to contribute to a healthy diet.

### ■ Interactions with other constituents of the diet

It is important to be aware of any potential interactions of the foods or food components with other constituents of the diet. Possible interactions include the bioavailability of a nutrient or other ingredient (both impaired or increased digestive absorption).

### ■ Impact on metabolic pathways and physiological function

The consumption of nutrients and other bioactive molecules can have diverse actions that may entail sustained metabolic changes, perhaps with toxicological significance. It is necessary to establish the nature of the effects and any response or reversibility of the claimed effect after ceasing use of a specific food or food component.

### ■ The intended consumer and vulnerable groups

Particular sections of the population such as the young, the elderly or those suffering from specific diseases or taking medications may be susceptible to new dietary behaviours. Relevant information should be provided where appropriate. Also the claim and evidence must be relevant to the intended consumer.

### ■ Overall toxicological assessments

Toxicological safety comprises basic aspects of toxicology such as dose (and associated aspects: over consumption, combined intakes from all sources, maximum safe intake levels, recommended amounts/usage levels), effect (interactions) and risk factors (vulnerable groups, target groups, possible allergens). It is important to know, where possible, the metabolic fate and biological distribution of a particular component of interest.



## ■ Post Launch Monitoring (PLM)

Long-term observation of consumers is important, especially if functional foods are targeted at special population groups. The objective of Post Launch Monitoring (PLM is the preferred terminology to discriminate from Post Market Surveillance, the terminology for pharmaceuticals) is 1) to establish dietary intakes and compare these with anticipated intakes, and 2) to identify any adverse effects that could not be identified in toxicological tests. PLM is explicitly not indicated to assess health outcomes: that carries the high risk of trying to establish efficacy in a largely uncontrolled “study” design. The execution of PLM should be considered on a case by case basis.

## ■ Quality assurance

Quality assurance (QA) is an essential element of toxicological safety testing. As concerns QA, a subdivision was made into the QA of studies (GLP – Good Laboratory Practice, GCP – Good Clinical Practice, GEP – Good Epidemiological Practice), Quality Control of the active principle in a food product, and GMP – Good Manufacturing Practice/Sanitary safety of the food product. There is as yet no requirement for GLP/GCP/GEP in the studies supporting the claims, and hence these are not considered essential. However, it is necessary to have insight into the actual levels of the bioactive ingredients contained in the foods. This involves quality control in the studies and GMP of the foods.

## ■ Ethical considerations

Studies with human volunteers and animals should comply with (inter)national regulations and be approved by the appropriate ethical committees.

## Process for the assessment of scientific support for health claims on foods

All health claims in advertising, labelling or promotion must be capable of substantiation. Whether generic or product-specific, the claimed benefit must be supported by scientifically valid evidence demonstrating the efficacy of the food(s) or food component(s) in humans and under typical conditions of use and exposure. The scientific evaluation must show that the scientific evidence for the health claim outweighs opposing evidence or opinion. The health benefits must take account of the best scientific evidence that is likely to stand the test of time.

When a health claim is used for a food or food com-

ponent, the following criteria must be demonstrated, if appropriate:

- That the food or food component in question will cause or contribute to a significant benefit when consumed by the target population in the context of a normal diet.
- That the claimed effect can be achieved by consuming a reasonable amount of the food or food component on a regular basis or by the food or food component making a reasonable contribution to the diet.
- That the effect is maintained over a reasonable period of time with continued consumption and is not a short-term response to which the body adjusts unless the resultant health claim is relevant only for a short- or medium-term benefit.
- The minimum and maximum amounts and the frequency of consumption required to achieve the effect, or that the food or food component provides a reasonable dietary contribution to that amount required to achieve the effect.
- Who can benefit from the effect, e.g. whether it is the entire population, “at risk” groups or population subgroups.
- How the effect is brought about, although the exact biological mechanism(s) may not be fully understood or explainable.
- Reasonable assurance that foods and food components with health claims do not have negative nutritional and health impacts at recommended levels of intake during long-term exposure.

## ■ Source and nature of scientific evidence: an evidence-based approach

Evidence-based science is being used for three features of public health nutrition: the establishment of dietary reference values, including recommended daily intakes, the development and revision of dietary guidelines and the validation of health claims on foods and food components [17]. Guidelines advise people, for example, to eat less saturated fat. Health claims declare a benefit, for example that saturated fat may increase the blood cholesterol level, a risk factor for cardiovascular disease, connected with a nutrition claim that a food contains less saturated fat than similar foods do.

The type and extent of the evidence required will be determined by whether the claim relates to a particular diet, a food group, a specific food, a proprietary food product, or a food component. The evidence must provide information on the scientific substantiation of the types of health-related claims.

Depending on the type of health claim, the following data should be considered for scientific substantiation, where applicable:

- Identification of all relevant studies

- Human intervention studies
- Human observational studies
- Animal studies and in vitro studies
- All other pertinent studies, such as consensus reports and evidence-based dietary guidelines.

The evidence should be based primarily on the results of well-designed human studies that are consistent with generally recognised scientific procedures and principles. The research should assess the effects of foods or food components on the health status of human subjects. In other words, the outcome – measured in clinical/observational, epidemiological and, where possible, nutrition intervention studies – should be the improvement in some indicators of health or well-being or the reduction of risk of diseases.

It is acceptable to provide evidence of the effects of the food(s) or food component(s) on appropriately identified, characterised and validated biomarkers.

## ■ The identification of all relevant studies

### Collecting the evidence

A health claim must be based on a systematic and objective compilation of all the available scientific evidence relating to the health claim, including published scientific literature. Compiling the evidence must be done in a balanced and unbiased way to ensure that all relevant data, both positive and negative, has been included in the documentation. It is expected that some studies may provide negative or contradictory results; however, the weight of the evidence must clearly substantiate the claim.

### Data searches

A successful review of the scientific data depends on a carefully considered and clearly defined health benefit. A systematic approach must be employed to search for data and retrieve all relevant information (Table 2). An explicit and reproducible methodology should be used and recorded clearly while the search is undertaken. Clear search terms and defined key words are required, and they must relate explicitly to the proposed health claim.

The use of relevant databases, including electronic database searches, requires judgement at every step of the process, about the suitability and quality of the evidence. It is sensible to search the evidence chronologically, on a yearly basis starting from the present, and organise the results in reverse chronological order, recording the different types and quality of the individual studies. A search of the latest issues of major journals for relevant articles may also provide additional and appropriate information.

**Table 2** An example of a procedure for reviewing the evidence (adapted from ref. 5)

<i>Proposed wording of health claim</i>
Defines and determines the
<i>Scientific question</i>
Which in turn defines and determines the
<i>Keywords for searching the evidence in databases</i>
Results in
<i>Reference list #1</i>
Including relevant documentation, which should be short-listed by assessing against
<i>Broad inclusion/exclusion criteria (pre-defined)</i>
To decide whether a particular study is linked directly to the health claim. If yes, include for further inspection under
<i>Reference list #2</i>
From which
<i>Abstracts will be retrieved and read</i>
And included or excluded based on
<i>Further refined inclusion criteria (pre-defined)</i>
Followed by
<i>Retrieval of the full articles of all relevant studies</i>
To undergo a brief assessment of the full article to
<i>Ensure direct relevance of each article to the health claim</i>
Followed by
<i>Full review and synopsis</i>
According to the review protocol and
<i>With key points presented consistently according to study type</i>
And individual study results represented, ideally, by a Forest plot (or odds ratio diagram).

It is essential that the selection of studies should be based on adherence to explicit and predefined inclusion and exclusion criteria, which link directly to the health claim. The reasons used for rejection of articles as flawed must be clear, the methodological quality of included studies must be high and each study should be carefully considered for its validity.

The search results will identify individual papers and reviews, and well-written abstracts should provide sufficient information to decide whether the study is relevant to the scientific question based around the health claim. The next stage is to retrieve the full article and to extract all the relevant information from all eligible studies. It is also helpful to present a synopsis of individual studies in a standardised way, which will help to determine whether the study is methodologically sound. The individual studies should be evaluated for rigour of design, appropriateness of methods and procedures, reliability of measures of intake and outcomes, sufficient statistical power, strength of conclusions and comprehensiveness of reporting (Table 3).

The presentation of the data can be done according to study type and design. Ideally, the overall results of the review, that is, a summary of all individual study results should be presented to illustrate the weight of scientific opinion.

**Table 3** Example for a synopsis protocol (adapted from ref. 5)

Following a review protocol and extracting the relevant data provides the Expert body with key information in a consistent and systematic manner. Individual studies should be presented in accordance with their study type and design to ensure greatest comparability.

Individual synopses should be kept brief and presented under the following headings:

- 1) Title of the study
- 2) Authors
- 3) Journal reference
- 4) Objective of the study
- 5) Study type/design

*If the study type/design is a pooled analysis (systematic review or meta-analysis) of many studies, then include:*

- (i) Inclusion/exclusion criteria for the studies, and
- (ii) Data extraction from the studies
- 6) Study population (inclusion/exclusion criteria)
- 7) Baseline characteristics of study subjects and controls
- 8) Duration of the study
- 9) Location of the study
- 10) Methodology (including quality of the active component)
- 11) Dietary assessment technique
- 12) Outcome measurement and other relevant measurements
- 13) Statistics
- 14) Results
- 15) Conclusion
- 16) Points to note/further comments

The literature search is likely to provide:

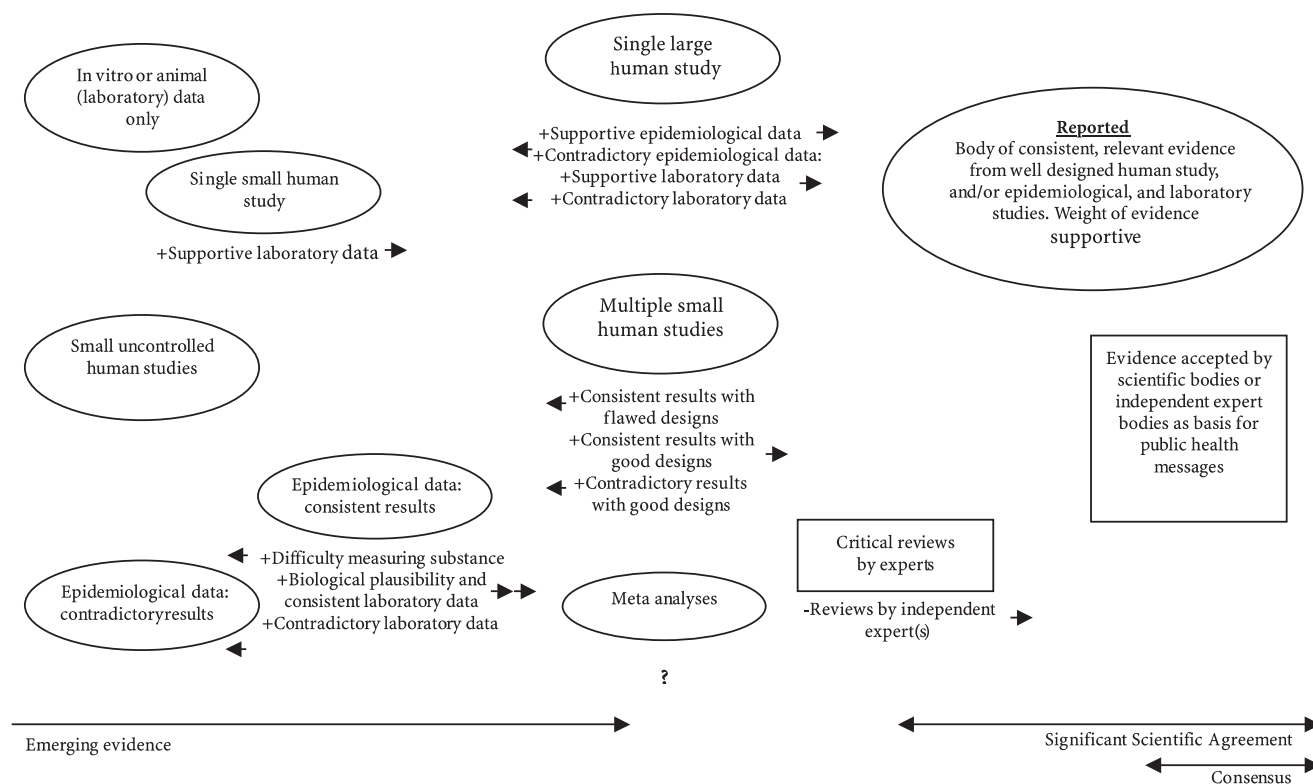
- A body of consistent, relevant evidence from well-designed studies
- Critical reviews of evidence by experts
- Nationally and internationally accepted evidence from expert bodies and health professional organisations, which forms the basis of public health recommendations.

The strength and consistency of the scientific evidence underpins the use of the term “significant scientific agreement” and that the balance of probabilities for the scientific link between a food or food component and a health benefit is justified (see Fig. 2).

### The nature of the scientific evidence

It is clear from all the international laws, codes of practice and guidelines that the claimed effect must be supported by scientifically valid evidence that demonstrates the efficacy of the food or food component in humans and under conditions that reflect the actual conditions of use and exposure.

Many proposed codes of practice suggest that the levels and kinds of evidence should be evaluated within a



**Fig. 2** Graphical representation for Assessing Strength and Consistency of Scientific Evidence Leading to Significant Scientific Agreement. US Food and Drug Administration Centre for Food Safety and Applied Nutrition, Office of Special Nutritionals (1999) Guidance for Industry: Significant Scientific Agreement in the review of Health Claims for Conventional Foods and Dietary Supplements. US Food and Drug Administration, Washington, D.C.

predefined hierarchical scheme. However, the relationship between dietary components and health benefits can be demonstrated by a number of different types of studies and designs, and methodological soundness overrides any hierarchy in studies on humans, given that validity depends not only on the appropriateness of the study type, but also on the quality of its design, execution and analysis. (The reader is referred to the FDA (2001) [18], the Canadian [19] and the Australia/New Zealand Guidance Notes [20] for further details.)

In brief, studies on human subjects are accorded greater weight than animal and in vitro (preclinical) studies, and intervention (clinical) studies have greater weight than observational studies. However, the critical review of the whole body of data is considered under the Totality of evidence section.

The principles summarised in sections Collecting the evidence, Data searches, and The nature of the scientific evidence relate primarily to claims based on a considerable body of published, and possibly to some extent unpublished, scientific evidence. This is the case for generic claims, and the process is similar to that underpinning the dietary recommendations issued by governmental or non-governmental bodies. In fact, such claims could rely directly on the evidence-based procedures carried out by such bodies for establishing dietary recommendations and guidelines (which is the case for the generic claims allowed in the Swedish Code [10, 21]).

In the case of product-specific claims for new food products, the substantiation will rely primarily on a limited number of human intervention studies carried out with the product in question. These studies should have the scientific standard described above and demonstrate the effect to be claimed at normal consumption. The number of studies required is generally not specified, although for example, the Dutch Code, states that “the evidence must be reproduced” [22]. In practice, the number of studies with the product in question, as well as the amount and nature of the supporting evidence required, will depend on the type of claim. For instance, one appropriate study might be regarded as sufficient to demonstrate that a component or ingredient retains its expected and well-established physiological effect after processing of a certain food product. On the other hand, at least two studies with the final product and appropriate supporting evidence, e.g. mechanistic animal studies, would be required to substantiate a truly “new” claim.

## ■ Sources of scientific data

### Human intervention studies

Well-designed, randomised controlled trials (RCTs) provide the most persuasive evidence of efficacy in hu-

man subjects. In a RCT, subjects similar to each other are randomly assigned either to receive the intervention or not to receive the intervention. As a result, subjects who are most likely to have a favourable outcome, independent of any intervention, are not preferentially selected to receive the intervention being studied (selection bias). Bias may be further reduced if the researcher who assesses the outcome does not know which subjects received the intervention (double blinding).

RCTs can be poor – when the number of subjects tested is too small, when there is no independent confirmation of the experimental dietary change, or when the outcome data may be insecure. RCTs of dietary change through to disease outcome are uncommon and are most likely to involve addition or subtraction of a single component or nutrient. For example, it may not be possible to use a placebo control group for food studies, and subjects in such studies may not be blinded to the intervention. As a result of the greater likelihood for confounders and bias, intervention studies with foods may generate data that have less certainty than data from drug or food supplement intervention studies. For some of the most firmly accepted precepts of healthy eating, RCT findings are unlikely to be available. Similarly, most of the health claims allowed by the USFDA have not been supported by RCTs. Hence, the lack of well-designed RCTs should not disqualify a body of substantiating evidence from other sources [17]. There are, however, hundreds of controlled trials of dietary change with a surrogate outcome – a risk factor such as plasma lipids, plasma glucose or blood pressure. Meta-analysis of collections of such trials can be used to establish scientific linkages between diet and disease. For example, saturated fat has been shown to increase plasma total cholesterol and many cohort studies have found that plasma total cholesterol is a biomarker for coronary heart disease (CHD). Hence, saturated fat increases the risk of CHD.

### Human observational studies

Whereas in an intervention study, the investigator controls whether the subjects receive an exposure or an intervention, in an observational study, the investigator has no control over the exposure or the intervention. There is no universally valid method for weighting categories of observational studies. In general, observational studies include – in descending order of persuasiveness – cohort (longitudinal) studies, case-control studies, cross-sectional studies, uncontrolled case series or cohort studies, time-series studies, ecological or cross-population studies, descriptive epidemiology, and case reports (see [23] for further detail). Observational studies may be prospective or retrospective. In prospective studies, investigators recruit subjects and observe them prior to the occurrence of the outcome. In retrospective



studies, investigators review the records of subjects and interview them after the outcome has occurred.

A common weakness of observational studies is the limited ability to ascertain the actual food, food component or nutrient intake for the population studied. Observational data are also generally restricted to the identification of associations between food substances and health outcomes, and often do not provide a sufficient basis for determining whether a substance/disease association reflects a causal rather than a coincidental relationship. Nevertheless, cohort (prospective) studies stand out among types of observational epidemiology for their driving role in building present concepts of diet and disease [17].

Human intervention and observational studies can uncover significant health-promoting or health-compromising nutritional effects in individuals, groups of individuals and in whole populations. The sequencing and annotation of the human genome and the development of genomics, proteomics and metabolomics will provide new opportunities to characterise the cause of the differences in biological responses and help to identify appropriate dietary measures that could make a profound contribution to health and well-being and the development of nutritional regimens for reducing the risk of disease [17, 24–27].

### Animal studies and in vitro studies

Animal studies and in vitro studies would be considered as evidence to support a health claim. They can provide information on the mechanism of action, dose-response relationships and the processes that cause a disease or health-related condition. These studies also permit greater control over confounding variables, such as diet and genetics, and allow for more aggressive interventions. The strongest animal evidence is likely to be based on the use of appropriate animal models and data that have been reproduced in different laboratories. Ultimately, all these studies suffer from the uncertainties of extrapolating results to physiological effects in humans.

### ■ The use of biomarkers in human studies

The reliability of measurements of both the indicators of health and well-being and dietary intakes of a food or food component are key factors for the review of data for health claims. This was addressed in a recent EU project on biomarkers in relation to health and disease [28–30].

Biomarkers are defined as indicators of actual or possible changes of systemic, organ, tissue, cellular and sub-cellular structured and functional integrity, which can be used singly or in batteries to monitor health and exposure to compounds in populations and individuals. The EU DG X11 Concerted Action on Functional Food

Science in Europe (FUFOSE) Consensus Document suggested an outline of a scheme to link health claims for foods or food components with beneficial physiological effects to solid scientific evidence. FUFOSE suggested that the primary source of evidence for “enhanced function” and “reduced risk of disease” is only justifiable when based on appropriate, validated markers of exposure, enhanced function or reduction of disease risk (see Fig. 1).

The development of validated and predictive biomarkers is an essential research objective. Biomarkers must be both biologically and methodologically valid and should reflect a future health outcome at a stage when dietary intervention will be effective. There are a number of factors that influence the nature of the link between diet and health, and that impact upon the use of biomarkers. These include predisposition and susceptibility, predictivity and intervention/reversibility. By consideration of these factors, it may be possible to prioritise the specific diet/health issues and assess those markers that are used to confirm the link between a food or a food component and a physiological effect [30].

The use of biomarkers must be subject to critical evaluations taking into account intra-individual variation; the use of single measurements; timing of measurements and progression of disease; intake; absorption; metabolism; homeostatic regulation; other dietary, environmental and genetic influences; quality control in collections, processing, storage and analysis. Within a study, the biomarker should change in a biologically relevant way and the change should be statistically significant for the target group.

### ■ The evaluation of the quality of individual studies

The provision of an explicit and standardised appraisal of all relevant studies that have been identified is the starting point for determining the overall strengths and weaknesses of the data and for assessing the overall weight and quality of the evidence.

The features that are most important to address include:

- Appropriateness and validity of the methodology used (e. g. quality of the design, conduct, analysis and interpretation of the study)
- Completeness and description of the analytical methodology and quality control procedures
- Adequacy of the sample size to provide sufficient statistical power to detect a significant effect. Statistical methodology to ensure good experimental design, the appropriateness of tests applied and proper interpretation of “statistical significance”, i. e. assess both statistical and biological significance.
- Adequacy of the description of the study population characteristics. For example, factors such as age, gen-



der, distribution, race, socio-economic status, geographic location, family history, health status and motivation and relevance of the population to which the health claim is to be targeted. It is also important to state inclusion/exclusion criteria for subjects in the study, recruitment procedures to minimise selection bias and for controlled intervention, the matching and randomisation procedures employed to assign the subjects to the control and test groups.

- Characteristics of the intervention to ensure an appropriate level of intake to achieve the desired physiological effect, the background diets to which the test substance was added, the nature of the placebo, if appropriate, “lead-in” and “wash-out” periods, dietary compliance, the use of well-defined outcomes, including biomarkers
- The susceptibility of the data to measurement bias and confounding variables. These aspects are particularly important because an added nutrient or component may displace other nutrients in the diet and an observed health outcome may be the result of an unintended change, e.g. a reduction in total dietary energy intake and subsequent weight loss of subjects. Other potential confounders include variability in the quantity or quality of the food being administered, including the bioavailability of the active component.
- Biological plausibility of the known or postulated mechanism by which exposure to a food or food component may reasonably alter a health outcome.

### ■ Totality of evidence

After relevant, good quality studies have been identified and their strengths and weaknesses assessed, the totality of the evidence needs to be evaluated. The initial review of the whole body of data is to determine whether most of the evidence is derived from the more persuasive types of study designs, and that the research methodologies are sound. The design features and the quality of the research methodology should be considered together. Determining the weight of evidence as a whole requires assessment of the persuasiveness of each relevant study. Factors to be considered include the consistency of results across different studies and study designs, consistency among various populations and within them, the magnitude of effect, strength of association, dose-response relationships, temporal relationships, biological plausibility, specificity of effect and statistical validity.

The overall assessment should involve the application of scientific judgement and critical interpretation of the data as a whole. A meta-analysis can be considered as supporting evidence, rather than as primary evidence, that can confirm the validity of data concerning a

hypothesis. The assessment should not be a numerical addition of studies for and against, rather, a critical overall consideration of the evidence. Studies cannot be evaluated in isolation. The surrounding context of the scientific evidence is just as important as the internal validity of individual studies. Wide variation in outcomes of studies and inconsistent or conflicting results will raise serious questions about the adequacy of a manufacturer’s substantiation. Where there are inconsistencies in the evidence, it is important to examine whether there is a plausible explanation for those inconsistencies [31].

The final assessment involves judging a relationship to be valid if the evidence in support of the relationship outweighs the evidence against it. The assessment of the totality of the evidence should also be sufficient to permit the conclusion that a change in the dietary intake of the food or food component will result in a health benefit and/or health outcome, including a change in a disease endpoint.

### ■ Assessment of significant scientific agreement

The use of health claims should be subjected to rigorous substantiation on a case-by-case basis. In order for qualified experts to reach an informed opinion regarding a particular claim, the data and information that pertain to the claim must be available to the relevant scientific assessors. This information could be available in peer-reviewed journals and/or in unpublished studies, some of which may include confidential and sensitive information of a proprietary nature. Whenever the health claim is used, the studies substantiating the claim should be available in total, if required, to competent authorities, and in an appropriate form in the public domain [16].

Significant scientific agreement refers to the extent of agreement among qualified experts in an appropriate field and reflects the process of scientific discovery. The point of agreement within the relevant scientific community that an association between a food or a food component and a health benefit is valid depends on the strength and consistency of the body of evidence.

Fig. 2 provides a graphical representation of the interplay of considerations that contribute to determining whether significant scientific agreement has been achieved. The scheme illustrates how the various types and amounts of data for a food or food component and a health benefit can be combined to assess the overall strength and consistency of the scientific evidence. The scheme also reflects judgement, flexibility and responsiveness to the variety of combinations of data from different types of good quality studies that give rise to a body of evidence sufficient to establish the validity of a health claim.

## Independent review of the substantiating evidence

Many existing codes recommend that the scientific review be conducted by using independent experts, qualified by training and experience. The evidence-based review should use scientific principles, be comprehensive, unbiased and authoritative.

The composition of an expert body must be flexible to accommodate the breadth of subject matter. A core group could, for example, be augmented by ad hoc experts in the specific subject matter under review. Following the scientific assessments, regulators and policy makers could then use the information in the relevant regulatory, legal and social contexts.

It is desirable that the review process should have clear time scales without compromising the rigour and independence of the review.

The totality of scientific evidence in support of a generic or product-specific health claim must be presented clearly. The documentation must demonstrate the specific physiological effects and reflect the totality of the evidence without misinterpretation or overemphasis of relevant information. Table 4 makes some suggestions for the layout of relevant information.

**Table 4** Documentation of evidence

It is suggested that the documentation should:

- Include a clear and truthful summary of the appropriate scientific data
- Describe how the scientific data supporting the health claim have been collected and evaluated
- Explain the plausibility in terms of scientific knowledge
- Indicate where and how the dossier could be made available to relevant bodies

In addition, information should be available on:

- A description of the foods or food components. A trademark, brand name, fancy name and a copy of the product label (in draft form if not printed) should be included if available
- Examples of health claims to be made in either public health campaigns or advertising and other promotions are useful to evaluate the methods of communication of the benefit
- Identification of specific components or combination of components for which the health claim is made, if appropriate
- Details of any chemical analysis carried out and appropriate nutrition labelling and ingredient list
- A statement of intended use (level and frequency of consumption, storage, preparation, instructions for use, shelf-life etc.)
- Appropriate contra-indications or warnings (e. g. potential allergy or intolerance factors)
- Name and address and contact details of the organisation or company

## References

1. International Association of Consumer Food Organizations (1999) Functional Foods. Public Health Boon or 21<sup>st</sup> Century Quackery? An International Comparison of Regulatory Requirements and Marketing Trends, Washington, DC, pp 1–85
2. Bellisle F, Diplock AT, Hornstra G, Koltzko B, Roberfroid M, Salminen S, Saris WHM (1998) Functional food science in Europe. *British Journal of Nutrition* 80:1–193
3. Diplock AT, Aggett PJ, Ashwell M, Bornet F, Fern EB, Roberfroid MB (1999) Scientific concepts of functional foods in Europe: Consensus Document. *British Journal of Nutrition* 81:S1–S19
4. European Health Claims Forum (2001) Conference Proceedings. Leatherhead Publishing, LFRA Ltd, Surrey, pp 1–82
5. The Joint Health Claims Initiative (UK) (2000) Code of Practice on Health Claims on Foods, <http://www.jhci.co.uk>
6. Richardson DP (1996) Functional foods – shades of gray: an industry perspective. *Nutr Rev* 54:S174–S185
7. Coppens P, Bijlsma M, Craddock N, Herreman I, Hurt E, Bail-Collet YL, Loosen P (2001) Are foods bearing health claims medicinal products? *Scandinavian Journal of Nutrition* 45: 140–145
8. Codex Alimentarius Commission (1993) Codex Guidelines on Nutrition Labelling. CAC/GL 2-1985 (Rev. 1-1993)
9. Codex Alimentarius Commission (2002) Proposed Draft recommendations for use of health and nutrition claims. In: Report of the Thirtieth Session of the Codex Committee on Food Labelling, Halifax, Canada, 6–10 May 2002. ALINORM 03/22, Appendix VII CAC, Rome, <http://www.codexalimentarius.net/reports.asp>
10. Asp NG, Laser Reuterswärd A (1998) Proposal for an extension of the Swedish code on health claims to functional food products. *Scandinavian Journal of Nutrition* 42:119
11. European Parliament and the Council (2002) Directive 2000/13/EC of the European Parliament and of the Council of 20 March 2000 on the approximation of the laws of the Member States related to labelling, presentation and advertising of foodstuffs. *Official Journal of the European Communities* No L 109 of 06. 05. 2000:29
12. Codex Alimentarius Commission (1985) General Standard for the Labelling of and Claims for Prepackaged Foods for Special Dietary Uses. CODEX STAN 146
13. Council of Europe (1989) Council Directive 89/398/EEC of 3 May 1989 on the approximation of the laws of the Member States relating to foodstuffs intended for particular uses. *Official Journal L186* of 30. 6. 1989, as amended by Council Position 52/96 (OJ L315/1) and Directive 1999/41/EC (OJ L172/38 8.7.99)0027–0032
14. European Commission (1999) Commission Directive 1999/21/EC of 25 March 1999 on dietary foods for special medical purposes. *Official Journal of the European Communities* No L 091:0029–0036
15. European Parliament and the Council (1997) Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients. *Official Journal of the European Communities* L 43 14/02/1997:1–7
16. Council of Europe (2001) Technical Document Guidelines concerning scientific substantiation of health related claims for functional food, Strasbourg P.18, [http://www.coe.fr/soc\\_sp](http://www.coe.fr/soc_sp)
17. Truswell AS (2001) Levels and kinds of evidence for public-health nutrition. *Lancet* 357:1061–1062

18. US Food and Drug Administration (2001) Claims that can be made for Conventional Foods and Dietary Supplements. US FDA, Washington DC, <http://vm.cfsan.fda.gov/~dms/hclaims.html>
19. Health Canada (2000) Consultation Document: Standards of Evidence for Evaluating Foods with Health Claims. A Proposed Framework. June 2000. Health Canada, Ottawa, [http://www.hc-sc.gc.ca/food-aliment/english/sub-jects/health\\_claims/Consultation\\_doc\\_en.pdf](http://www.hc-sc.gc.ca/food-aliment/english/sub-jects/health_claims/Consultation_doc_en.pdf)
20. Australia New Zealand Food Authority (2000) Development of Joint Australia New Zealand Food Standards as part of the process of the Review of the Food Standards Code: Review of Health and Related Claims Full Assessment Report Proposal P153 and Pilot for Management Framework for Health Claims Draft Inquiry Report Proposal P170. ANZFA, Canberra, [http://www.anzfa.gov.au/documents/information\\_circular\\_02-01/p153.pdf](http://www.anzfa.gov.au/documents/information_circular_02-01/p153.pdf)
21. Asp NG, Laser Reuterswärd A (1998) Proposal for an extension of the Swedish code on health claims to functional food products. *Scandinavian Journal of Nutrition* 42:119
22. Netherlands Nutrition Centre (1998) Code of Practice assessing the scientific evidence for health benefits stated in health claims on food and drink products, <http://www.voedingscentrum.nl>
23. US Food and Drug Administration, Center for Food Safety and Applied Nutrition Office of Special Nutritionals (1999) Guidance for Industry. Significant Scientific Agreement in the Review of Health Claims for Conventional Foods and Dietary Supplements. US FDA, Washington DC, <http://vm.cfsan.fda.gov/~dms/ssaguide.html>
24. DellaPenna D (1999) Nutritional genomics: manipulating plant micronutrients to improve human health. *Science* 285:375–379
25. Guengerich FP (2001) Functional genomics and proteomics applied to the study of nutritional metabolism. *Nutr Rev* 59:259–263
26. Minihane AM (2001) The postgenome era: opportunities for the food industry to meet the nutritional needs of the future. *Nutrition Bulletin* 26:341–343
27. Trayhurn P (2000) Proteomics and nutrition – a science for the first decade of the new millennium. *Br J Nutr* 83:1–2
28. Crews H, Alink G, Andersen R, Braesco V, Holst B, Maiani G, Ovesen L, Scotter M, Solfrizzo M, van den BR, Verhagen H, Williamson G (2001) A critical assessment of some biomarker approaches linked with dietary intake. *Br J Nutr* 86(Suppl 1):S5–35
29. Wild CP, Andersson C, O'Brien NM, Wilson L, Woods JA (2001) A critical evaluation of the application of biomarkers in epidemiological studies on diet and health. *Br J Nutr* 86(Suppl 1):S37–S53
30. Branca F, Hanley AB, Pool-Zobel B, Verhagen H (2001) Biomarkers in disease and health. *Br J Nutr* 86(Suppl 1):S55–S92
31. Federal Trade Commission (2002) Dietary Supplements: An Advertising Guide for Industry. FTC, Washington DC, <http://www.ftc.gov/bcp/online/pubs/buspubs/dietsupp.htm>
32. Swedish Nutrition Foundation (1996) Health claims in the labelling and marketing of food products, the food industry rules (self regulating programme). Revised Programme
33. Department of Health and Human Services. Food and Drug Administration (2000) Regulations on Statements made for Dietary Supplements Concerning the Effect of the Products on the Structure or Function of the Body; Final Rule. 21 CFR Part 101 (65, number 4), pp 999–1050 <http://www.cfsan.fda.gov/~lrd/fr001006.html>
34. CIAA (2002) Code of Practice on the use of health Claims. CIAA, CIAA Document MIN/066/9E Final, Brussels, Belgium, <http://www.ciaa.be>
35. The Ministry of Health, Labour and Welfare Japan (27–3–2001) Revisions and Guidelines regarding the System for Food and Health Claims. Shokushinhatsu, No.17, Japan
36. US Food and Drug Administration (1998) Guidance for Industry. Notification of a Health Claim or Nutrient Content Claim Based on an Authoritative Statement of a Scientific Body. US FDA, Washington DC, <http://vm.cfsan.fda.gov/~dms/hclmguid.html>
37. Fédération de l'Industrie Alimentaire (FEVIA) (1998) Health Claims, Code of Conduct Definitions, scope, principles. Draft