Eur J Nutr (2005) [Suppl 1] 44 : I/5–I/30
DOI 10.1007/s00394-005-1104-3

PASSCLAIM*
Consensus on Criteria

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EJN 1104

Executive summary

The Process for the Assessment of Scientific Support for Claims on Foods (PASSCLAIM) had the following principal objectives:

- to evaluate existing schemes which assess scientific substantiation;
- to produce a generic tool for assessing the scientific support for health claims for foods;
- to establish criteria for markers which can be used to explore the links between diet and health.

It has involved more than 160 experts from academia, industry, public interest groups and the regulatory environment. It has been supported by the Fifth European Community Framework Programme for Research and Technological Development and was co-ordinated by ILSI Europe.

Through an iterative process of discussion in expert groups and workshops, a set of criteria which define requirements for assessing the quality of scientific data reporting the impact of foods and food components on health and well-being have been proposed and progressively refined. As a basis for the development of the criteria, seven comprehensive reviews were produced covering examples of areas of diet, health and performance in which health claims are likely to be made. An eighth paper reviewed existing processes and regulations.

The criteria:

- emphasise the need for direct evidence of benefit to humans in circumstances consistent with the likely use of the food in order for a case to be made;
- recognise the usefulness of markers of intermediate effects when ideal endpoints are not accessible to measurement;
- stress the importance of using only those markers which are of proven validity; and
- highlight the necessity of ensuring that the magnitude and character of effects on which claims are based are statistically and biologically meaningful.

The criteria are presented in summary form, with an outline of the context within which the detailed assessment of the scientific evidence is to be undertaken. The criteria and the context within which they are to be assessed are further discussed and explained in depth in the present document. Whereas requirements relating to safety and other aspects of legislation are part of the context in which foods carrying claims are presented, and must be complied with, they are not part of the PASSCLAIM process and are excluded from the scope of the criteria.

The context within which a claim and the case made in its support should be assessed, involves considering existing legislation and dietary guidelines; the need for review in the light of evolving science; and the comprehensibility of the claim to consumers. These aspects are not thought to be part of the scientific criteria reviewed by PASSCLAIM. They nevertheless provide the background against which the scientific validity of claims should be justified.

Criteria for the scientific substantiation of claims

1. **The food or food component to which the claimed effect is attributed should be characterised.**
2. **Substantiation of a claim should be based on human data, primarily from intervention studies the design of which should include the following considerations:**
   - **2 (a) Study groups that are representative of the target group.**
   - **2 (b) Appropriate controls.**
   - **2 (c) An adequate duration of exposure and follow up to demonstrate the intended effect.**
   - **2 (d) Characterisation of the study groups' background diet and other relevant aspects of lifestyle.**
   - **2 (e) An amount of the food or food component consistent with its intended pattern of consumption.**
   - **2 (f) The influence of the food matrix and dietary context on the functional effect of the component.**
   - **2 (g) Monitoring of subjects' compliance concerning intake of food or food component under test.**
   - **2 (h) The statistical power to test the hypothesis.**
3. **When the true endpoint of a claimed benefit cannot be measured directly, studies should use markers.**
4. **Markers should be:**
   - **– biologically valid in that they have a known relationship to the final outcome and their variability within the target population is known;**
   - **– methodologically valid with respect to their analytical characteristics.**
5. **Within a study the target variable should change in a statistically significant way and the change should be biologically meaningful for the target group consistent with the claim to be supported.**
6. **A claim should be scientifically substantiated by taking into account the totality of the available data and by weighing of the evidence.**

This document presents a consensus view of criteria which, if met, provide a reasonable assurance that scientific data underpinning health claims made for foods are adequate for the purpose and that the claims can be considered valid. It also discusses the relative strengths and limitations of types of scientific approaches and data

that are relevant to different health and disease states. The discussion provides guidance on the interpretation of the criteria.

The criteria describe the standards by which the quality and relevance of the scientific evidence including new data should be judged, and thus the extent to which claims based on them can be said to be scientifically valid. As the view of a broad-based partnership of scientific and other experts, the criteria provide a basis for harmonising the requirements for, and the assessment of, scientific data supporting health claims made on foods which has a potential for positive impact across a spectrum of stakeholder activities, including those of interest groups within (consumers, health professionals and industry) and across (national and international regulatory agencies) geographic regions.

By raising the level of awareness of the essential attributes of the scientific data supporting health claims, the criteria have the potential to increase public confidence in the role of diet in maintaining and improving health and well-being. By defining the quality and type of scientific data required to substantiate health claims, the criteria will assist industry, including small and medium sized enterprises, to identify the scope for new products offering health benefits to consumers. Where there is a lack of specific expertise or resource to undertake development projects, the need for sound evidence bases, as illustrated by these criteria, could be seen as a stimulus for industry and government to encourage and support co-operative initiatives. Thus a harmonised regulatory approach to health claims for foods, operating within a EU single market in an ethos of increased consumer awareness of nutrition, along with confidence in the validity of claims, will provide a driver for innovative production of healthier foods appropriate for modern and changing lifestyles and needs. Collectively these factors should benefit public health and increase the competitiveness of the European agri-food industry in the global market.

Abbreviations

BMD	Bone mineral density
EC	European Commission
FAO	Food and Agricultural Organization
FOSIE	Food Safety in Europe
FUFOSE	Functional Food Science in Europe
HDL	High-density lipoproteins
IUPAC	International Union of Pure and Applied Chemistry
LDL	Low-density lipoproteins
PASSCLAIM	Process for the Assessment of Scientific Support for Claims on Foods
QC	Quality control
RCT	Randomised controlled trial
SME	Small or Medium sized Enterprise
WHO	World Health Organization

Introduction

Background and objectives

Much attention is now being paid to health claims on foods, including enhanced function claims, reduction of disease risk claims and also nutrient function claims. There are already on the market many food products with claims about health effects beyond the simple provision of nutrients. One important basis for claims is the increasing number of reports of the effects of dietary components on body functions. However there is no scientific consensus as to how claims based on these reports should be evaluated at European level [1]. In the absence of such a consensus, different national and international bodies are applying various approaches in their attempt to regulate an evolving market. The resultant fragmentation of the regulatory framework for claims leads to diverse and, perhaps, contradictory messages to consumers about diet and health, and uncertainty for the industry. With this background, ILSI Europe initiated the Concerted Action 'Process for the Assessment of Scientific Support for Claims on Foods' (PASSCLAIM). Its objective is to define criteria for assessing the scientific support for claims made in relation to foods. There are three main reasons for assessing the scientific substantiation of claims: 1) to provide truthful information and to support consumer confidence in foods with claims, 2) to satisfy regulatory requirements, and 3) to allow fair market competition. The availability of agreed criteria for this process should facilitate the achievement of these goals in a harmonised fashion.

The project builds on a previous major EU project, 'Functional Food Science in Europe' (FUFOSE). The main thrust of the FUFOSE Consensus Document on Scientific Concepts of Functional Foods in Europe, produced as the final deliverable from the FUFOSE project, was a scheme to link claims for functional foods to solid scientific evidence [2]. FUFOSE suggested that any claim for 'enhanced function' and 'reduced risk of disease' should be scientifically justified. The key importance of valid markers of exposure, enhanced function or reduction of disease risk was highlighted (Fig. 1).

In particular with respect to disease risk reduction claims, it was noted that the true disease endpoint often cannot be measured directly for ethical or practical reasons. Therefore, the identification and validation of suitable markers were considered as key issues. Markers were classified as related to 1) exposure, 2) a target function or biological response, and 3) an appropriate intermediate endpoint of an improved state of health and well-being, or reduction of the risk of disease, or both.

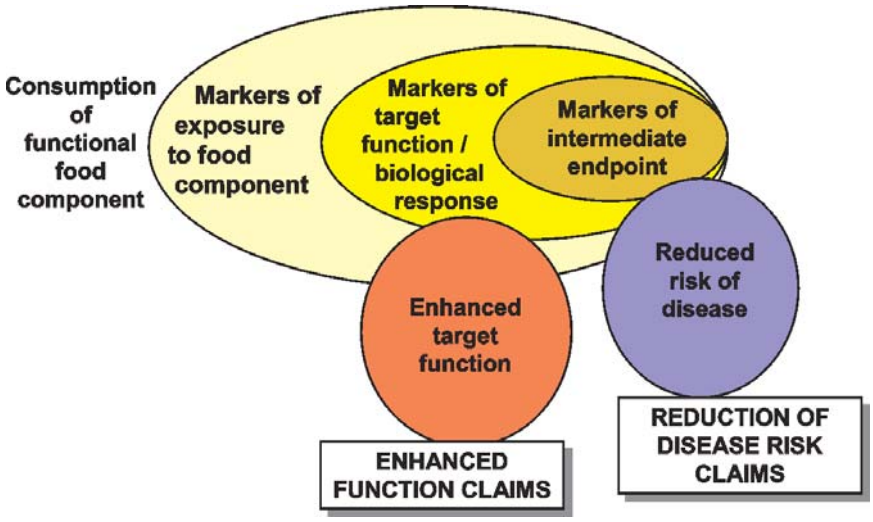

Fig. 1 FUFOSE concept of scientific evidence and corresponding health claims

The main objective of PASSCLAIM has been to produce a guidance tool to assess the scientific support for claims for foods and food components. The main outcome of the project is a set of common criteria that can be used as a basis for assessment of the scientific substantiation of claims. The way to develop valid scientific study designs and to identify, validate and use markers to explore the effects of diet on health was dealt with by seven expert groups, each focussed on a specific theme, and produced comprehensive reviews covering examples of areas of diet, health and performance. In addition, an eighth expert group comprehensively and critically evaluated existing legislation and voluntary codes of practice used to assess the scientific substantiation of claims around the world; this has been presented in a comprehensive review.

The PASSCLAIM project focussed on beneficial effects of foods and food components on health. Safety is a prerequisite for all foods. Considerations of nutritional safety are particularly relevant for foods for which claims are made relating to nutrition and health. However, safety is not a consideration in the data supporting the scientific validity of the claims themselves and safety issues were not within the scope of the PASSCLAIM project. Safety was the subject of another major European Commission (EC) concerted action, Food Safety in Europe (FOSIE) – Risk Assessment of Chemicals in Food and Diet [3]. The discussions in both projects underlined the need to look at risk assessments and benefit assessments in combination. As a consequence, a programme has been initiated to develop a common basis for the comparison of risks and benefits associated with a given food product or product modification.

Enhanced function claims were defined in FUFOSE [2] as claims that concern specific beneficial effects of nutrients and other substances on physiological and psychological functions or biological activities beyond their established role in growth, development and other normal functions of the body. In Codex Alimentarius working groups, nutrient function claims, referring to the normal physiological effects of nutrients in growth, development and normal functions of the body, have been included under health claims. In Codex terms, "Other function claims" are more or less equivalent to enhanced function claims. In the proposed EU regulation [4], "health claims describing a generally accepted role of a nutrient or other substance" would include both nutrient function claims and other function claims (Table 1).

A major legislative issue so far has been the fact that claims about prevention, alleviation and cure of diseases are confined to medicinal products. Accordingly, the mention of food effects in relation to disease on food labels or in other promotional material has been regarded as a medicinal claim. However, disease risk reduction by means of healthy diets is a well-established concept in nutrition and is a basis for official dietary recommendations. Accordingly, authorities in the USA have allowed generic disease risk reduction claims for certain foods since 1993. A major breakthrough in developments in Europe is that recently the EU Commission has also appreciated that foods may contribute to the reduction of the risk of disease and that such effects should be regulated in the context of food legislation [4]. This has provided the basis for the current development of an EU regulation on nutrition and health claims for foods, including the possibility to use disease risk reduction claims. The distinction between "the prevention of a disease" and "the reduction of the risk of a disease" is still being discussed.

The FUFOSE conclusions and principles are now taken to the next logical stage, which is that of applying the principles. The project 'Process for the Assessment of Scientific Support for Claims on Foods (PASSCLAIM)' starts with, and builds upon, the principles defined

Table 1 Health claims classification according to FUFOSE, Council of Europe, Codex Alimentarius and the proposed EU regulation

FUFOSE (1998)	Council of Europe (2001)	Codex Alimentarius (2003)	Proposed EU regulation (2003)
Nutrient function claims not considered	Nutrient function claims not considered	Nutrient function claims	Health claims related to the generally accepted role of nutrients and other substances
A. Enhanced function claims	A. Enhanced function claims	Other function claims	
B. Disease risk reduction claims	B. Disease risk reduction claims	Disease risk reduction claims	Health claims related to disease risk reduction

Nutrient function claims (sometimes referred to as structure function claims), enhanced function claims, and other function claims are closely related, but have been introduced at different stages of the claim development discussion. The dotted lines indicate that there is no absolute delineation between "nutrient function claims" on the one hand and "enhanced function/other function claims" on the other hand. A "new" function of a nutrient may be regarded as an enhanced/other function until, through further documentation, practice and familiarity, it becomes generally recognised as a "nutrient function claim". A function of a non-nutrient would be regarded as "other function" according to Codex, but as science advances, it may later fall under "generally recognised effects of nutrients and other substances" according to the proposed EU regulation [1]

within the FUFOSE project. The Concerted Action PASSCLAIM (QLK1–2000–00086) was supported by the EC, Quality of Life and Management of Living Resources Programme (QoL), Key Action 1 (KA1) on Food, Nutrition and Health, and is coordinated by ILSI Europe.

In the context of this report, the term "health claim" is understood in the sense defined by Codex Alimentarius – i. e. "any representation that states, suggests, or implies that a relationship exists between a food or a constituent of that food and health". In this paper, the word "claim" means "health claim" and includes all claims related to health, well-being and performance (including both physical and mental performance). The term "food component" includes components such as ingredients and food additives intentionally added to foods, as well as components that are part of the natural composition of foods.

Structure

Experts from academia, industry, public interest groups and regulatory bodies in 24 countries have contributed to the PASSCLAIM Project. In order to meet the project objectives, eight expert groups ("Individual Theme Groups" or ITGs) were set up involving experts from academia, regulatory bodies and the food industry. Representatives of public interest groups were also approached. Seven of the expert groups reviewed the scientific basis for claims in various areas of health and disease with a focus on markers. One group critically evaluated existing international approaches to the scientific substantiation of claims.

The development of criteria for the scientific substantiation of claims, based on the results of the expert groups, was the focus of a first and a second plenary meeting. A first set of draft interim criteria was discussed and modified at the first plenary meeting [5]. The interim criteria were then tested through practical application by the second phase expert groups and further developed at the second plenary meeting [6].

The structure of the project is illustrated in Fig. 2. The steps taken by the different expert groups were to:

- collate examples of potential types of claims in different areas from the perspective of physiological functions and, if it was relevant, disease states;
- describe the scientific requirements for the quality of data needed to support these claims and to evaluate the relevance of the scientific support;
- assess the usability of markers for the scientific substantiation of the claims;
- develop a list of criteria for use in assessing the portfolio of evidence submitted to substantiate identified and potential claims.

Phase One expert groups

Initially, in 2001, four 'Phase One' expert groups were set up [5]. The following summary reflects the discussions and conclusions of these expert groups.

Synthesis and review of existing processes [1]. This group critically evaluated most of the existing international codes of practices and regulations in relation to the scientific substantiation of claims with a view to identifying common ideas, definitions, best practice and methodology to underpin current and future developments. The group summarised the regulatory approaches to claims as set out by seven countries and two international organisations. A common feature in all these approaches is the requirement for solid scientific substantiation. The group focussed on processes existing up to 2002 for assessing the scientific substantiation of claims, which includes identification of all relevant studies, evaluation and interpretation of the totality of the evidence and the concept of "significant scientific agreement". The group proposed a procedure for reviewing the evidence in support of claims, a protocol for extracting data from individual research papers in a systematic and consistent manner and a template for the documentation of evidence.

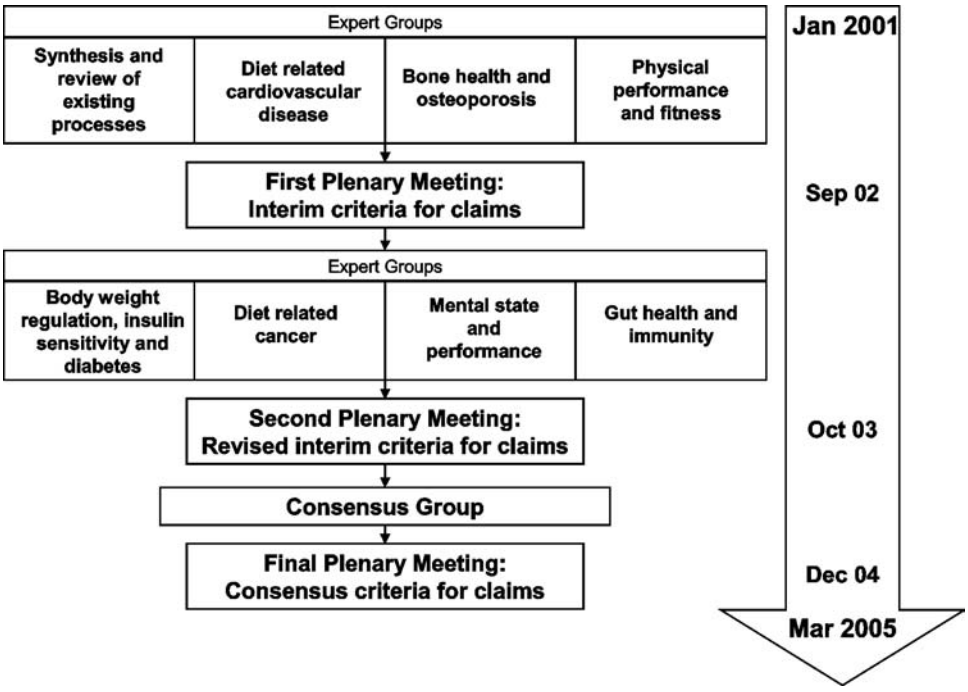

Fig. 2 Structure of the PASSCLAIM project

Diet-related cardiovascular disease [7]. From the wealth of publications in one of the most researched areas of food and health, the group concluded that LDL cholesterol and blood pressure are well-established markers generally accepted as related to changes in risk of cardiovascular diseases. Claims for enhanced function could be made for diet-related changes in LDL cholesterol and blood pressure and, since the relationship with disease risk is well-established, changes in these markers would also support disease risk reduction claims. HDL cholesterol, fasting triacylglycerol and plasma homocysteine are established as examples of markers sensitive to dietary factors and are validated methodologically, but it is as yet not clear to what extent changes in these markers reflect enhanced function and reduction of disease risk. For haemostatic function and oxidative damage, there is a need to develop and validate markers of enhanced function and disease risk reduction that are sensitive to dietary changes.

Bone health and osteoporosis [8]. Although bone health problems encompass many skeletal disorders, the group focussed on osteoporosis because this is a major public health issue in the EU. Bone mineral density (BMD), a measure of the calcium content in bones, was identified as an example of a marker of enhanced function in relation to bone strength for people of any age and sex. For people over 50 years of age living in countries with a high risk of fracture, BMD was considered to be a good marker of fracture risk, meaning that changes in BMD caused by a food component could provide evidence of a reduction in disease risk, that is reduced risk of fractures.

Physical performance and fitness [9]. The group reviewed claims relating to muscular strength and power, endurance, energy supply and recovery, hydration status, flexibility, tissue growth, and general immune functions. Many methods for measuring these fitness parameters as evidence for claims were examined, including tests of muscle strength, energy metabolism, food intake, body composition, gastrointestinal function and immune function. A database of methods including advantages and disadvantages of use of these methods was generated. The group concluded that for all physical performance and fitness domains, there are markers and endpoints available that fulfil the criteria for the substantiation of claims. For most areas, reliability and validity were considered to be good. On the other hand, with respect to immune functions in relation to physical performance and fitness, interpretation of the available markers and endpoints was considered problematic.

First Plenary Meeting

The information resulting from the Phase One expert groups provided the building blocks for a first draft set of interim criteria for the scientific substantiation of claims on foods and food components. This was the starting point for discussions at the first Plenary Meeting, held in Berlin, Germany in September 2002, and interim criteria were the main output from the meeting.

The reports of "Phase One" expert groups and an interim set of criteria were published [5].

Phase Two expert groups

In the Second Phase of the project, the "interim criteria" [5] were used by four further expert groups ("Phase Two" expert groups) during 2002–2003 to explore the following additional areas [6], and the principal conclusions from these groups are summarised below.

Body weight regulation, insulin sensitivity and diabetes [10]. The biological functions underlying these three conditions were characterised and related to the corresponding diseases overweight, metabolic syndrome and diabetes. The group was able to identify good markers and reliable measurement methods for the modulation of each key target function with its range of associated functions. Regarding body weight regulation, the target function is body fat deposition, which can be measured with both laboratory and field methods. A number of associated functions involved in the regulation of body fat can be measured as well. Insulin sensitivity is the target function in the metabolic syndrome and validated methods are available for its measurement. Measurable functions associated with insulin sensitivity include lipotoxicity, body fat composition, oxidative stress, inflammation and vascular function. In diabetes mellitus, the target function is regulation of blood glucose level, associated with functions such as glucose delivery to the bloodstream, glucose utilisation, and insulin secretion and sensitivity.

Diet-related cancer [11]. It has been suggested that approximately one third of all cancers are caused by inappropriate intakes and imbalances of food components. It is therefore of key importance to develop clear criteria to substantiate cancer risk reduction claims for foods or food components. The group focused on tumours of the colon, lung, breast and prostate. Eighteen markers were identified that represent events at various points in the chain from the initial exposure to carcinogens to the overt malignant tumour. The true endpoint in this area – the malignant human tumour – usually cannot be measured as a basis for claims. Pre-cancerous lesions, such as polyps in the colon, were regarded as a good example of a strong marker, and the recurrence of polyps in humans was regarded as the only good marker currently available on which to base reduction of disease risk claims. The development of markers of events in the pathogenic process, which can be used as surrogate endpoints, is therefore essential.

Mental state and performance [12]. Foods and drinks can influence brain functions and affect mental state and performance. Claims relating to several aspects of mental function can be substantiated using validated scientific instruments (tests, questionnaires etc.). The group examined mood, arousal (including activation, vigilance, attention and sleep), motivation and effort, perception, memory and intelligence. For each of these functions, a critical review of validated instruments was presented. In the area of mental effects, the final endpoint (improved function) can often be assessed directly using appropriate tests as opposed to physiological or other intermediate markers. In other cases, markers can be used as in other fields. The group concluded that validated methodologies exist to generate sound scientific evidence supporting the beneficial influence of many foods and nutrients on a broad variety of mental functions.

Gut health and immunity [13]. Many parameters of digestion can be measured, such as absorption and secretion, bowel habit and transit time, the gut flora, gastric emptying and motility, but interpretation is complicated by the large individual variability within what is considered to be a normal range. The group defined normal function as far as possible and methods for measuring it. The well recognised but ill-defined concept of gastrointestinal well-being was also discussed and identified as an important area for future method development. The immune system was seen as being difficult to make quantitative judgements about. No single test can define immune function but measurement of several parameters in combination can be used to assess functional capacity.

Second Plenary Meeting

The interim criteria resulting from the First Plenary Meeting were developed further at the Second Plenary Meeting held in Bordeaux, France in October 2003, taking into consideration the outcome of the Phase Two expert groups. Their reports formed the starting point for discussions at the meeting. The meeting resulted in proposals for a number of changes to the interim criteria and a summary of the discussion and comments from the meeting participants have been published [6].

Consensus Group

In the third phase of the PASSCLAIM project during 2004, a Consensus Group* was formed whose role was to refine and clarify the criteria for the assessment of the scientific support for claims on foods and food components taking into account the input from the expert groups, from the working groups and general discussions at the First and Second Plenary Meetings, and from individual comments.

* The members of the Consensus Group are the authors of this document.

Final Plenary Meeting

The draft set of criteria proposed by the Consensus Group was reviewed by the Final Plenary Meeting held in Lisbon, Portugal in December 2004, resulting in the final set of criteria presented in this document.

A number of general points have been discussed which relate to the context in which claims must be assessed. Fulfilling these is a prerequisite to the assessment of the portfolio of submitted evidence. After these contextual conditions are discussed, the proposed final criteria are presented, accompanied by summaries of the motives, explanations, comments and discussions behind their development.

The criteria relate specifically to the assessment of scientific evidence and information submitted to support claims on foods. They have not been developed as guidelines for study protocols and the acquisition of that evidence, but they nevertheless indicate the quality and nature of the evidence such protocols should produce.

Context for the scientific substantiation of claims

Evidence for the substantiation of claims needs to address some core principles which should be followed in providing an evidence-based justification for a claim. Some general aspects are outside the scope of the PASSCLAIM project because they do not deal with the science base. Others have generic implications relating to the scientific evidence and these are reviewed here. The specific characteristics of the evidence to be presented in the scientific substantiation of claims are considered in later sections of this document.

Foods and food components for which a claim is made should comply with existing legislation and fit into a healthy diet

Foods with claims should comply with all relevant regulations, including those relating to safety. The need for compliance with all relevant legislation and dietary guidelines in their respective markets relates primarily to ensuring the safety, including nutritional safety, of foods. A major purpose of food legislation is to ensure that under normal conditions of use a food is safe for the consumer. Accordingly, foods and food components for which claims are made need to be assessed for possible undesired side effects, including undesirable nutritional effects, according to the same standards that are applied to other foods and food components. They should also fit into a healthy diet.

Regulations should in principle reflect the evolving science base taking into account new scientific developments as appropriate

Regulatory and advisory agencies should be alert and responsive to the continuous research and improving scientific knowledge concerning the functionality of foods. The developing science base would be expected to lead not only to new claims but also to the need periodically to re-assess existing claims.

FUFOSE [2] and the expert groups within PASSCLAIM have demonstrated the principles for the scientific substantiation of a wide range of health benefits, and have illustrated these with specific examples, relating to physiological, psychological and mental functions [12, 14], of which several have been accepted as bases for claims by national authorities [1]. The decision on the justification of a claim should give due weight to current knowledge and the evidence-base for outcomes, and the primary basis for allowing a claim should be the soundness of the science or evidence-base.

A claim should reflect its scientific basis and, at the same time, should be understandable, and not be misleading for the intended consumer

A claim needs to be scientifically correct and understood by the intended consumers. Conversely, the need to use consumer friendly language should not conceal any lack of scientific substantiation of the proposed claim. If only part or parts of the population can be expected to experience the claimed benefit, this should be clearly stated and those who would be expected to experience the benefit should be identified. Otherwise consumers may be misled.

Claims can help to translate scientific learning into useful communication to the consumer. Ultimately, in this context, the investment is only justified if research demonstrates a clear health benefit that is communicated to the consumer. As such, claims may be a valuable means of promoting public understanding of science.

Criteria for the scientific substantiation of claims

Criterion 1. The food or food component to which the claimed effect is attributed should be characterised.

The food or food component for which a claim is made must be sufficiently characterised and described in the submission to allow an assessment of the validity of the scientific case made in support of the claim. The proper design of a programme of scientific studies requires that the food or food component be sufficiently characterised at the outset to enable comparability between studies and to ensure that the levels of exposure can be linked quantitatively to the claimed effect. Knowledge of effects, either beneficial or adverse, may need also to be related to the particular composition of the food matrix (see criterion 2 (f)).

Some aspects of this criterion would be covered by

existing legislation (Context for the scientific substantiation of claims) but it is important to emphasise that information should be provided on the origin and nature (including processing methods) of the component or product for which the claim is being made. Furthermore, evidence should be provided that the food or component of the food for which the claim is made is sufficiently standardised to ensure that the composition of the marketed product reflects fully and consistently the composition and nature of the material for which the data (see criterion 2) are provided. It is also important that the characterised food or food component relates to the food or component as it is consumed.

Criterion 2. Substantiation of a claim should be based on human data, primarily from intervention studies the design of which should include the following considerations:

- **2 (a) Study groups that are representative of the target group.**
- **2 (b) Appropriate controls.**
- **2 (c) An adequate duration of exposure and follow up to demonstrate the intended effect.**
- **2 (d) Characterisation of the study groups' background diet and other relevant aspects of lifestyle.**
- **2 (e) An amount of the food or food component consistent with its intended pattern of consumption.**
- **2 (f) The influence of the food matrix and dietary context on the functional effect of the component.**
- **2 (g) Monitoring of subjects' compliance concerning intake of food or food component under test.**
- **2 (h) The statistical power to test the hypothesis.**

2. Substantiation of a claim should be based on human data, primarily from intervention studies.

A claim can only be considered substantiated if there is a body of evidence that demonstrates an effect in the target population (see Table 2).

There are many forms of human studies, which can broadly be classified into intervention and observational. Supporting evidence may be based on animal, in vitro or modelling experiments.

Intervention studies include the randomised controlled trial (RCT) in healthy subjects, or in patients in which case they are called clinical trials, and studies looking at physiological or psychological effects. Of all studies, RCTs are thought to provide the best standard of evidence. An RCT is a study in which people are allocated at random to receive one of two or more interventions, one of which would usually be an inactive or control intervention. They are often the final piece of evidence for a claim, after data have been gathered from observational and other types of study. Endpoints can include markers of risk as well as physiological changes and other health outcomes. Since reproducibility of an effect is fundamental to progress in biological science, more than one RCT are desirable.

Table 2 Categories of evidence that may be used in the substantiation process

Intervention
Randomised controlled trials
Clinical trials
Physiological and psychological trials
Observational
Prospective (cohort)
Cross-sectional (analytical)
Case-control
Supporting
Animal
In vitro cell and molecular
Studies of genotype
Modelling (of mechanism)

Physiological and psychological studies have a long and distinguished history in the testing of hypotheses linking food and food components to health. These studies are also hypothesis driven and have to meet rigorous standards of research governance and laboratory practice, statistical design and ethical probity and still form one of the major inputs into understanding the role of diet and health. In the historical context, such studies were the predecessors of the modern RCT study design. In the current context, they provide means for a detailed characterisation of effects and their possible mechanistic bases. They require healthy subjects in a highly controlled environment and allow integration of cellular and molecular studies into whole body metabolism. They also provide a good basis for dose-response studies. In addition, they may be carried out in a randomised fashion, with or without cross-over between conditions.

Clinical studies (i. e. studies in patients) might be used for substantiation of claims for the general population although they are essentially studies of people who are ill and who may be receiving treatment such as drugs and whose physiological functions may be disturbed in many ways. There are potential problems with these studies because ill health can affect dietary intake, nutritional state and metabolism and there can be difficulties selecting an appropriate control group. However, there is often a continuous spectrum in a physiological variable, such as blood pressure, cholesterol, or bowel habit between healthy and disease states, and subjects

"at risk" are legitimate targets for claims. In these circumstances clinical studies can usefully contribute to the process.

Observational studies are often loosely referred to as epidemiological studies. They include prospective (cohort) studies, case control and cross-sectional (analytical) studies. In a cross-sectional study, observations on suspected causes and outcomes are made at one point in time. Variables, such as salt intake in individuals and blood pressure, can be measured in a group of subjects and an assessment made of whether they are associated. Gross national measures of dietary intake, for example red wine consumption, can be related across different populations to national death rates of cardiovascular diseases. An important drawback from the cross-sectional approach is that it is not known whether exposure to the putative cause being measured actually preceded the outcome of interest. Case-control studies aim to address this limitation by comparing subjects with and without disease and assessing past exposure in both groups in relation to suspected causes. In this type of study, however, recall bias arising from the retrospective estimation of exposure is a drawback. This shortcoming can be addressed by a prospective study design in which a group of subjects without disease (a "cohort") are followed in time and their exposure to putative causative factors and the subsequent development of disease are monitored with a view to establishing whether the temporal incidence of disease can be related to exposure to the factors of interest. The main remaining drawback with this type of study is the difficulty of accounting for unknown confounding factors, which influence the incidence of disease.

The probability of a causal relationship in human studies can, according to Bradford-Hill, be analysed with reference to five key features [15, 16] if these are applied to the interpretation of data relating to evidence supporting claims for food then they are:

- Temporality: exposure to the possible cause must precede the outcome;
- The strength of the relationship: the stronger the association, the more probable that it is causal;
- A dose-response effect;
- Consistency across all lines of evidence and studies;
- Existence of an analogy.

The strength of evidence derived from observational studies differs depending on methodology. If they are all well designed, well performed and well analysed findings in prospective cohort studies should receive more weight than data from case-control and cross-sectional studies.

For studies of food, the anatomy and physiology of humans and animals are generally not sufficiently comparable to allow evidence from animal experiments to provide the basis for claims for humans. There are major differences in the amount and composition of food intake and in longevity, lipid metabolism, gastrointestinal function and microbiology amongst species. Animal studies can, however, provide insights that may be used in the design of human studies and may be necessary in circumstances where the use of human subjects is unethical. They may provide supporting evidence in cases where the comparability of specific parameters between animal and human has been established.

In vitro cellular and molecular studies often provide supportive evidence of the effect of food and food components on cell function. They do not on their own indicate a health benefit or change in physiology that might be the basis for a claim. However, such studies can provide insights into mechanisms and can lead to the identification of markers for use in other studies. They are considered especially useful for looking at the genetic control of metabolism. Such studies should:

- use cell lines appropriate to human tissue;
- have functionally relevant genes and proteins expressed;
- use defined exposures to the food or food component;
- be repeatable in more than one experimental system.

Many laboratory or computer based models are now used in nutrition to circumvent the long and costly procedure of human studies, to dissect out mechanisms and predict behaviour in biological systems. Such models can provide additional evidence for the substantiation process.

For all studies and methodologies, quality and power may take precedence over the type of study in weighing evidence for the substantiation process (criterion 6).

International and national expert review panels, such as the Food and Agricultural Organization of the United Nations (FAO) and the World Health Organization (WHO), from time to time publish a collective view on diet and a particular aspect of health. These reviews, which may be based on many of the same strands of evidence as would be used in the substantiation process for a claim, can be used to inform this process and provide valuable background information, especially to support generic claims.

Mechanism. A mechanism expressed in terms of a physiological, psychological or cellular function that explains the association between observed dietary intake and resulting health effects, adds credibility to a claim, and provides strategies for the development of markers (see criterion 3). Historically, however, elucidation of mechanisms has often followed the demonstration of health benefits of food components or foods and the implementation of public policy. A classic example of this would be the recommendation more than 50 years ago, resultant upon the Seven Countries Studies, of a reduction in dietary saturated fat to decrease the risk of coro-

nary heart disease. The mechanisms involved in fat, lipid metabolism and atheroma are still not yet fully understood. For substantiation of a claim, it is, therefore, currently more important to demonstrate a consistent effect of a food or food component on health across a range of studies than to have a scientifically substantiated mechanism.

A mechanism, therefore, is not essential, but could be important in studies where markers were being used as surrogates because the relevant health endpoints such as, for example, prevention of fracture or reduction of risk of cancer, cannot be assessed directly. A problem with mechanisms that should also be taken into consideration is that the understanding of them tends to evolve as experimental data are forthcoming. At a point in time, therefore, one mechanism may be accepted, but later another may be better demonstrated. This then alters the perception of the nature of health itself and the understanding of the role of diet, which can change from generation to generation.

Nevertheless, an understanding of mechanisms is valuable because it allows the development of products more specifically to alter physiological systems with benefit to health. Therefore, human intervention studies designed for the development of mechanistic hypotheses, including collection of data on absorption, distribution, metabolism and excretion of the food or food component under test, should be encouraged.

Although a clear mechanism is not essential to progress claims in relation to dietary components, most if not all of the PASSCLAIM expert groups detailed the physiological, metabolic and molecular events that link markers with physiological and health effects. In other words, for many claims substantial bodies of knowledge already exist which allow mechanisms to be proposed and hypotheses for the effect to be described.

The design of studies should include the following considerations:

2(a) Study groups that are representative of the target group

Study groups should match as nearly as possible the target group, considering, as is appropriate for the food or food component and outcome under study, physiological and other variability arising from, for example, age, gender, diet, activity and smoking habits and other lifestyle factors. Where relevant, genotype should be taken into account.

Results gathered from a study group will be extrapolated to the group targeted by the claim. This could be either the whole population, or a specific sub-group (elderly, obese, smokers, runners, students, pregnant women). The effects induced by a food or food component in the study group are expected to occur in the targeted group, therefore the physiology or psychology of the study group should be representative of the target group. When the functions and the mechanisms involved in the claimed effect are distributed in the same way in the whole population there is no need to have specific data on sub-groups.

When a claim is specifically addressing a target group, obese people for example, studies on cohorts from this target group are essential. The appropriateness of the study group must always be considered on a case by case basis.

Identification of genotype pertinent to the physiological or psychological process under study is becoming increasingly feasible, and important for interpretation of results. For example there are now well recognised polymorphisms in the genes controlling the metabolism of folic acid, isoflavones and lipoproteins, which may affect the outcome of studies.

The issue generally is to avoid a study group that is not representative of the target population. For example, reduction of osteoporosis in post-menopausal women cannot be extrapolated from studies on young women nor from studies on men.

In all human studies the following factors should be considered and addressed when relevant:

- Age
- Gender
- Ethnic origin
- Genotype relevant to the function under study
- Lifestyle factors, for example – smoking, physical activity, alcohol consumption
- Body weight and height
- Menstrual cycle
- Usual diet
- Environmental conditions such as climate

2(b) Appropriate controls

Defining an appropriate control is often not easy in dietetic and nutritional studies. The amount of food consumed every day is roughly constant and when a new food is added to a diet, another may be left out or eaten in a smaller quantity. Therefore the addition of a food or food component may induce an effect by itself by the removal or displacement of another food. This is known as a passive effect and was the original explanation for the effect on cholesterol that is seen when dietary saturated fat is substituted with polyunsaturated fat.

The second difficulty is that many foods cannot be studied in a 'blinded' way. For example it would be difficult to find a suitable control in a study supporting the beneficial effect of consuming fruits and vegetables. An appropriate design and randomisation is required, including, in cross-over studies, adequate wash-out periods, and the control will be a usual food providing similar nutrients. On the other hand, when a component can be hidden in a product then the use of a control product without the component is recommended. Whenever possible a control product should be used.

The postulated active principals of the tested food must be either absent, or present at a known concentration, in the food given to the control group. This concentration must be significantly different from (usually significantly lower than) that in the test food.

Not only the food or food component, but the process of the study itself can have objective or subjective effects or both, on the study outcome. These may not actually be related to specific effects emanating from the test substance. Such placebo or nocebo phenomena may happen for both control and test products and need to be considered in the study design.

The claim must be assessed on the product as it is intended to be consumed. This means that normally the test and control material should be the same as, or closely represent the food or food component as it is intended to be marketed and purchased.

Subjects should be selected on the basis that the appropriate control group is one with a typical diet, and not a special diet that might interfere with the intended benefit. For example, it might not be appropriate to use vegetarians to test the effect of an added fibre.

2(c) An adequate duration of exposure and follow up to demonstrate the intended effect

There are two aspects to this criterion. These are ensuring (i) that there has been a suitable period of exposure to the food or food component (period of intake), and (ii) that the duration of observation is long enough for the expected effect to occur, and, if necessary, to show that the benefit is sustained.

The effects of a food may appear after consumption on a single or few occasions; for example the effect of glucose on memory performance or the effect of low glycaemic index foods on post-meal satiety. Alternatively a food may need to be consumed over a number of weeks before an effect occurs; examples of this include changes induced by prebiotics on intestinal function; or by stanols or sterols on cholesterol metabolism. Sometimes months or years might be needed to observe key effects; for example changes in bone density in response to calcium: any evidence of a reduced risk of certain cancers: and the impact of low glycaemic index foods on the risk of diabetes and obesity. A human intervention study must ensure that the product is ingested long enough to allow the claimed effect to appear. In many instances this will not be practicable and alternative approaches to assessing the claimed benefits are needed (criterion 3).

Equally important is that effects can appear in people after variable delays following intake of the food. In the simplest situation, an effect appears after a predictable time delay, increases to reach a plateau and then decreases and disappears. Other effects are bi-phasic: a change in a biological parameter can be followed by an opposite change. Some but not all effects are cumulative over time. Some substances may progressively induce tolerance, so that the observed effect becomes attenuated. There may be certain periods during which effects would occur and need to be observed. Intervention studies should consider if and how all these possibilities should be addressed.

The sustainability and nature of the effect with continuing and discontinuing intakes need to be characterised. For example, a pro- or prebiotic may produce a change in gut bacteria within a few days but the sustainability of this effect with continued ingestion of the prebiotic, or the persistence of the effect if consumption of the prebiotic stops, need to be known.

A further example is the functional effect of low glycaemic index foods, which can be assessed at various intervals after single or repeated intakes. Post-ingestive glycaemic and insulinaemic effects should be studied in the hours following intake and satiety should also be studied over the hours that follow ingestion. Changes in body fat, especially visceral fat, can be observed following repeated daily intake over weeks or months. A decreased risk of developing the metabolic syndrome, also called the insulin resistance syndrome, can be assessed over months or years of regular intake. The risk of developing diabetes mellitus and cardiovascular diseases should also be assessed over several years. Similar arguments can be made in relation to diet and the prevention of cancer, which is a multistage process occurring over many years.

2(d) Characterisation of the study groups' background diet and other relevant aspects of lifestyle

The substantiation of claims should include characterisation of the study groups' background diet and adjust not only for diet but also for lifestyle factors that might affect the outcome of the study (see 2(a) above). If a control has been used, and the study groups are randomised, then adjusting for background factors becomes less important. The baseline diet of the target population and the study group must be taken into account when planning or evaluating an intervention. If the baseline diet has not been described, it is important that the decision to disregard this should be scientifically justified. As has been mentioned in criterion 2(b) above there can be a "study effect" simply occurring because a subject has entered a trial, and these and other factors may influence outcome.

Humans are exposed to many active substances in their diet. Intervention studies dealing with one functional agent should determine whether or not the active substance is already present in the diets of the population or sub-groups of interest. Consideration should also be given as to whether any substance provided by the diet could potentially interact with the tested substance to amplify or decrease its effect. For example, when testing the functional effect of antioxidant vitamins on the reduction of cancer risk, it is necessary to

know the habitual dietary intake of these vitamins so as to assess the extent of the dietary change induced by the experimental manipulation and to control for different levels of intake in different sub-groups of the study population.

The difficulties in determining dietary intake are frequently underestimated and dietary assessment needs a rigorous approach based on a high degree of competence. Methodological challenges exist both for the collection of information on foods consumed, and for the assessment of the composition of these foods. Various methods of dietary assessment have been developed and their strengths and limitations have been reviewed by many authors [17–20], in particular in a Joint FAO/WHO Report [21]. Independent markers of intake or exposure are helpful for assuring the fidelity of dietary intake data. For example plasma levels or urinary excretion can also be used as main sources of data or in association with intake assessment [22–25]. As an example, a recent study used plasma vitamin levels and urinary potassium excretion as markers of fruit and vegetable intake [26]. Other independent markers include doubly labelled water for energy expenditure, and urinary nitrogen, sodium and sulphate. Body weight and weight changes may also be important measurements to make.

In situations where valid markers of exposure do not exist, intakes of individual food constituents can be estimated on the basis of the amount and composition of the foods consumed. This requires not only that people report their food intake reliably but also that reliable information on the composition of foods for that population is available. The conventional food composition tables often differ from country to country, in some cases due to true differences in the foods consumed in different regions, in other cases due to differences in methodology and/or the frequency of accounting for changes in food composition over time. A similar issue exists for the classification of foods where food categories are often very broadly defined, for example the inclusion of potato crisps, pretzels and nuts under the generic heading of "snacks", and where definitions, for example, of meat cuts, differ. An EU "Network of Excellence" (EuroFIR – European Food Information Resource) started in 2004 attempts to harmonise both food composition tables and food classification approaches in order to improve comparability of results.

The demands associated with a valid description of intake were considered in the context of the FUFOSE project [2, 14]. Although several methods for assessing intake exist, their validity has been questioned in recent years, particularly after the development of the doubly-labelled water methodology to measure body energy expenditures and therefore body energy needs. This method disclosed important discrepancies between what people report in dietary surveys, and the measured level of their energy needs. About 20 % of the general population underreport, and some people, particularly those with weight control problems (who constitute a growing proportion of modern populations), underreport by up to 50 %. Underreporting is not consistent for all foods. For example it affects fats and sugars more than proteins.

These well-documented levels of misreporting of food intake, especially in obese subjects, underline the need for the accurate determination of dietary intake [17, 27–30]. The task of characterising the habitual intake of a population or study group is not easy and precautions should be taken to maximise the validity of the data. Both retrospective and prospective methodologies are available but are subject to systematic error due, in particular, to underreporting of true intake. Subjects might also report according to expected instead of real intake. Furthermore, the act of recording is thought to influence the respondent's food choices and intake. Riccardi et al. [10] suggest that the Dietary Record method, which consists of a prospective/concurrent self-monitoring of food and drink intake over a specified period, could be used to determine baseline status and to track intake patterns during and after treatment. However, the respondent burden with this method is heavy and food selection and intake may be altered.

2(e) An amount of the food or food component consistent with its intended pattern of consumption

The amount of food or food component that will be tested should match its intended use and the way and frequency with which it will be eaten. Where dose response studies are performed, the range of doses must include the amount of food or food component expected to be consumed.

There is a tendency in some experimental studies to use diets or individual food components at levels that are too high to be achieved in daily practice with the intended food. Such studies are unrealistic and their results need to be confirmed at more achievable intakes. For example, extreme diets may be used in weight reduction programmes and in studies intended to demonstrate the benefits of foods or food components to high levels of physical performance. The role of these in promoting health and in serving as the bases for claims need to be considered carefully in the light of population exposure to the food components in question, particularly in groups that may be at risk of excessive intakes. An intake response relationship can identify an optimum effective intake, but this is not crucial to substantiate a claim.

2(f) The influence of the food matrix and dietary context on the functional effect of the component

The functional effect of a food or food component depends on the active component gaining access to the functional target site. For systemic effects this means

that the component needs to be taken up by the gut mucosa, transferred into the body and then distributed to the respective sites where its effects are active: the overall efficiency of this process, which is usually expressed as a percentage, is regarded by nutritionists as the bioavailability of the component. Bioavailability is influenced by a variety of factors arising from characteristics of the host, the diet as a whole, and the food itself. Host factors, and the need to characterise and control for them would be an aspect of data evaluation under criterion 2(b).

This criterion (2(f)) relates to the influence that physico-chemical properties of the food, the diet and the intestinal luminal milieu would have on the stability of the active component and on the efficiency with which it is released from the food either to be absorbed for systemic effects, or to have effects within the intestinal lumen (e. g. on the microflora) or at the intestinal mucosa. The food matrix, both in its raw state and after storage (e. g. freezing), or culinary preparation can have a significant influence on the "activity" or release of the key component. This can be measured in food free aqueous systems *in vitro*, and such systems enable comparison of the release of components from different dietary matrices. This "intrinsic availability" can vary considerably and is particularly relevant to assessing non-systemic, i. e. gut related effects of foods. It is relevant also as a component of the evaluation of evidence relevant to nutritional bioavailability. Weighting the relevance of these components of bioavailability needs to be considered on a case by case basis. There are few generalisable points applicable to all foods and food components. Thus a claim obtained with one particular diet or food matrix cannot necessarily be extrapolated to a second product containing the same component within a different matrix: extension of a claim to a product with another composition requires evidence that the component remains functionally effective to the extent claimed.

It might be necessary to substantiate the claimed effect for each individual product separately. Where differences in the matrix are small, and where evidence indicates that differences are unlikely to affect the availability of the key component for which the claim is made, it may not be necessary to substantiate the claim *in vivo* separately for each product. On the other hand, transfer of the key component to a totally different matrix, say from a fruit juice to a biscuit or cereal product, might well need further studies to demonstrate efficacy, and possibly to redefine dose or intake-response relationships. As an extreme example, a lipid soluble component would be expected to need dietary fat to ensure absorption, and provision in an aqueous environment would not seem to be a sensible development. On the other hand a minor change, such as a change in flavour variety, would not necessarily be considered a significant change in the matrix.

These considerations further emphasise why the characteristics of the food supporting the claim must be provided and must be consistent all along the studies supporting the claim (see criterion 1).

It may be possible to develop validated *in vitro* models to support the equivalence of different food matrices and to reduce the need for in vivo studies to show efficacy in every case.

On a similar basis, it might be important to consider the overall context of the diet in which the food is going to be eaten or even the type of meal, that is to say – breakfast, snack food or major meal, at which the food will be eaten.

2(g) Monitoring of subjects' compliance concerning intake of food or food component under test

In any study of diet and health it is essential to know the actual dietary intake of the subjects and to confirm that they have taken the food or food component in question in the right amount at the right time and over the specified period. If the subjects have done this, they can be said to have complied with the protocol and the study will therefore be an adequate test of the benefit of the food. Monitoring to confirm compliance is essential for assurance that the study is valid. Poor compliance can result in failure to demonstrate an effect, and an assumption, on a false basis, of "non-responsiveness", i. e. that the functional effect does not occur. Such a "false negative" result clearly does not show the absence of an effect, but unless one knew that the compliance of study participants was poor this would not be realised. Similarly, this insight also helps one appreciate that further systematic study is needed to establish whether there is a positive effect or not.

Examples of compliance measures include blood or tissue levels of the known component or its metabolites, such as red cell membrane phospholipid composition, breath hydrogen excretion in the case of fermented components, and urinary excretion of metabolites. Another approach is to add to the food in question a marker that can be detected in blood, urine or breath, which will allow compliance to be determined. Examples of such markers are para-aminobenzoic acid or lithium, which are excreted in urine or a bacterium that can be readily detected in faeces in the case of a probiotic food.

A more difficult question relates to levels of compliance and what standards need to be set that should be achieved to designate adequate compliance. Clearly, 100 % compliance with a protocol is usually not achieved in human intervention studies. In the analysis of the data of a randomised study, one may choose to exclude data of subjects whose adherence to the intervention or treatment protocol was below a certain, arbitrarily chosen minimum level. This may, however, cause selection bias and spurious results. A highly valued approach is to evaluate the 'intention-to-treat' effect [31]. This includes

data on all subjects, including those whose adherence was low or even nil. In this type of analysis the risk of bias is minimal. As compared to the first approach, the conclusions based on the latter depict more closely the expected effect of the intervention in 'real life', where the food might not be eaten daily or in the optimum amounts.

Where studies of dietary compliance have been attempted, the results have often suggested that compliance was much less than was expected and exclusion of non-compliant subjects can make a major difference to interpretation of results. Some changes in the diet such as those in relation to fat intake can be monitored rather more easily than global changes in the diet, for example, reduction in meat intake that might be used in studies of cancer prevention. Consequently, the development of markers of dietary intake is greatly needed to progress in this area.

2(h) The statistical power to test the hypothesis

Studies providing evidence for a claimed effect of a food should indicate the statistical criteria that were used in the design of the intervention trials.

When assessing a study design, one needs to estimate the study size, or power, needed to achieve a level of statistical significance. This minimal effect size will usually be the one that is biologically or practically relevant. To estimate the study size some prior knowledge of the statistical characteristics (for example the expected variance) of the outcome measure is needed.

Once the study has been carried out, estimates of the size of the effect and its statistical significance are calculated to allow valid conclusions to be drawn. Note that statistical power may turn out to differ from *a priori* estimates if, for example, the variance in the outcome variable turned out to be different to that expected [32]. In cases where the magnitude of effect is substantial but falls short of statistical significance the data will not normally, on their own, be sufficient to substantiate a claim. However, they may be valuable for the purpose of guiding further research and should not be discarded entirely. In comparing studies that differ in their outcomes, greater weight should be given to those trials that have the best design and adequate numbers of subjects.

Randomised controlled trials should comply with Consolidated Standards of Reporting Trials (CONSORT) guidelines [31] and consider Directive 2001/20/EC of the EU on good clinical practice [33].

Criterion 3. When the true endpoint of a claimed benefit cannot be measured directly, studies should use markers.

Whenever possible the claimed benefit, that is the true endpoint, should be measured directly. However, even though the ideal or target endpoint for human intervention studies of health, performance and well-being may be identified, it may not be measurable in practice. There are several possible reasons for this. There could be a long-time period between the introduction of the intervention and the desired outcome (for example a reduced incidence of a disease as evidence of a reduced risk); it might not be feasible or ethical to access the appropriate target tissues or biochemical processes (for example in the vascular wall or bronchial mucosa). Alternatively, although it is possible to measure the desired outcome, such as the components of measuring energy metabolism, protein turnover, lipoprotein and lipid metabolism, and glucose kinetics, the processes of actually doing so in a large-scale study would be excessively demanding of expertise and resource, which might be unpractical.

FUFOSE has recommended that when the definitive endpoint cannot be determined, more easily measured markers may be used as proxies or surrogates for the real or desired outcome. The robustness of such markers and their relevance to the key measure or target endpoint (meeting the quality indicators described in criteria 4 and 5) need to be assured. The FUFOSE consensus indicated how this could be achieved [2].

FUFOSE classified markers of relevant functional outcomes according to whether they:

- *Relate to the exposure to the food component being studied*, such as a serum, faecal, breath, urinary or tissue marker. For instance, the increased level of red blood cell folate is a marker of exposure to folate in food and the increased level of blood tryptophan is a marker of exposure to tryptophan in food. Markers relating to exposure to the food component can give some indication, but not absolute proof, of the bioavailability of the food component, or its presence, or that of a functional derivative or metabolite, at the functional target site.
- *Relate to the target function or biological response* such as changes in body fluids, levels of a metabolite, protein or enzyme (for example, the reduction in levels of plasma homocysteine as a possible response to dietary folate) or changes in a given function (for example, blood pressure in response to dietary caffeine).
- *Relate to an appropriate intermediate endpoint of an improved state of health and well-being or reduction of risk of disease, or both*, such as the measurement of biological processes that relate directly to the endpoint (for example, the extent of narrowing of the carotid artery as evidence of cardiovascular disease, or bone mineral density as a marker for risk of bone fracture). The target endpoint itself, if it were accessible, should be measured in some way. If this is possible, such measurement can be used as a basis for the validation of markers of intermediate endpoints to be used in subsequent studies.

The more remote markers are from the endpoint, the less specific and more attenuated and subject to confounding variables they become. Conversely, they become more specific and quantitatively related the closer they are to the endpoint in question. The characterisation of the mechanisms and pathways leading to outcomes would refine the identification of markers and inform how they may be selected. The generation of this knowledge, including approaches based on genomics and post-genomic molecular biology, underpins the biological and physiological validity of markers (see criteria 4 and 5), is fundamental to advances in nutrition, and integral to the development of foods with claims (nutrient function claims, enhanced function claims and reduced risk of disease claims) (Fig. 3).

All markers, irrespective of whether they are biochemical, physiological or behavioural in nature, should be valid (see criterion 4).

In some cases an individual marker may not provide sufficiently robust support for the desired claim. It may be that a combination of several relevant but not necessarily closely related markers can be used to justify the claim. This approach would need biological and statistical evaluation and an understanding of the independent strengths of association and the overall probability that their combined use strengthens the justification of the claim.

Criterion 4. Markers should be:
- **biologically valid in that they have a known relationship to the outcome and their variability within the target population is known;**
- **methodologically valid with respect to their analytical characteristics.**

There should be evidence that any particular marker reflects a meaningful biological effect and can be reliably and reproducibly measured. The validity of a marker comprises two aspects: 1) the biological validity and 2) the technical or methodological validity. Whereas the biological validity is common to all laboratories, the methodological validity needs to be established for each laboratory.

Biological validity. Biological validity concerns the extent to which a marker reflects a certain health outcome of interest and the process leading to it. It is not dependent on the technical competence of any individual laboratory. The biological validity of a marker derives from its relationship to the biological processes leading to the health effect and requires that the marker changes in line with a changing event or circumstances (for example the consumption of a particular food). In addition to insight into the biological process, it is necessary to have knowledge of the sensitivity and specificity of the marker for the health effect (see Annex 1, [34, 35]). As is noted above (criterion 3), a marker is not the same outcome as the health endpoint. The existence of an association between a marker and a disease risk does not necessarily mean that changing the variable changes the disease risk. Such modification can be effective only if the relationship is causal, and if effects already induced are reversible [36]. Hence the appropriateness of a marker needs to be considered on a case-by-case basis. It might be that a single marker does not meet all the criteria required for complete substantiation of a health effect. The marker may nevertheless contribute usefully to the totality of the evidence (see criterion 3).

Methodological validity and quality control. Any laboratory performing measurements should be competent to perform the measurements and to certify that the values produced can be trusted – that is, the method is technically valid in its performance by that laboratory. Study requirements for documentation and control, such as Good Laboratory Practice (GLP), Good Clinical Practice (GCP) and Good Epidemiological Practice (GEP),

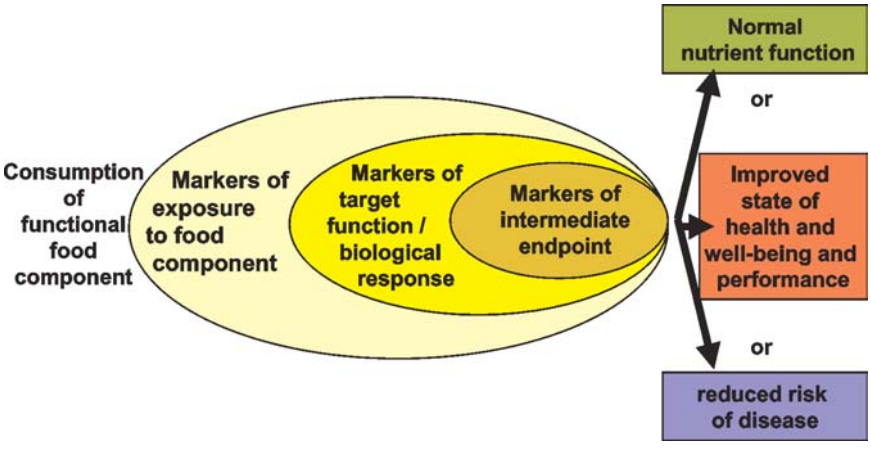

Fig. 3 PASSCLAIM classification of markers relevant to health claims

should not be confused with technical requirements prior to running analyses. As concerns the latter, Quality Control (QC) is important for claims in terms of technical validation of measurements and encompasses aspects such as accuracy, precision, repeatability, reproducibility and linear and dynamic range (see Annex 2). Requirements for these can be found on web-sites from chemical societies and national and international committees for analytical validation (for example www.fasor.com/iso25/, www.aoac.org, www.nmkl.org, www.ich.org). During method development, data on validity can be collected and compiled in a test method dossier, which is unique to each laboratory. After method validation, routine analyses can be performed. For these, quality control is typically performed by running concurrent control samples, and checking the actual results versus means and their standard deviation.

The total variability in the measurement of any parameter of interest is a combination of the biological variability and the methodological variability. The best results in a study can be obtained by having insight into the biological and the methodological validity at the design stage of the study.

Whereas, historically, research using markers has been done in a reductionist way (that is, by using one or only a few markers simultaneously), genomic and post-genomic molecular biology can perhaps generate a more integrated approach including molecular and whole body studies to establish claims. Even so the requirements for biological and methodological validity will remain.

Criterion 5. Within a study the target variable should change in a statistically significant way and the change should be biologically meaningful for the target group consistent with the claim to be supported.

This criterion reflects the importance of both the statistical significance and the biological meaningfulness of an effect.

At the level of statistical significance, biological relevance can be attached to very small changes in a marker. This is exemplified by reference to blood cholesterol levels (total cholesterol, LDL-cholesterol) in which, at the population level, a few percent change has large implications for the public health burden of coronary heart disease. The same applies to changes in blood pressure of only a few mm Hg [7]. Also, a minor gain in physical performance can have great effects in sport in which, at the top level, fractions of seconds may make the difference between success and failure [9]. Conversely, a change of several tens of percent in immune function parameters or stool weight, although perhaps significant statistically, may not have any biological relevance [13]. It is necessary that the conditions of both statistical significance and biological relevance are met if the outcome of a study is to provide support for a claim.

Criterion 6. A claim should be scientifically substantiated by taking into account the totality of the available data and by weighing of the evidence.

When assessing the validity of a claim, the reviewing bodies should have access to, and consider on their scientific merit, all relevant data.

The criteria are intended to ensure the scientific quality of studies and evidence to be used for the substantiation of claims. However, in many cases, results from individual studies may allow different interpretations or provide conflicting evidence. The quality of individual studies may differ and it is possible that not all research will be done to the highest, or even a common, standard. This can be due to the complexities of research in humans but also because data to support a claim may be used opportunistically from studies which had a different primary objective. There may however be a complementarity between individually incomplete studies which allows an assessment of the totality of the evidence to substantiate a claim. Conversely, a review of all studies taken together may reveal evidential inconsistencies that are not apparent from the review of a single study in isolation. The types of studies and evidence which can contribute to the substantiation of a claim are discussed under Criterion 2 and summarised in Table 2 (page I/13).

Selective presentation or consideration of studies and their outcomes is acceptable only if this is transparent and done on the basis of the quality of the data, for example if the selection of data is based on principles described in the commentary to these criteria.

In the evidence, overall, there should ideally be:

- consistency of results across the various categories of evidence and methodologies;
- valid dietary methods;
- randomised sampling;
- a dose response relationship between intakes of food or food components and the effects and health effect, if relevant;
- biological plausibility;

with all data supported by the use of valid markers (see criteria 3, 4 and 5).

Selective presentation of data depending on whether or not they would support the claim is not acceptable.

The evaluation of the available data may leave some questions unanswered. In such cases it should be considered whether these questions need to be answered by additional research, or whether or not the evidence overall supports the proposed claim.

All published studies should be reviewed and unpub-

lished data, including those that have been held back from publication for reasons of confidentiality, must also be considered.

Concluding comments and discussion

A set of criteria has been developed which defines the requirements for data submitted in the scientific substantiation of claims made on foods (see box below).

Criteria for the scientific substantiation of claims

1. **The food or food component to which the claimed effect is attributed should be characterised.**
2. **Substantiation of a claim should be based on human data, primarily from intervention studies the design of which should include the following considerations:**
   - **2(a) Study groups that are representative of the target group.**
   - **2(b) Appropriate controls.**
   - **2(c) An adequate duration of exposure and follow up to demonstrate the intended effect.**
   - **2(d) Characterisation of the study groups' background diet and other relevant aspects of lifestyle.**
   - **2(e) An amount of the food or food component consistent with its intended pattern of consumption.**
   - **2(f) The influence of the food matrix and dietary context on the functional effect of the component.**
   - **2(g) Monitoring of subjects' compliance concerning intake of food or food component under test.**
   - **2 (h) The statistical power to test the hypothesis.**
3. **When the true endpoint of a claimed benefit cannot be measured directly, studies should use markers.**
4. **Markers should be:**
   - **– biologically valid in that they have a known relationship to the final outcome and their variability within the target population is known; methodologically valid with respect to their analytical characteristics.**
5. **Within a study the target variable should change in a statistically significant way and the change should be biologically meaningful for the target group consistent with the claim to be supported.**
6. **A claim should be scientifically substantiated by taking into account the totality of the available data and by weighing of the evidence.**

The criteria have been subjected to rigorous peer reviews by groups comprised of a broad-base of scientific and regulatory experts in three successive workshops. The criteria constitute a scientifically robust tool for evaluating the quality of data submitted in support of claims.

The PASSCLAIM Concerted Action has involved extensive collaboration and debate amongst different sectors including scientists and related expertise from academia and research institutes, industry, consumer interests and regulatory bodies. It has been elaborated by a process which has drawn on examples of existing best practice in respect of the use of investigative studies to monitor several health and well-being states and the reduction of disease risk, and of existing regulatory and advisory processes for the evaluation of claims.

The action has produced a consensus on the objective and transparent assessment of scientific evidence submitted to support a claim related to a food or food component. This approach is broken down to core issues that describe the context within which claims need to be considered, and into separate criteria that will facilitate the objective assessment and assist in the compilation of guidelines on the preparation of submissions. It emphasises that the overall consistency and coherence of all the evidence, i. e. the totality of the evidence, should be assessed. This approach should help those who are submitting evidence as well as those who are responsible for evaluating it, and this structure should also enable feedback to those submitting portfolios of evidence.

Thus this practical framework for the evaluation of scientific dossiers supporting claims can be expected to expedite and improve the efficiency of the regulatory review processes. It is hoped that this would give the European food manufacturing industry a competitive edge in the global market both from the establishment of claims, and also from an improved science base that this process might be expected to generate. This integrated strategy addresses consumer concerns and will assist in generating more consumer confidence in science-based claims on foods. Consumers should benefit through the availability of more foods with substantiated claims.

In the above respects the PASSCLAIM Concerted Action has met its objectives. Nonetheless, the action has identified other issues that need to be addressed. An important point that should be appreciated is that the template for the evaluative process, in its present form as it emerges from the PASSCLAIM process, essentially provides only guidance. The template needs to be applied intelligently and sensitively on a case by case basis with respect both to gaps in knowledge and to the development of new knowledge. It is to be expected that assessment of, for example, the validity of markers, study designs and the influence of dietary matrices on the effects of active components will require expert advice. Assessment of the totality, consistency and complementarity of evidence and the extrapolation of demonstrated benefits across gender and generation groups will also require expert judgement. Thus there will still

be a need for informed scientific advice in the regulatory process.

The systematic analyses of existing and potential claims carried out by expert groups during the course of the PASSCLAIM exercise have resulted in reviews of the availability of indicators of health and disease states within their respective areas of expertise [5–7, 9–12]. They have demonstrated the limitations of existing markers and have identified the need for better markers. In particular, the development of genomic and post-genomic molecular biology would be expected to improve the characterisation of populations, and the early detection of responses to interventions with foods and food components. The availability of such markers may facilitate the substantiation of claims by enabling more practicable and cost-efficient study protocols and timescales.

Nonetheless, the scientific substantiation of claims according to the PASSCLAIM criteria might require substantial and expensive studies in humans that would therefore, at a first glance, appear possible only for large companies who have the relevant economic and personnel resources. This may be particularly true for product specific claims but the criteria are also applicable to the substantiation of generic claims that can be made on a range of products containing the active food component.

PASSCLAIM agreed that the evidence required to support nutrient function, enhanced function, and reduction of disease risk claims needs to be of similar quality, and that as such these claims could be related to the schema developed in the previous concerted action on functional food science in Europe (FUFOSE). Nutrient function claims were not considered in FUFOSE but are now generally regarded as health claims (see Table 1). The particular issue relating to this spectrum of claims (see Fig. 4) is that they are in practice a continuum, and that it can be expected that on some occasions ambiguities and difficulties will arise in classifying claims that are submitted for approval. In essence Nutrient Function Claims will draw for substantiation on a broad "generally accepted base" such as that expressed recently in a WHO report [37], whereas Enhanced Function Claims will be more specific and will need "specific scientific studies" for their support. Disease Reduction Claims may need to draw on the broad spectrum of scientific data. However, there is no definite rule, each claim would need to be assessed in its own right.

There are some broader, more political, implications arising from this document.

Firstly, given the resource implications of developing and supporting enhanced function and disease risk reduction claims, it should be expected that producers will seek support to enable them to assert intellectual property rights for their innovations. As the regulatory environment for claims develops, this aspect will need to be considered, if the competitiveness of the EU food industry and the incentive for its investment in healthy foods are to be maximised.

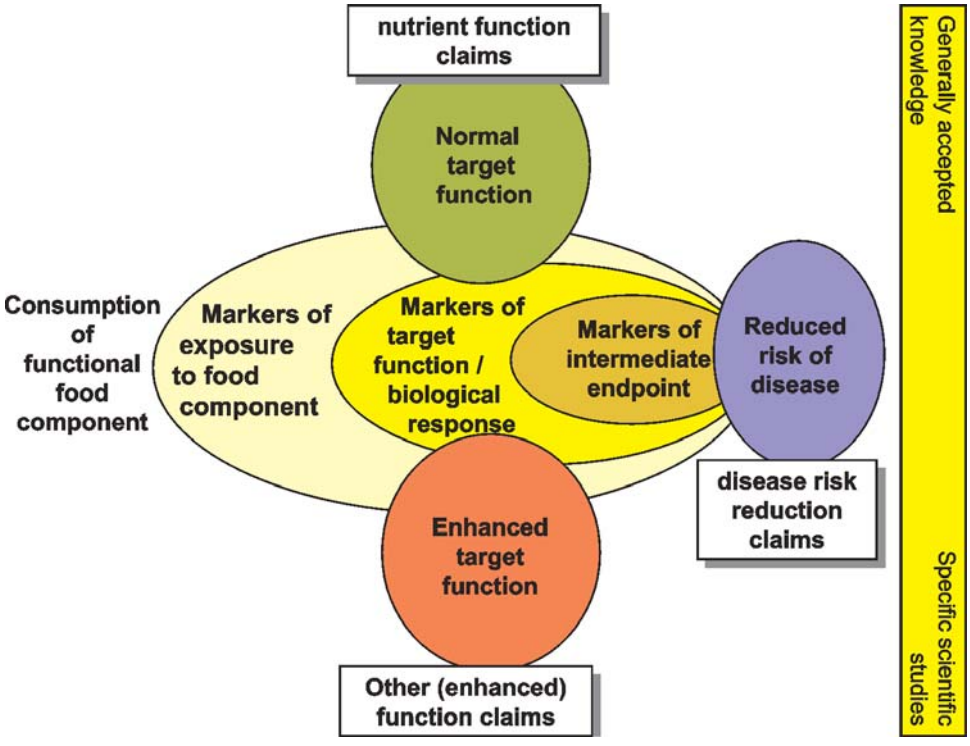

Fig. 4 Relationship between health claims addressed by PASSCLAIM and the FUFOSE concept of underlying scientific evidence

Secondly, it is appreciated that the criteria would be useful for innovative SMEs at an early stage of development of functional foods, in order to judge the feasibility of developing new products. There may be a need to identify common approaches to establishing the science bases for claims, which can be shared by large companies and SMEs to the benefit of both sectors. This may mean sharing resource and other means of collaboration. There may be a strategic need for competent authorities to support SMEs by investing in scientific support and networks, e. g. to undertake human nutrition studies.

Consumer confidence in claims is a key issue, from the producers' as well as from the consumers' points of view. Defining common criteria for the scientific substantiation of claims, supported by a broad group of European scientists representing both academia and industry, is an important step in establishing an environment in which consumers can be assured that claims made on foods are well-founded. Well-founded claims and associated explanations will contribute to consumer education. Consumer nutritional insight and knowledge will increase, and resultantly such informed consumers will be more able to choose products with benefits for health and well-being. In this way, claims substantiated in agreement with the PASSCLAIM criteria will contribute broadly to healthier diets for Europeans, and thereby to a decrease in the burden of diet-related diseases.

In summary, a number of potential benefits follow from these criteria. Achievement of these will require action to be taken to bring the criteria to a wider audience:

- The criteria provide a scientific framework that will facilitate the assessment of scientific support for claims on foods.
- This, in turn, will enable the compilation of guidelines on the preparation of submissions for regulatory review and approval of claims on foods.
- By establishing a robust standard for the quality of scientific data submitted in support of health claims, the criteria provide a basis for the harmonisation of the regulatory review and approval of such claims.
- The compliance of data submissions with the criteria will provide consumers with the assurance that claims based on the data are well founded and justified.
- By establishing a standard for the data to be submitted in support of claims, the criteria will provide the agri-food industry with a stable frame within which new products to meet consumer needs and expectations for foods with benefits for health and well-being can be developed.
- Systematic use of the criteria will engender a more informed use of scientific data in support of claims.

Acknowledgements ILSI Europe thanks all the collaborators in the PASSCLAIM Concerted Action (see list below) for providing their expertise, sharing their knowledge and devoting their time to produce this final PASSCLAIM publication. We thank the ILSI Europe Functional Food Task Force members and the PASSCLAIM Steering Committee members for their support and guidance. ILSI Europe is very grateful to Prof. Aggett, Prof. Asp, Dr. Antoine, Dr. Bellisle, Prof. German, Dr. Müller, Prof. Rechkemmer and Dr. Verhagen for their continuous input during more than four years, which led to a successful completion of the objectives of this Concerted Action. Finally, we thank the European Commission for positively evaluating this submission, providing continuous support to the various needs that arose during the course of the project and supporting financially the whole endeavour.

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Glossary

Bioavailability: The fractional amount of a nutrient or other bioactive substance that, after ingestion, becomes available for use in target tissues.

Case-control study: Study that compares the exposure to a suspected cause of a disease in people with that disease (the cases) to the exposure in those without that disease (controls); exposure is thus assessed retrospectively. See also 'cross-sectional study'.

Claim: Any message or representation, including pictorial, graphic or symbolic representation, which states, suggests or implies that a food has particular characteristics.

Clinical study: Study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analysis are fully integrated into a single report.

Codex Alimentarius: Literally: 'Food Code'. An organisation that creates and compiles standards, codes of practice and recommendations. Membership is open to all countries associated with the Food and Agricultural Organization of the United Nations and with the World Health Organization. At present (2005) Codex has 168 members and covers more than 98% of the world's countries. Also non-governmental organisations have input in Codex (www.codexalimentarius.net).

Cohort study: Prospective observational study in which data on exposure to suspected causes of e. g. a disease are collected in a selected/recruited group of people who do not yet have the disease(s) under investigation. The subjects are then followed for a period of time, after which it can be assessed whether development of disease is related to the (presence of) suspected causes.

Confounding factors, confounders: A certain exposure may be associated with a disease or other outcome, without this association being causal. This can result from a third factor being a cause of both; such a factor is referred to as 'confounder'. In other words: an alternative cause for the disease in question that is unequally distributed among those exposed and non-exposed to the putative agent (Hayes 2001 in FOSIE [3]).

Cross-sectional study: A study design that relates the rates of a certain exposure to the levels of an outcome of interest in a number of individuals or populations. Key feature is that exposure and outcome are measured at the same point in time.

Disease risk reduction claim: A claim that states or implies that consumption of a product reduces the risk of occurrence of a certain disease. See also 'enhanced function claim', 'health claim', 'medical claim' and 'prevention of disease'.

Dose-response relationship: The finding that the level of variable A changes as changes in the level of variable B occur. 'A' may be the level of a function or parameter in the body, or the risk of a disease and 'B' may be the intake of a food component. The existence of such a relationship adds to the probability that the observed relationship is causal.

Endpoint: A variable or outcome that is relevant in itself, e. g. survival time after medical surgery, time to run a marathon, fewer periods of gastrointestinal discomfort, or a reduced risk of a disease. The level of a surrogate or intermediate endpoint – also referred to as 'marker' – is in itself not relevant, but is indirectly relevant because it reflects a relevant endpoint. See also 'marker'.

Enhanced function claim: A claim that states or implies that the consumption of a product enhances a bodily function. 'Enhanced' aims to distinguish effects on functions other than the currently well-established effects of nutrients (so-called 'nutrient function claims'). As a result, a newly discovered effect on a function may initially give rise to an 'enhanced function claim', whereas once well established it would render a 'nutrient function claim'. See also 'disease risk reduction claim', 'health claim' and 'medical claim'.

Epidemiology: The study of health and the occurrence of diseases and their predictors and causes.

Food: Material used in the body to sustain growth, repair and other vital processes [38]. That which can be eaten … to stay alive and to grow ([39]). Any substance or product, … , intended to be ingested by humans. 'Food' includes drink, … [40].

Food component: components such as ingredients and food additives intentionally added to foods, and also components inherently present as part of the essential composition of foods.

FUFOSE: "Functional Food Science in Europe"; a European Commission Concerted Action, coordinated by ILSI Europe and completed in 1999 [2].

Generic claim: A claim based on knowledge from evidence generally available in the scientific literature and/or on recommendations from national or international public health bodies.

Glycaemic index: The glycaemic index is defined as the incremental

area under the blood glucose response curve of a 50 g carbohydrate portion of a test food expressed as a percent of the response to the same amount of carbohydrate from a standard food taken by the same subject [41].

Good clinical practice (GCP): a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected [42].

Good laboratory practice (GLP): a set of principles that provides a framework within which laboratory studies are planned, performed, monitored, recorded, reported and archived. These studies are undertaken to generate data by which the hazards and risks to users, consumers and third parties, including the environment, can be assessed for pharmaceuticals, agrochemicals, cosmetics, food and feed additives and contaminants, novel foods and biocides. GLP helps assure regulatory authorities that the data submitted are a true reflection of the results obtained during the study and can therefore be relied upon when making risk/safety assessments [43].

Health: a state of complete physical, mental and social well-being and not merely the absence of diseases or infirmity [44].

Health claim: Any representation that states, suggests, or implies that a relationship exists between a – constituent of a – food and health (www.codexalimentarius.net/reports.asp). See also 'disease risk reduction claim', 'enhanced function claim' and 'medical claim'.

Intervention study: Study in which investigators intervene by allocating and establishing one or more treatments ("interventions") to or in certain subjects. See also 'observational study'. See also 'randomised controlled trial'.

Marker: A variable that is of interest because it marks or reflects a certain phenomenon of interest. One preferably avoids the confusing terms 'surrogate marker' and 'intermediate marker'. See also 'endpoint' and 'valid'.

To match: To be equal to; corresponding with regard to certain characteristics [39]. A method used to create study groups that are maximally similar, in order to ascribe differences in outcome to a certain factor in which the groups do differ. In e. g. a case control study one may 'match' controls to the identified cases by selecting a group of other patients in the cases' hospital who do not have the disease under study, but have similar age, ethnic background and gender. See also 'randomise'.

Matrix: Substance in which something is embedded [39].

Medical/medicinal claim: A claim (see 'claim') that states or implies that a food or a food component has the property of treating, preventing or curing human disease or makes any reference to such property. 'Human disease' means any injury, ailment or adverse condition, whether body or mind. Such claims are prohibited on foods; this prohibition creates the legal separation between foods and medicines. See also 'disease risk reduction claim', 'enhanced function claim', 'health claim' and 'prevention of disease'.

Meta-analysis: A quantitative summary of several individual studies of a similar type. Both intervention and observational studies can be meta-analysed. See also 'pooled analysis'.

Nocebo: see 'Placebo'.

Nutrient function claim: A claim that describes the physiological role of a nutrient in growth, development and normal functions of the body.

Nutrition: The act or process of nourishing; the process by which foods are taken in and utilised by the body for growth, normal function and maintenance of health [38].

Observational: From 'to observe': to see and notice; to watch carefully [39]. In an observational study, researchers do not intervene but only observe outcomes of interest and – the levels of – their suspected causes, e. g. cohort or case-control study. See also 'cross-sectional study' and 'intervention study'. Observational studies are often loosely referred to as epidemiological studies.

Placebo: an inert or innocuous substance used especially in controlled experiments testing the efficacy of another substance (as a drug) [38]. A "placebo" is especially useful to control for any beneficial effect that would occur in an experiment (due to the testing conditions themselves) but that would not be caused by the active agent in the tested food or food ingredient. Alternatively, a "nocebo" effect (an undesirable consequence induced by the particular test conditions) can also occur and should be discriminated from the action of the active substance under test.

Pooled analysis: An analysis of the combined, original data of several individual studies. See also 'meta-analysis'.

(Statistical) Power: The minimum size effect that can be demonstrated with statistical significance, given a certain study design and sample size. Based on the power required, one *a priori* calculates the sample size, and hence the study size, needed to achieve that. See also 'statistical significance'.

Prevention of disease: Hindrance [39] of the onset of disease. This hindrance may reduce the probability or risk of a disease to zero, but in diet-related diseases it usually reduces the risk to a lesser degree. See also 'disease risk reduction claim' and 'medical claim'.

P(robability)-value: The probability of observing in a subgroup or sample – by chance – an effect (a difference, an association) of minimally a certain size, in the situation that the effect does actually not exist in the original or overall population. See also 'statistical significance'.

Product-specific claim: A claim that a relationship exists between a specific food product, or a component of a specific food product, and health.

Randomisation: In intervention studies subjects may be randomly (i. e. determined by fate/chance) allocated either to undergo a certain intervention or to be part of a control group (or to undergo another intervention). Purpose of randomisation is to create groups that are likely to differ only with regard to the intervention under study. As a result, the effects observed can principally be ascribed to the intervention. See also 'to match'.

Randomised controlled trial (RCT): Study design in which subjects are randomly allocated to study groups. As a result the groups will expectedly not differ systematically, except with regard to an intervention that one group will undergo and the other will not. As a result, the effects observed can principally be ascribed to the intervention. See also 'intervention study' and 'to randomise'.

Representative: Serving as an example of a class or group; typical specimen of a group [39]. A sample out of a larger group is representative in certain aspects for that larger group if it does not differ systematically from that group in these aspects; if it is typical for that group.

Risk: Probability or chance of meeting a certain – usually unwanted – event [39]. The probability of loss or peril [38]. The probability and severity of an adverse effect/event occurring to man or the environ-

ment following exposure, under defined conditions, to a risk source [40].

Statistical significance: If the p-value for a certain observed effect is smaller than, e. g., 5 %, the assumption or hypothesis that the effect does not exist is refuted. The observed effect is then referred to as 'statistically significant'. See 'p(robability)-value'. A statement about statistical significance is a generalisation of a probability from a sample to the universe from which it has been drawn [16].

Target function/variable: A bodily function that is a target for intervention and measurement, in the scope of maintainance or improvement of health, or reduction of risk of disease.

Well-being: A positive and sustainable state that allows individuals, groups or nations to thrive and flourish. At the level of an individual, well-being refers to psychological, physical and social states that are distinctively positive [45].

Annex 1: Sensitivity and specificity

In evaluating and selecting markers, the sensitivity and specificity of the marker are important. In studies with humans, sensitivity is commonly defined as the proportion of a population with a certain characteristic (e. g. disease, health status) that is correctly classified on the basis of measurements as subjects with that characteristic. In the following Table, sensitivity can be quantified as A/(A + C). A high sensitivity implies a low proportion of false-negatives (category C). A study is only successful, however, if the proportion of false-positives (category B) is small as well. Thus the study has to be specific as well, i. e. a large proportion of subjects without disease or health status are correctly classified as such: D/(B + D) must be high.

		Reality	
		+	–
test	+	A	B
	–	C	D

A number of true positives, *B* number of false positives, *C* number of false negatives, *D* number of true negatives, *Sensitivity* probability of a positive test in people with the disease (A/A + C), *Specificity* probability of a negative test in people without the disease (D/B + D), *Positive predictive value* probability of a person having the disease when the test is positive (A/A + B), *Negative predictive value* probability of a person not having the disease when the test is negative (D/C + D)

Annex 2: Accuracy, precision, repeatability, reproducibility, linear and dynamic range – as used in criterion 4

It is important to have an insight into the practical performance of an analytical method. Control of the analytical performance of measurements is a prerequisite for a good and true study result. A high repeatability and reproducibility can reduce the number of measurements that need to be done. Precision refers to how close measurements of the same quantity are to each other, even if they are not close to the true value. A high precision, in addition to knowledge on biological variation, can reduce the number of subjects needed in a study. Accuracy refers to how close a measurement is to the true value of what is being measured. A high accuracy allows comparison of data across laboratories. The linear and dynamic range determine how many data/subjects can be considered in the overall assessment of the results.

The distinction between accuracy and precision is illustrated in Fig. 5 in which the symbols distributed over the targets represent a series of measurements. A symbol positioned at the bull's eye represents a perfect measurement – a measurement giving a value exactly the same as the true value.

The official definitions of accuracy, precision, repeatability, reproducibility, linear range and dynamic range are according to IUPAC Compendium of Chemical Terminology 2nd Edition (1997); (http://www.iupac.org/publications/compendium/R.html). An additional reference for these quality criteria can be found in ISO norm 5725: (http://www.iso.ch/iso/en/CatalogueDetailPage.CatalogueDetail?CSNUMBER = 11837).

Accuracy (of measurement)

Closeness of the agreement between the result of a measurement and a true value of the measurand.

Notes:

1. Accuracy is a qualitative concept.
2. The term precision should not be used for accuracy.

Precision

The closeness of agreement between independent test results obtained by applying the experimental procedure under stipulated conditions. The smaller the random part of the experimental errors

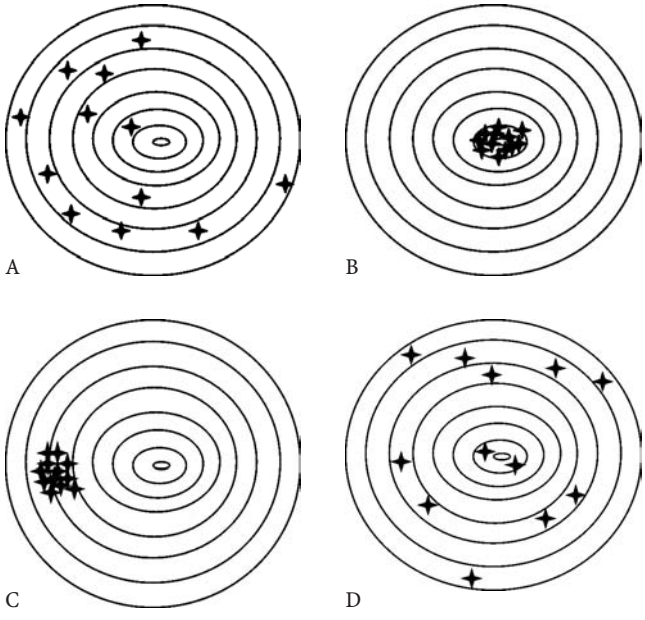

Fig. 5 Precision and accuracy. **A** Neither precise nor accurate. Since none of the darts are close to the bull's eye, the measurements they represent are not very accurate. Also, since the darts are not very close to each other, the set of five measurements here is not very precise either. **B** Both precise and accurate. The measurements are all close to the true value, so they are accurate. Also, the measurements are all close to each other, so they are precise. **C** Precise but not accurate. Since all of the measurements are close together, they are precise, but since they are not close to the true value, they are not accurate. **D** Accurate but not precise. The mean of all of the measurements is close to the true value, but since they are not very close together, they are not precise.

which affect the results, the more precise the procedure. A measure of precision (or imprecision) is the standard deviation.

Comment: Precision is sometimes misused for accuracy. This problem will be avoided if one recognizes that precision relates only to dispersion, not to deviation from the (conventional) true value. Imprecision has been defined as 'the standard error of the reported value.'

Repeatability

The closeness of agreement between independent results obtained with the same method on identical test material, under the same conditions (same operator, same apparatus, same laboratory and after short intervals of time). The measure of repeatability is the standard deviation qualified with the term: 'repeatability' as repeatability standard deviation. In some contexts repeatability may be defined as the value below which the absolute difference between two single test results obtained under the above conditions, may be expected to lie with a specified probability.

Reproducibility

The closeness of agreement between independent results obtained with the same method on identical test material but under different conditions (different operators, different apparatus, different laboratories and/or after different intervals of time). The measure of reproducibility is the standard deviation qualified with the term 'reproducibility' as reproducibility standard deviation.

In some contexts reproducibility may be defined as the value below which the absolute difference between two single test results on identical material obtained under the above conditions, may be expected to lie with a specified probability. Note that a complete statement of reproducibility requires specification of the experimental conditions which differ.

Linear range

Concentration range over which the intensity of the signal obtained is directly proportional to the concentration of the species producing the signal.

Dynamic range (of an analyser)

The ratio between the maximum usable indication and the minimum usable indication (detection limit). A distinction may be made between the linear dynamic range, where the response is directly proportional to concentration, and the dynamic range where the response may be non-linear, especially at higher concentrations.

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