Scientific substantiation of health claims

A global analysis

IADSA
International Alliance of Dietary/
Food Supplement Associations

The International Alliance of Dietary/Food Supplement Associations (IADSA) brings together over 50 associations of dietary supplement manufacturers and distributors from across the world. IADSA's central goal is to ensure a greater exchange of information about the science and regulation of dietary supplements and ingredients among industry, scientists, regulators and consumers.

The Scientific Substantiation of Health Claims has been researched and drafted by Professor David P. Richardson in cooperation with IADSA's Scientific Group of leading international scientists.

Scientific substantiation of health claims
A global analysis

Prepared on behalf of IADSA by

Professor David P. Richardson
Scientific Adviser to CRN UK, Member of the IADSA Scientific Group

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Executive summary

The clear aims of global legislation on the scientific substantiation of health claims are to achieve a high degree of consumer protection, to ensure confidence in claims on foods and food supplements, to promote fair trade, to stimulate academic research and to encourage product innovation in the food and food supplement industries.

Consumers should be able to make choices based on clear and accurate information and to have confidence in the scientific and regulatory process used to support health claims.

This IADSA report reviews ongoing recent developments and initiatives on the scientific substantiation of health claims around the world, such as the Codex Alimentarius Commission guidelines as well as developments in the European Union, the USA, China, Japan, the ASEAN countries and Latin America. The report provides a snapshot of recent developments for methodologies for the assessment of the totality of the available data and for the development of a scientific framework for weighing the strength, consistency and biological plausibility of the evidence. The substantiating evidence should be proportionate to the claim and the approaches should be transparent and embrace the use of appropriate qualifying language or graphics to reflect the weight of the evidence on which the claim is based in order to facilitate consumer understanding and consumer choice.

Key issues that are addressed in the report include:

- The strengths and limitations of different sources of evidence (e.g. randomised controlled trials/ human intervention studies and epidemiological prospective cohort studies, animal and *in vitro* studies, history of use etc.) that contribute to the totality of the available data.
- The need to develop a suitable scientific framework for weighing the evidence in order to reflect state-of-the-art nutrition science, to promote future research and to determine the extent to which a causal relationship can be demonstrated.
- A critical examination of the application of the model for evidence-based medicine (EBM) in nutrition science. EBM is designed to evaluate the effects of drugs and not the unique properties, complex effects and interactions of nutrients and bioactive substances.
- The need to address and define evidence-based nutrition (EBN).
- The identification and validation of relevant biomarkers that can predict potential benefits relating to maintenance or improvement of a function and those associated with reduced risk of disease.
- The determination of the strength of recommendations for regulatory use by risk managers and for the wording of a claim to reflect the extent to which, or probability that, a particular food/constituent health benefit is true and is likely to be refined (not reversed) by subsequent scientific research.

The report concludes that it is necessary to construct a robust and pragmatic scientific framework for weighing the totality of the available data and for expressing the strength and consistency of the evidence in order to stimulate future academic research, to promote product innovation and to communicate accurate and truthful nutrition and health messages to the public.

1. Introduction

There is a broad international consensus that any regulatory framework should protect the consumer, promote fair trade, stimulate research and encourage innovation in the food and food supplement industries. Hence, an important objective for the development of global legislation is to ensure that nutrition and health claims for foods and food constituents are justified and scientifically substantiated. Consumers should be able to make choices based on clear and accurate information and to have confidence in the scientific and regulatory process used to support health claims on foods and food supplements (Richardson, 2005 a, b).

The concept that diet can have beneficial physiological and nutritional effects beyond the widely accepted nutritional effects has been significantly developed internationally in recent years. The concept of functional foods was first developed in Japan. In the face of escalating health care costs of an ageing population, a regulatory system was initiated that approved certain foods and food constituents with documented health benefits (Hasler, 2002; Yamada *et al.* 2008). In the late 1990s in Europe, a concerted action 'Functional Food Science' (FUFOSE) stated that diet can not only help achieve optimal health and development, but might also play an important part in reducing the risk of disease (Diplock *et al.* 1999). The shift of concept from hunger satisfaction and adequate nutrition to optimum nutrition and delaying the onset and development of major diseases such as cardiovascular disease (CVD), certain cancers and osteoporosis was proclaimed as a stimulus for food science and technology and a renaissance for scientific research on human nutrition.

In the USA, the Nutrition Labelling and Education Act (NLEA) 1990 was designed to give consumers more scientifically valid information about the foods they eat. Among other provisions, the NLEA directed the Food and Drugs Administration (FDA) to issue regulations providing for the use of statements that describe the relationship between a food substance and a disease in the labelling of foods, including dietary supplements, after such statements have been reviewed and authorised by the FDA.

Although nutritional and medical sciences have long recognised that diet, individual foods or food constituents can contribute towards reduction of risk of disease, until recently food laws prevented the communication of these benefits to consumers. Today, worldwide regulatory frameworks recognise the 'functional' and 'health-promoting' benefits of foods and food constituents in such a way as to facilitate the use of functional health claims and reduction of disease risk claims – a concept outside the scope of medicinal law and claims for the prevention, cure and alleviation of disease. However, in Europe the use of more general, non-specific benefits of a nutrient or food for overall good health or health-related wellbeing will only be permitted if accompanied by a specific claimed physiological effect (European Parliament and of the Council 2007). This focus on more scientific terminology for a single claimed effect may detract from the use of more general, consumer-orientated language to communicate to the public.

These global regulatory developments reflect the fact that foods and food supplements with health claims are aimed primarily at the normal healthy population who may wish to optimise their nutritional status and/or to reduce the likelihood of getting a particular chronic disease in later life. The legislation also recognises that the cause of chronic disease is multi-factorial and includes genetic, behavioural and environmental factors as well as dietary factors. Hence, health claims are permitted in the context of a varied and balanced diet and a healthy lifestyle.

The current paper explores the methodologies for scientific substantiation of health claims on foods and food constituents based on an assessment of the totality of the available data and a framework for weighing the strength, consistency and biological plausibility of the evidence. The approach also embraces the use of appropriate qualifying language to reflect the weight of the evidence on which the claim is based to facilitate consumer understanding and consumer choice.

2. Definitions and terminology

There is a clear need to have a uniform understanding, terminology and description of types of nutrition and health claims. The Codex Guidelines for the Use of Nutrition and Health Claims (2004) and the European legislation on nutrition and health claims on foods (2006) provide the basis of two broad categories: **content claims**, i.e. what the food or food supplement product contains regarding nutrients and/or other substances with nutritional or physiological effects; and **health claims**, which relate to what the food or food constituent does with regard to contributing to health maintenance and health improvement. The health claim categories in Codex (2004) include well established nutrient function claims, other function claims and reduction of disease risk reduction claims. The types of claims and terminologies that are often seen and used in regulations are summarised below:

Food

Food or food constituent refers to energy, nutrients, related substances, ingredients, and any other feature of a food, a whole food, or a category of foods on which the health claim is based. The category of food is included in the definition because the category itself may be assigned a common property of some of the individual foods making it up.

Dietary supplement

Also known as a food supplement or nutritional supplement, a dietary supplement is a preparation intended to supplement the diet and provide nutrients such as vitamins, minerals, fibre, fatty acids or amino acids, that may be missing or may not be consumed in sufficient quantity in a person's diet. In the USA, a dietary supplement is a product intended to supplement the diet. It may contain any of the following dietary ingredients: a vitamin, a mineral, a herb or other botanical (excluding tobacco), an amino acid, a concentrate, metabolite, constituent, extract or combination of any of the above.

Nutrient

Any substance normally consumed as a constituent of food:

(a) that provides energy, or

(b) that is needed for growth and development and maintenance of healthy life, or

(c) a deficit of which will cause characteristic biochemical or physiological changes to occur.

Essential nutrient

Any substance normally consumed as a constituent of food that is needed for growth and development and the maintenance of healthy life and that cannot be synthesised in adequate amounts by the body.

A related substance/other substance

A constituent of food (other than a nutrient) that has a favourable physiological effect. The term 'other substance' is defined as a substance other than a nutrient that has a nutritional or physiological effect.

Claim

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

Nutrition claim

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

Nutrient content claim

A nutrition claim that describes the level of a nutrient contained in the food (e.g. 'source of calcium', 'high in fibre' and 'low in fat').

Comparative claim

A claim that compares the nutrient levels and/or energy value of two or more foods (e.g. 'reduced', 'less than', 'fewer', increased', 'more than', 'lite/light').

Structure/function claim

Describes the role of a nutrient or dietary ingredient intended to affect a structure or function in humans. In addition, such claims characterise the means by which a nutrient or dietary ingredient acts to maintain such a structure or function, or they may describe general wellbeing from consumption of a nutrient or dietary ingredient.

Health

A state of complete physical, mental and social wellbeing and not merely the absence of disease or infirmity.

Health claim

Any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health. Health claims include:

Nutrient function claims that describe the physiological role of a nutrient in growth, development and normal functions of the body.

Other function claims that describe specific beneficial effects of the consumption of foods and their constituents in the context of the total diet on physiological functions or biological activities, but do not include nutrient function claims. Such claims relate to a positive contribution to health or to the improvement of a function or to the modification or preservation of health.

Reduction of disease risk claims that state, suggest or imply that a food or food constituent, in the context of the total diet, reduces the risk of developing a disease or health-related condition.

Risk reduction claims that refer to the significant alteration of a major risk factor(s) for a disease or health-related condition. Diseases have multiple risk factors, and presentation of risk reduction claims must ensure, for example, by use of appropriate language and reference to other risk factors, that consumers do not interpret them as prevention claims.

Generic health claims that refer to those claims based on well-established, generally accepted knowledge from evidence in the scientific literature and/or to recommendations from nationally or internationally recognised public health bodies. A generic claim may be relevant for complying diets, foods or food constituents. A complying food or food constituent comprises or contains the functional component in sufficient quantity to produce the claimed effect(s), or falls within the category of foods to which the generic claim applies. Generally, companies may use a generic health claim on complying foods without further documentation.

Product-specific claims that refer to any claim that a relationship exists between a specific food or food constituent and health. This type of claim concerns the health-promoting effect of the product itself. The food or food supplement product must have been designed to provide a specific and documented effect.

Functional foods

i. Functional foods can be considered to be those whole, fortified, enriched or enhanced foods that provide health benefits beyond the provision of essential nutrients (e.g. vitamins and minerals) when they are consumed at efficacious levels as part of a varied diet on a regular basis (Hasler, 2002).

ii. A food can be regarded as functional if it is satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant either to an improved state of health and wellbeing and/or a reduction of risk of disease (Diplock *et al.* 1999).

iii. A health (functional) food refers to a food or food supplement that has special health functions or is able to supply vitamins or minerals. It is suitable for consumption by special groups of people and has the function of regulating human body functions but it is not used for therapeutic purposes. Furthermore, it will not cause any harm whether acute, sub-acute or chronic (State Food and Drug Administration (SFDA) of China, 2005).

Disease

Includes any injury, ailment or adverse condition, whether of body or mind. Diet-related, chronic, non-communicable diseases (NCDs)—including obesity, diabetes mellitus, cardiovascular disease, hypertension and stroke, and some types of cancer—are increasingly significant causes of disability and premature death around the world (World Health Organisation 2003).

Medicinal product

Any substance or combination of substances presented as having properties for treating or preventing disease in human beings, and any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

Medicinal claims

State or imply that a food or a food component (including a nutrient) has the property of treating, preventing or curing human disease, or makes references to such a property. Such claims are prohibited absolutely in the labelling and advertising of foods or food components.

US definition of disease or health-related condition

Refers to 'a disease or health-related condition', which is damage to an organ, part, structure or system of the body such that it does not function properly, (e.g. cardiovascular disease), or a state of health leading to such dysfunctioning (e.g. hypertension). The USA Guidance for Industry 2007 publication states that studies should identify a **measurable** disease or health-related condition by either measuring incidence, associated mortality, or validated surrogate endpoints that predict risk of a specific disease.

Benefit/Beneficial effect

The probability of a positive health effect and/or the probability of a reduction of an adverse health effect in an organism, system or (sub)population, in reaction to exposure to an agent (European Food Safety Authority [EFSA] Scientific Opinion: Guidance on Human Health Risk-Benefit Assessment of Foods, 2010).

3. Process for the scientific substantiation of health claims

All health claims used in the labelling, advertising or promotion of a food or food supplement must be capable of substantiation based on the totality of the available scientific data and the weight of the evidence. Whether generic or product specific, the claimed functional effect or property must be supported by scientifically valid evidence demonstrating the effect of the food or food constituent in humans, under typical conditions of use and exposure.

3.1 PASSCLAIM: Process for the Assessment of Scientific Support for Claims on Foods

In June 2005, the International Life Sciences Institute (ILSI) Europe, supported by the European Commission published the consensus on criteria for the assessment of scientific support for claims on foods (Aggett *et al.* 2005). The criteria are presented in summary form in Table 1. These 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. The criteria have potential to increase public confidence in the role of diet in maintaining and improving wellbeing. By defining the quality and type of scientific data required to substantiate health claims, the criteria have helped underpin regulatory developments in Europe and around the world, and the criteria will also assist industry, including small and medium-sized enterprises to identify opportunities for new products that offer health benefits to consumers.

3.2 Codex Alimentarius guidelines for use of nutrition and health claims (Codex Alimentarius Commission, 2009)

The Codex recommendations are intended to assist national authorities in their evaluation of health claims in order to determine their acceptability for use by industry. The recommendations focus on the criteria for substantiating a health claim and the general principles for the systematic review of the scientific evidence. Because of the global importance of Codex, the key areas are set out below:

3.2.1 Process for the substantiation of health claims

Such a process typically includes the following steps:

(a) Identify the proposed relationship between the food or food constituent and the health effect.

(b) Identify appropriate valid measurements for all the food or food constituents and for the health effect.

(c) Identify and categorise all the relevant scientific data.

(d) Assess the quality of and interpret each relevant study.

(e) Evaluate the totality of the available relevant scientific data, weigh the evidence across studies and determine if, and under what circumstances, a claimed relationship is substantiated.

3.2.2 Criteria for the substantiation of health claims

The following criteria are applicable to the three types of health claim as defined in the Guidelines for use of nutrition and health claims:

(a) Health claims should primarily be based on evidence provided by well-designed human intervention studies. Human observational studies are not generally sufficient *per se* to substantiate a health claim but where relevant they may contribute to the totality of evidence. Animal model studies, *ex vivo* or *in vitro* data may be provided as supporting knowledge base for the relationship between the food or food constituent and the health effect but cannot be considered as sufficient *per se* to substantiate any type of health claim.

(b) The totality of the evidence, including unpublished data where appropriate, should be identified and reviewed, including: evidence to support the claimed effect; evidence that contradicts the claimed effect; and evidence that is ambiguous or unclear.

(c) Evidence based on human studies should demonstrate a consistent association between the food or food constituent and the health effect, with little or no evidence to the contrary.

Although a high quality of scientific evidence should always be maintained, substantiation may take into account specific situations and alternate processes, such as:

(a) 'Nutrient function' claims may be substantiated based on generally accepted authoritative statements by recognised expert scientific bodies that have been verified and validated over time.

(b) Some health claims, such as those involving a relationship between a food category and a health effect, may be substantiated based on observational evidence such as epidemiological studies. Such studies should provide a consistent body of evidence from a number of well-designed studies. Evidence-based dietary guidelines and authoritative statements prepared or endorsed by a competent authoritative body and meeting the same high scientific standards may also be used.

3.2.3 Consideration of the evidence

The scientific studies considered relevant for the substantiation of health claim are those addressing the relationship between the food or food constituent and the health effect. In case of a claimed health effect that cannot be measured directly, relevant validated biomarkers may be used (e.g. plasma cholesterol concentrations for cardiovascular disease risk).

The scientific data should provide adequate characterization of the food or food constituent considered as responsible for the health effect. Where applicable, the characterization includes a summary of the studies undertaken on production conditions, batch-to-batch variability, analytical procedures, results and conclusions of the stability studies, and the conclusions with respect to storage conditions and shelf-life.

The relevant data and rationale that the constituent for which the health claim is made is in a form that is available to be used by the human body should be provided where applicable. If absorption is not necessary to produce the claimed effect (e.g. plant sterols, fibres, lactic acid bacteria), the relevant data and rationale that the constituent reaches the target site or mediates the effect are provided. All available data on factors (e.g. forms of the constituents) that could affect the absorption or utilisation in the body of the constituent for which the health claim is made should also be provided.

The methodological quality of each type of study should be assessed, including study design and statistical analysis.

(a) The design of human intervention studies should notably include an appropriate control group, characterize the study groups' background diet and other relevant aspects of lifestyle, be of an adequate duration, take account of the level of consumption of the food or food constituent that can be reasonably achieved in a balanced diet, and assess the influence of the food matrix and total dietary context on the health effect.

(b) Statistical analysis of the data should be conducted with methods recognized as appropriate for such studies by the scientific community and with proper interpretation of statistical significance.

Studies should be excluded from further review and not included in the relevant scientific data if they do not use appropriate measurements for the food or food constituent and health effect, have major design flaws, or are not applicable to the targeted population for a health claim.

By taking into account the totality of the available relevant scientific data and by weighing the evidence, the systematic review should demonstrate the extent to which:

(c) The claimed effect of the food or food constituent is beneficial for human health.

(d) A cause and effect relationship is established between consumption of the food or food constituent and the claimed effect in humans such as the strength, consistency, specificity, dose-response, where appropriate, and biological plausibility of the relationship.

(e) The quantity of the food or food constituent and pattern of consumption required to obtain the claimed effect could reasonably be achieved as part of a balanced diet as relevant for the target population for which the claim is intended.

(f) The specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.

Based on this evaluation and the substantiation criteria, national authorities can determine if, and under what circumstances, a claimed relationship is substantiated.

The Codex guidelines set out a common approach for substantiation of health claims, which is an important step for their use around the world. Grossklaus (2009), in his paper on the Codex recommendations on the scientific basis of health claims, concluded that health claims need to reflect the totality of the available data for emerging as well as consensus science. He also concluded that the substantiating evidence should be proportionate to the claim.

3.3 European Union

The regulation on nutrition and health claims made on foods (European Parliament and Council, 2006) applies to nutrition and health claims made in commercial communications – whether labelling, presentation or advertising across all the member states of the European Union. The law sets out the conditions for their use, establishes a system for scientific evaluation and creates European Union lists of authorised claims. All claims have to comply with the general principles that they are not false, ambiguous or misleading, and they have to be scientifically substantiated. To ensure a harmonised scientific assessment of a health claim, the European Food Safety Authority (EFSA) carries out such assessments.

The regulation states that health claims are only authorised for use in the European Union after a scientific assessment of the highest possible standard. The claims must be based on generally accepted scientific evidence and be substantiated by taking into account the totality of the available scientific data and by weighing the evidence. References to general, non-specific benefits of the nutrient or food for overall good health or health-related wellbeing may only be made if accompanied by a specific health claim included in the authorised Community lists. As a result, an application for authorisation must be prepared for each single claimed beneficial effect (European Commission 2008).

3.3.1 Main issues addressed by EFSA (2008, 2009 a): a two-step process

Each relationship between a food/constituent and a claimed effect is assessed separately; however, individual assessments are combined, as appropriate, to form coherent opinions.

In assessing each specific food/health relationship, EFSA considers **the extent** to which:

Step 1

- A food/constituent is defined and characterised.
- The claimed effect is defined and is a beneficial nutritional or physiological effect ('beneficial to human health').
- A cause and effect relationship is established between the consumption of the food/constituent and the claimed effect (for the target group under the proposed conditions of use).

Step 2

If a cause and effect relationship is considered to be established:

- Can the quantity of food/pattern of consumption required to obtain the claimed effect be reasonably consumed within a balanced diet?
- Does the proposed wording reflect the scientific evidence?
- Does the proposed wording comply with the criteria for the use of claims specified in the Regulation?
- Are the proposed conditions/restrictions of use appropriate?

Substantiation of the claim is dependent on a favourable outcome of the assessment of both Steps 1 and 2. Whether the evidence is sufficient to represent generally accepted scientific evidence to substantiate the claim is a scientific judgement of EFSA.

3.3.2 The totality of the available scientific data and weighing of the evidence

European Commission Regulation EC 353/2008 establishing implementing rules for an application for authorisation of health claims states that each application must cover only one relationship between a nutrient or other substance, or a food or category of food and a single claimed effect. The scientific studies must consist primarily of studies in humans and, in the case of claims referring to children's development and health, from studies in children. In addition, the studies must be presented according to a hierarchy of study designs, reflecting the relative strength of evidence that may be obtained from different types of studies.

The human data must be classified and organised in an application for authorisation of a health claim in the following order:

(a) Human intervention studies, randomised controlled studies, other randomised studies (non-controlled), controlled (non-randomised) studies, other intervention studies.

(b) Human observational studies, cohort studies, case-control studies, cross-sectional studies, other observational studies such as case reports.

(c) Other human studies dealing with the mechanisms by which the food could be responsible for the claimed effect, including the studies on bioavailability.

Non-human data provides supporting evidence and includes:

(a) Animal data including studies that investigate aspects related to absorption, distribution, metabolism, excretion of the food, mechanistic studies and other studies.

(b) *Ex vivo* or *in vitro* data based on either human or animal biological samples related to the mechanisms of action by which the food could be responsible for the claimed effect, and other non-human studies.

The structure of an application for authorisation of a health claim is set out in Regulation 353/2008. EFSA has also published scientific and technical guidance for the preparation and presentation of the application (EFSA, 2007).

3.3.3 Pertinent studies for substantiation of a claim

Key questions to be addressed by EFSA are:

- Have the studies been carried out with the food/constituent for which the claim is made? This question requires that there is sufficient definition and characterisation of the food/constituent.
- Have the human studies used an appropriate outcome measure(s) of the claimed effect?
- How do the conditions under which the human studies were performed relate to the conditions of use (e.g. food/constituent quantity and pattern of consumption) proposed for the claim?
- Have the human studies been carried out in a study group representative of the population group for which the claim is intended? Can the results obtained in the population studied be extrapolated to the target population?
- To what extent can evidence derived from studies in animals/in vitro support the claimed effect in humans?

3.3.4 Weighing the evidence

The decision on whether or not a health claim on a food/constituent is substantiated takes into account the totality of the available scientific data and the weight of the evidence. The beneficial effect of the food/constituent may be on a physiological function in the body or on a reduction of a risk factor for reduction of disease risk. The probability of a beneficial effect and the health claim must be based on, and substantiated by, 'generally accepted scientific evidence' (EC Regulations 1924/2006 and 353/2008). The assessment of each specific food/health relationship that forms the basis of the claim is therefore based on a scientific judgement on the extent to which a cause and effect relationship is established by taking into account the nature and quality of different sources of evidence (EFSA, 2009 a).

The evidence is weighed with respect to the overall strength, consistency and biological plausibility (i.e. likelihood), but currently a grade of evidence is not assigned. In Europe, the outcome of each assessment has one of three conclusions:

i. A cause and effect relationship has been established between the consumption of the food/constituent and the claimed effect. YES

ii. The evidence provided is insufficient to establish a cause and effect relationship between the consumption of the food/constituent and the claimed effect, i.e. the evidence of cause and effect is not conclusive because the evidence is emerging and/or conflicting, and the claim is not substantiated by 'generally accepted scientific evidence'. NO

iii. A cause and effect relationship is not established between the consumption of the food/constituent and the claimed effect (i.e. where the scientific evidence is limited and is not supported by 'generally accepted scientific evidence'). NO

The PASSCLAIM criterion number 6 in Table 1 concerns the evaluation of the totality of the data and weighing of the evidence. Both matters were considered important in view of different interpretations of conflicting evidence and the potential variation in quality amongst individual studies. The quality of individual studies may differ and it is possible that not all research has been or will be done to the highest standard, or even to a common standard. This can be due to the complexities of research in human subjects and also because data in support of a claim may have been taken from studies that had a different primary objective. PASSCLAIM stated that despite potential limitations in the research base, there may be complementarity between individually incomplete studies that allows an assessment of the totality of the evidence to substantiate a claim. Conversely, a review of all the studies taken together may reveal evidential inconsistencies that are not apparent from the review of a single study in isolation (Aggett *et al.* 2005).

PASSCLAIM also stated in the concluding comments on the six criteria for the scientific substantiation of claims, shown in Table 1, that the template needs to be applied intelligently and sensitively to existing and potential claims on a case-by-case basis with respect to both gaps in knowledge and to the development of new knowledge.

Although PASSCLAIM provided a scientific framework to facilitate the assessment of scientific support for claims on foods, the project did not specifically address the second part of criterion 6 on the weighing of evidence. However, it was emphasised that the evaluation process should be transparent and that the grading of evidence into categories including 'convincing', 'probable', 'possible' and 'insufficient' could be considered useful in scientific evaluations, and to monitor the development of scientific substantiation (Asp & Bryngelsson, 2008).

3.4 United States of America

3.4.1 Regulatory framework

In the USA, structure/function claims describe the role of substances that affect the normal structure or function in humans, whereas all health claims must be about reducing the risk of a disease or health-related condition. The Food and Drug Administration (FDA) controls health claims in three ways (Lupton, 2009):

i. FDA issues a regulation for claims that involve significant scientific agreement (SSA). If the strength of the relationship between the substance and decreased risk of a disease reaches the level of SSA, the Nutrition Labeling and Education Act of 1990 (NLEA) provides for the FDA to issue regulations authorising health claims. Guidance for industry on the SSA standard is available online (FDA/CFSAN, 1999).

ii. FDA prohibits or modifies, by regulation, a health claim that is submitted based on an authoritative statement from a scientific body of the US Government or the National Academy of Sciences. Guidance is available from the FDA Center for Food Safety and Nutrition (FDA/CFSAN, 1998).

iii. FDA issues a letter of enforcement discretion for qualified health claims. In 2003, the FDA Consumer Health Information for Better Nutrition initiative provided for qualified health claims on foods and food supplements where the evidence for the diet-health relationship does not achieve the SSA standard, but where the weight of the scientific evidence is in favour of the relationship. This ability to make qualified health claims is a significant advance to reflect emerging science. Information on qualified health claims and the criteria for their evaluation is available on the FDA/CFSAN website (2007).

3.4.2 Evidence-based review system for the scientific evaluation of health claims

The most recent guidance for industry published in 2009 by the US FDA/CFSAN sets out the agency's current approaches to the scientific evaluation of health claims. Elwood *et al*. (2009) reviewed the process for assessing the strength of the scientific evidence for a claim reaching scientific agreement and for those that require qualifying language. There are many common aspects with other evidence-based reviews around the world. For example, the type of study design is an important consideration in determining the strength of the evidence, and the concept is to minimise bias. A randomised clinical trial is rated more highly than a prospective cohort study, which in turn is rated more highly than a cross-sectional observational study. The ranking of studies in the assessment of the totality of the available scientific data in descending order of persuasiveness is shown in Table 2.

Many studies rely on surrogate biomarkers, which must be approved by the FDA and National Institute of Health. In the evaluation of human studies, FDA critically evaluates elements of each study such as design, data collection, data analysis etc. Key questions considered by FDA are shown in Table 3.

In the USA, 'reduction of disease risk claims' have been allowed on certain foods since 1993 (Food and Drugs Administration, 1993). These foods contain components for which the Food and Drug Administration (FDA) has accepted there is objective evidence for a correlation between nutrients or foods in the diet and certain diseases on the basis of 'the totality of publicly available scientific evidence, and where there is substantial agreement amongst qualified experts that claims were supported by the evidence'. By 1998, there were 11 FDA-approved correlations between foods, or components, and diseases. These claims for beneficial relationships with foods and food components included foods that are high in calcium and the reduced risk of osteoporosis, claims for foods that are low in saturated fats and reduced risk of coronary heart disease (CHD), and the claim for sugar alcohols in relation to reduced risk of dental caries. The claim relating diets containing soluble fibre with reduced risk of CHD was amended twice to allow claims for the soluble fibre from whole oats and from psyllium seed husk. Elwood *et al*. (2009) tabulated the health claims that meet the standard of significant scientific agreement and for qualified health claims supported by credible evidence that are subject to enforcement discretion. The FDA also announced that claims could be based on 'authoritative statements' of a Federal Scientific Body, such as the National Institute of Health and Centers for Disease Control, as well as from the National Academy of Sciences (FDA Modernisation Act, 1997), e.g diets rich in whole grain and other plant foods and low in total fat, saturated fat and cholesterol may reduce the risk of heart disease and some cancers. Elwood *et al.* (2009) tabulated the health claims meeting the standard of significant scientific agreement and qualified health claims supported by credible evidence.

3.5 Japan

In Japan, research on functional foods began in the early 1980s. In 1991, the concept of Foods for Special Health Use (FOSHU) was established. The scope of FOSHU includes processed foods (products) including tablets and capsule forms that contain dietary ingredients that have beneficial effects on the physiological functions of the human body, maintain or promote health and improve health-related conditions. Health claims on these foods correspond to the category of 'other functions' claims of Codex Alimentarius or structure/function claims in the USA.

Applicants for FOSHU status must validate the quality, effectiveness and safety of the product, and FOSHU-labelled foods may use a logo that is the seal of approval and that symbolises the notion of jumping for health. The existing FOSHU health claims are broadly classified into eight groups, namely glycaemic index (GI) condition, blood pressure, serum cholesterol, blood glucose, absorption of minerals, blood neutral fat, dental health and bone health (Yamada *et al.* 2008).

Claims for disease risk reduction are also currently allowed under FOSHU. However, there are only two such claims, namely calcium and reduced risk of osteoporosis and folic acid and reduced risk of neural tube defects. It is likely that disease risk reduction claims will be permitted in harmony with Codex Alimentarius.

In 2005, the FOSHU system was modified to include 'qualified' FOSHU claims on products that do not have sufficient scientific evidence, but nevertheless are considered to have a certain efficacy.

The labelling of health claims requires documentation of the clinical and nutritional evidence, including *in vitro* and biochemical studies, in vivo studies and randomised, controlled trials on healthy Japanese people. The overall philosophy of the regulatory approaches is to maintain and improve the health status of people and to reduce risk of chronic, non-communicable diseases through a well balanced diet as well as through the use of health foods, including foods with health claims (Yamada *et al.* 2008, Shimizu, 2009). Comprehensive reviews by Ohama *et al.* (2006, 2008) on health foods and foods with health claims set out the details of the approval system for FOSHU products in Japan.

3.6 Association of South East Asian Nations (ASEAN)

ASEAN was established in 1967, bringing together Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand and Vietnam. ASEAN is the geopolitical and economic organisation of these 10 countries, and since the adoption of the ASEAN Free Trade Agreement (AFTA) in 1992, several regional economic integration initiatives are in progress.

For example, the AFTA work in the areas of health supplements, traditional medicines and food products includes harmonisation of standards, technical regulation and mutual recognition arrangements. A key activity towards harmonisation includes the definition of a health supplement, which means any product that is used to supplement a diet in order to maintain, enhance or improve the health function of the human body, and which contains one or more, or a combination of the following:

i. Vitamins, minerals, amino acids, fatty acids, enzymes, probiotics and other bioactive substances.
ii. Substances derived from natural sources, including animal, mineral and botanical materials in the form of extracts, isolates, concentrates and metabolites.
iii. Synthetic sources of ingredients mentioned in (i) and (ii) may only be used when their safety has been proven.

The ASEAN countries have established a health claims framework based on Codex Alimentarius, and work is underway on the detailed requirements that will permit a common system to be implemented. The different types of claim must be substantiated by adequate levels of evidence, i.e. the scientific evidence for a functional claim is proportionately greater than that for a nutritional or general claim. In turn, disease risk reduction claims will require proportionately greater scientific support than for functional claims (Tsi, 2010).

Overall, the totality of the scientific evidence should demonstrate the beneficial effect using generally recognised markers based on evidence from human studies (observational and intervention), authoritative bodies, scientific reviews, and animal and *in vitro* studies. The objective is to guide companies to make truthful claims with adequate supporting scientific and/or traditional usage evidence.

3.7 Korea

In Korea, the scope of 'health functional food' (HFF) includes foods, manufactured or processed, and any form of foods, including food supplements (e.g. tablets, capsules etc), with ingredients or components that possess a functionality that is useful for the human body. The regulatory system was established in 2002 and makes provision for two different categories of HFF. There are 'generic' HFFs, for which the specification and standards are in an HFF code, and 'product specific' HFFs, for which it is necessary to register the specific ingredients and to obtain regulatory pre-market approval. As of July 2010, there are 39 ingredients listed in the generic HFF code, and over 200 ingredients have been approved as product-specific HFF ingredients since 2004.

The Korean regulation and the use of three types of nutrition and health claims are compatible with Codex Alimentarius (e.g. nutrient function claims, other function claims and reduction of disease claims). For other function claims, the Korean Food and Drug Administration (KFDA) defined three levels of scientific evidence in support of a claim: 'convincing', 'probable' and 'insufficient'. To date, applications for claims related to reduction of disease risk are still limited. The KFDA is responsible for pre-market approval and sets standards for the specification of the new active ingredient, its safety and efficacy. The scientific evaluation of efficacy is consistent with the guidelines established by Codex Alimentarius.

3.8 China

Functional foods are very important in Chinese society in terms of public health and economic benefits and they are based on traditional dietary culture (Yang, 2008). The State Food and Drugs Administration (SFDA) has been authorised to direct and conduct all affairs relating to functional foods since 2003, and in 2005, a health (functional) food was defined as *'a food that has special health functions or is able to supply vitamins or minerals. It is suitable for consumption by special groups of people and has the function of regulating human body functions, but is not used for therapeutic purposes. And it will not cause any harm whether acute, subacute or chronic'* (SFDA, 2005).

For each functional food, many tests are required before an application can be made, including tests of toxicity, functionality, stability, hygiene etc. All the tests should be done according to the standard procedures by specialised agencies or laboratories approved by the SFDA and Ministry of Health. Currently in China, there are 27 categories of product-specific health claims that are function related or refer to reduction of disease risk (Table 4). Applicants select from the 27 permitted claims for their product and provide a dossier containing evidence from testing of the product itself, as performed by the approved agencies and evidence from literature based on generally accepted knowledge from a textbook or a recommendation from national or international bodies, or evidence from human testing. If a herb is used, historical and traditional use, as well as present-day use should also be provided (Ministry of Health, 1996; SFDA, 2005). Human data from intervention trials, safety studies, epidemiological data, consumption data and history of use should be provided. Animal or *in vitro* studies are included only as supporting evidence. A comprehensive systematic and transparent literature review is required. Currently, there is no specification in the regulation reflecting the relative strength of the evidence that may be obtained from different types of studies, according to a hierarchy of study designs.

The SFDA regulations (2005) made provision for the introduction of a new functional category based on appropriate test methods (animal and human) and two sets of test results, the second of which must be conducted by a SFDA-approved laboratory. In practice, no new functions have been introduced.

The debate on the future regulation of functional foods and health claims in China is continuing, particularly in relation to scientific substantiation. The Codex guidelines (Codex Alimentarius Commission, 2009) are currently being considered. The evaluation programme is also expected to develop a means to classify the grades and qualifying strength of scientific evidence for foods and food constituents, as well as a review of the procedures for function claim testing.

3.9 Latin America

Currently, there are no harmonised provisions on the use and substantiation of health claims. Hence, national legislation in countries such as Argentina, Brazil, Chile, .Colombia and Mexico on food labelling, food advertising, food supplements etc. has to be considered separately.

For example, in Argentina, health claims are not specifically covered by the main food regulation, but claims referring to diseases, pathological conditions and to therapeutic properties are prohibited on foods and food supplements. For food supplements, advertisements, including web advertising, can describe the physiological effect of nutrients (mainly vitamins and minerals), but only for those nutrients that have a substantiated effect on any structure or physiological state of the organism of healthy people.

In Brazil, the labelling of foods and food supplements with health claims is regulated. A positive list for functional or health claims was approved in July 2008 for 18 nutrients/ingredients. The registration of foods bearing claims is based on the supporting evidence. The sources of evidence consist of (1) nutritional and/or physiological and/or toxicological trials conducted on laboratory animals; (2) biochemical trials; (3) epidemiological studies; (4) clinical trials; (5) proof of effect through safe traditional use observed in the population, and (6) evidence from the scientific literature.

In Chile and Colombia, health claims are defined and regulated nationally. In Chile, there are 18 health associations and conditions of use. In Colombia, claims must be based on scientific evidence, and the amount of the nutrient/ingredient present in the food product must comply with the minimum levels to achieve the desired beneficial effect. The claims can be expressed using words such as ‘can’, ‘helps’ and ‘contributes to’.

In Mexico, there are guidelines for nutrition and health claims, and they are based on Codex Alimentarius standards.

It is likely that the Codex Alimentarius guidelines described in Section 3.2 of this report will help towards the achievement of a harmonised regulatory framework for nutrition and health claims in Latin America.

4. Biomarkers and risk factors

One fundamental and challenging approach to the substantiation of health claims is the identification and validation of relevant biomarkers that can predict potential benefits on risks relating to a target function in the body. For function claims, a beneficial effect may relate to maintenance or improvement of a function (EFSA, 2009 a). A risk factor is a factor associated with a risk of a disease that may serve as a predictor of development of that disease. EFSA stated in its responses to Frequently Asked Questions (2009 b), which were related to the EFSA assessment of health claims applications, that for reduction of a risk factor to be considered beneficial in the context of a reduction of disease risk claim depends on the extent to which it is established that:

- the risk factor is an independent predictor of disease risk (this may be established from intervention and/or observational studies).
- the relationship of the risk factor to the development of the disease is biologically plausible.

For some risk factors, there is strong evidence that they meet both criteria, e.g. elevated serum Low Density Lipoprotein (LDL) cholesterol is a risk factor for coronary heart disease. A reduction in systolic blood pressure may be considered beneficial in the context of a reduction of disease risk claim for CHD and stroke.

Likewise, the USA Guidance for Industry (FDA, 2007) states that studies should identify a *measurable* disease or health-related condition either by measuring incidence associated with mortality or validated surrogate endpoints that predict risk of a specific disease. Whereas the US legislation includes either measurement of incidence of a disease, associated mortality or validated surrogate endpoints that predict the risk of a specific disease, the European legislation requires that the food or one of its constituents significantly reduces a risk factor in the development of a human disease. Currently, the EU law pays sole attention to the regulatory requirement for a **reduced risk factor** in the case of disease risk reduction claims. The absence of a reduced risk factor, as previously noted, is now interpreted by the EC and EFSA as being outside the scope of Article 14 of Regulation EC 1924/2006, and if such a claim were made with a reference to a human disease, it would take the claim into Article 2(1)(6) of Directive 2000/13/EC as a form of prevention of a disease claim. A medicinal claim on normal foods would be illegal. All Article 14 disease risk reduction claims therefore must have a *reduced risk factor*. This particular interpretation is challenging from the regulatory and scientific perspectives. EFSA has also focused on physiological risk factors, which are surrogate endpoints that have been shown to be valid predictors of disease risk. In contrast, in its definition of reduction of disease risk claims, Codex states that risk reduction means significantly *altering* a major risk factor(s) for a disease or health-related condition. Codex goes on to state that diseases have

multiple risk factors, and altering one of these risk factors may or may not have a beneficial effect. More importantly, the US Guidance states that risk biomarkers may be used in place of clinical measurement of the incidence of the disease. It points out that it may not be possible to carry out the study for a long enough period to see a statistically meaningful difference in the incidence of disease among study subjects in the treatment and control groups. The FDA also recognises that accepted surrogate endpoints that are involved in a single pathway may not be applicable to certain substances that are involved in a different pathway.

Examples of surrogate endpoints of disease risk included serum low-density lipoprotein (LDL) cholesterol, total serum cholesterol concentration and blood pressure for cardiovascular disease, bone mineral density for osteoporosis, adenomatous polyps for colon/rectal cancer, elevated blood sugar concentrations and insulin resistance for type 2 diabetes, and mild cognitive impairment for dementia.

How the EC/EFSA will handle a beneficial *raised* risk factor remains to be seen! Key discussion points relate, however, to what the EC/EFSA consider to be a risk factor and whether or not a disease risk reduction claim can ever be authorised under the current health claim regulation if the evidence is based on a true outcome of a disease from well designed observational studies, but without a reduced surrogate biomarker from a human intervention study.

4.1 FUFOSE and PASSCLAIM

FUFOSE attempted to describe markers of exposure and markers of biological response as either **factors** that are causally related to the endpoint, or **indicators** that are indirectly related. Markers of intermediate endpoint were stated to be more likely to be factors. FUFOSE stated that reduction of disease risk claims would only be justified if the evidence for the effect of a food or food constituent were based on an intermediate endpoint marker of disease. This marker would also have to be shown to be significantly and consistently modulated by the food/constituent for the evidence to be acceptable (Diplock *et al.* 1999). FUFOSE also set out criteria for markers, which included **biochemical, physiological** or **behavioural** markers that should be feasible, valid, reproducible, sensitive and specific. FUFOSE stated, "Markers should represent relatively immediate outcomes, which can be used to assess interventions in a reasonable timescale; they could, therefore, wherever possible, *replace* later and more remote outcomes as have been used in some epidemiological studies". This particular statement in FUFOSE is a clear indication that if the claimed effect can be measured directly, these measures should take precedence over the use of a surrogate biomarker of the claimed effect, i.e. risk factors are second best and replace a true endpoint or outcome of a disease, from well designed and executed epidemiological studies.

PASSCLAIM set out to develop consensus criteria for the scientific substantiation of claims (Aggett *et al.* 2005). Criterion 3 as shown in Table 1 states, "When the true endpoint of a claimed effect cannot be measured directly, studies should use markers". Criterion 4 states, "Markers should be:

- biologically validated 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.

PASSCLAIM also noted that, with respect to disease risk reduction claims, 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 an important research objective.

FUFOSE and PASSCLAIM recognised that, wherever 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 may be identified, it may not be measurable in practice. For example, there could be a long time period between the introduction of the intervention and the desired outcome (e.g. a reduced incidence of a disease as evidence of a reduced risk), and it may not be feasible or ethical to access the appropriate target tissues or biochemical processes (e.g. in the vascular wall). Large-scale intervention studies for disease risk reduction claims are, in many cases, excessively demanding of expertise and resources, impractical and are unlikely to reflect the onset and progression of the disease process. FUFOSE and PASSCLAIM state 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. For disease risk reduction, the target endpoint, if possible and if accessible, should be measured in some way (e.g. 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 more remote markers are from the endpoint, the less specific and more attenuated and subject to confounding variables they become. In a sense, most if not all biomarkers are correlational and are derived from disease states. 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 modifications can be effective only if the diet-health relationship is causal, if effects already induced are reversible and dependent on the presence of other risk markers that may have stronger effects. Hence, the appropriateness of a marker needs to be considered on a case by case basis. True outcomes and surrogate biomarkers from different types of human studies do, however, contribute to the totality of the evidence.

Hence, the scientific and regulatory issues relate to the following questions:

- what are considered to be nutritional and physiological beneficial effects?
- what is the definition of a risk factor and does it include both nutritional and physiological risk factors?
- are behavioural risk factors such as a low, or reduced or increased intake of a food/constituent included?
- should only measurable physiological surrogate biomarkers be required?
- how many risk factors/surrogate biomarkers are considered to be validated?
- what use is evidence from epidemiological/observational studies where true outcomes of disease and statistical evaluation of relative risk (RR) can be estimated?

Globally, the claimed physiological or nutritional effect needs to be specific enough to be testable and measurable by generally accepted methods. For example, EFSA now considers 'gut health' or 'digestive health' to be too general, whereas 'transit time' is specific and measurable by generally accepted methods. However, the number of validated surrogate biomarkers is discouragingly low, and in many health relationships it is possible only to describe or refer to the role of a nutrient or other substance in growth, development and the functions of the body rather than measure specific nutritional effects (Richardson, 2009). Reliance on testable and measurable effects could impact significantly on the use of health claims, and it may limit the application of existing scientific knowledge in product innovation and communications to consumers about food constituents and their relationship to health.

5. Evidence-based nutrition (EBN): the need for a scientific framework to underpin policy decisions

5.1 The totality of the available scientific data

Evidence-based nutrition is being used for three features of public health nutrition: (1) the establishment of Dietary Reference Values (DRV), including recommended daily intakes (EFSA, 2010); (2) the development and revision of dietary guidelines; and (3) the validation of health claims on foods and food constituents (Truswell, 2001). Guidelines advise people, for example, to eat less saturated fat. Health claims declare a benefit that lowering dietary saturated fat can lower the blood cholesterol level, a risk factor for cardiovascular disease, connected with a nutrition claim that a food is low in saturated fat.

The type and extent of the evidence required will be determined by whether the claim relates to a particular diet, a food category, a specific food, a proprietary (product-specific) product or a food constituent. Across all the global regulatory environments, there are invariably set requirements for scientific substantiation of claims, usually with human intervention trials placed at the top of a predefined hierarchy of evidence. For example, EFSA has published a hierarchy of study designs as stated in Section 3.2.2. However, the research should reflect the effects of foods/constituents on the health status of human subjects from different sources of evidence. In other words, the outcome - measured in clinical studies, observational, epidemiological and, where possible, nutrition intervention studies - should be the improvement in some indicators of health, wellbeing or reduction of risk of diseases (Richardson *et al.* 2003). The beneficial effects of foods/constituents can use true endpoints/outcomes (e.g. fatal or non-fatal cardiac events) as well as appropriately identified, characterised and validated physiological biomarkers.

Clearly, the relationship between dietary components and health benefits can be demonstrated by a number of different types of studies and designs, and methodological soundness overrides any hierarchy in study type, but also on the quality of its design, execution and analysis (Richardson *et al.* 2003).

In brief, in all the regulatory approaches around the world, studies on human subjects are accorded greater weight than animal and *in vitro* studies, and intervention studies have greater weight than observational studies. However, the critical review of the totality of the available data and weighing of the evidence should form the basis of the substantiation of a health claim on a case by case basis. In this respect, Codex recognises that the complete body of evidence includes authoritative statements prepared or endorsed by a competent authoritative body and which meet the same high scientific standards (Section 3.2.2.b). In the case of botanicals, there is often a long history of use and the main sources of information come from monographs and botanical textbooks that are published by recognised authorities around the world. Such sources of expert evidence on history of use or traditional use describe the generally accepted beneficial

effects of botanicals, and they should be considered for inclusion as part of the acceptable body of evidence. The overall assessment of the totality of the evidence should involve the application of scientific judgement and critical interpretation of the data as a whole.

5.2 Human intervention studies

Well designed, randomised controlled trials (RCTs) provide the most persuasive evidence of efficacy in human subjects and this investigational design permits strong causal inferences. Most other experimental designs lumped together under the term 'observational studies' are unable to distinguish whether the observed difference is due to the intervention or to some other unrecognised and often unmeasured factor. However, appropriate study designs and statistical methods can be used to minimise the effects of confounding variables.

The success of RCTs in evaluating medical treatments and pharmaceuticals does not mean that this method is always the most appropriate for the evaluation of nutritional effects (Heaney, 2008; Blumberg *et al.* 2010). It is important to compare and contrast the features of foods and food constituents that do not fit the RCT paradigm. For example, the contrasts between drugs and nutrients are shown in Table 5.

Drugs are intended for, and evaluated in, sick people. Food and food constituents with health claims are aimed at the normal healthy population. Drugs typically have only one, or a few, principal endpoints or outcome measures; the effect of a drug is usually measurably large; drug trials require the elimination or minimisation of co-therapies with other agents that might affect the endpoint, and the response to a drug is typically evaluated relative to its absence. In most cases, drugs act quickly and their endpoints can be measured over relatively short periods of time. Few of these features fit the nutrition context. Nutrients and other substances that contribute to nutritional or beneficial physiological effects tend to manifest themselves in small differences over longer periods of time. Nutrients work together rather than in isolation, and often their effects will not develop when intakes of other dietary components are suboptimal. There is, in effect, rarely a nutrient-free state against which the nutrient effects can be compared. Typically, studies compare a low intake with a high intake, but responses will be influenced by threshold characteristics, e.g. calcium absorptive response to vitamin D or haemoglobin response to iron. The dilemmas of focusing on pharmaceutical approaches to evidence-based nutrition are highlighted by Heaney (2008). The reliance on RCTs to assess nutrition questions fails to address the limitations of this pharmaceutical approach to nutrition and may explain in part the heterogenicity of results from different research centres and investigators and the different sources of evidence.

5.3 Disease risk reduction

Given the complex nature both of the disease process and of the characterisation of diet and physical activity over a lifetime, a simple hierarchical approach to evidence on causal links cannot rely on RCTs (Wiseman, 2008). Apart from the obvious inability to mask differences in dietary interventions based on real foods, in practice it is equally impossible to secure sufficiently

large or sustained differences in lifestyle including diet between intervention groups. Long-term observational studies of cohorts of healthy individuals can identify hard outcomes of chronic disease, e.g. incidence of mortality in typical populations consuming real diets over extended periods or even decades. However, observational studies, unlike randomised trials, are subject to confounding, making causal inferences less robust. Scientists are correct in noting that observational studies only provide an association, not definitive proof of cause and effect. However, well controlled and executed epidemiological studies have provided much of what we already know about human nutrition and health and the knowledge that underpins national and international dietary recommendations. Observational studies can also provide low to high quintiles of intake (i.e. a dose response), statistical measurements of relative risk (RR) and true outcomes of disease (e.g. fatal or non-fatal cardiac events in the case of CHD). Clearly, the scientific substantiation of all health claims, but particularly disease risk reduction claims for diseases with long latency periods needs to be undertaken intelligently and sensitively on a case by case basis, taking into account the totality of the available data and by weighing the evidence. It is the appreciation of the strengths and limitations of different types of study, the integration of the findings from different types of evidence and the degree of consistency between them that is the gold standard that needs to be applied in the scientific assessment of the strength of the evidence between a food/constituent and a health benefit.

5.4 Homeostasis and normal physiological adaptation

In general, diet-related diseases are caused by chronic exposure to unbalanced diets and not by acute exposures. The body's physiology may cope with variations in diet through feedback mechanisms, the buffering capacity of homeostasis and, if necessary, repair mechanisms. Adaptation to habitual consumption of such a diet or diets with unbalanced composition modulates the acute response and produces less dramatic alterations in molecular and physiological processes (Ommen *et al.* 2009).

Adaptive responses attempt to keep physiology within an individual's 'normal' range. While physiological adaptation will result in maintenance of functional biomarkers within the healthy range, these biomarkers may show a very different response in one healthy individual versus another, more susceptible individual. Nutrition has a function in maintaining homeostasis in metabolic processes such as oxidative stress and inflammation. Because of the large variation in 'normality', the effects of nutritional interventions may remain hidden because of the dynamic and multifactorial nature of the homeostatic processes.

Ideally, biomarkers of health should quantify the subtle but relevant effects in the healthy general population that precede the onset of disease, to identify predispositions or predict our capacity to deal with dietary and age-related stresses. Most validated biomarkers currently used in nutrition intervention studies are associated with the diagnostic and prognostic use for chronic disease and since most complex diseases are of late onset, biomarkers are typically associated with surrogate endpoints. Such endpoints would be equivalent to the clinical endpoint. The use of patients with

a particular disease or condition is common in nutrition science, and of key importance is to weigh up how representative the clinical studies are for the general population. Health is a continuous process involving multiple organs, metabolic pathways and genes all interacting to maintain homeostasis. Clearly, studies in patients are valuable sources of evidence. However, scientific conclusions on the relevance of patient studies to the normal healthy population need a coherent and transparent approach on a case by case basis. Research is needed to identify physiological responses of adaptation that will expand our knowledge of how health is maintained and optimised, and when homeostasis is disturbed, leading to the onset of disease.

5.5 Assessing the strength, consistency and biological plausibility of the evidence

All sources of evidence, whether from RCTs or observational studies, have inherent strengths and limitations, and all the regulatory frameworks and the Codex guidelines of 2009 base the substantiation of a health claim on the totality of the available data and weighing of the evidence. The US FDA (2009) determines whether the evidence and individual studies meet the SSA standard or whether such evidence is sufficiently credible to support a qualified health claim. Evidence is reviewed for quantity of studies, methodological quality (high, moderate or low), outcomes (beneficial effect, no effect or adverse effect) from studies of different types, consistency among studies showing a beneficial effect and relevance to the general population.

In Europe, the PASSCLAIM criteria shown in Table 1 offer a standard against which the quality of existing evidence can be transparently graded. The EU legislation requires an assessment of the weight of the evidence and the extent to which a cause and effect relationship is demonstrated, taking into account the nature and quantity of different sources of evidence (EFSA, 2009 a). The evidence is weighed with respect to the overall strength, consistency and biological plausibility (i.e. likelihood), but, as previously noted in Section 3.3.4, a grade of evidence is not assigned.

National and international organisations have used various systems to assess the level of evidence from different types of studies. One common approach is the distinction between different levels of evidence into categories including "convincing", "probable", "possible" and “insufficient”. This classification of the evidence has proven to be a useful tool in scientific evaluations. For instance the World Health Organisation (WHO, 2003) and the World Cancer Research Fund (WCRF, 2007) have published comprehensive and rigorous evaluations of the strength and consistency of evidence between certain nutrition risk factors and different chronic diseases (see Table 6). The two judgments characterised as being "convincing" or "probable" were considered strong enough to justify population goals.

Health claims undoubtedly require a high standard of evidence. However, there is currently no consensus about how the beneficial associations between foods/constituents and health can be tested and firmly established, and whether the requirement for conclusive evidence of cause and effect is proportionate and achievable in nutrition science. Key questions relate to what constitutes the totality of the evidence and by what means it should be developed and weighed. Without a clear framework for the assessment of the strength of the evidence, applicants for a health claim have little idea where their research lies on the continuum of ‘emerging science’,

through ‘generally accepted’ science to ‘conclusive evidence of cause and effect’ (Richardson, 2005 b, 2009). Hence, for regulatory managers, who have to consider the societal, economic and political dimensions when weighing up the extent to which cause and effect is demonstrated, a scientific and regulatory framework is needed for expressing the strength, consistency and biological plausibility of the evidence.

5.6 A scientific framework for weighing the evidence

It is necessary to have a transparent framework for commenting on the nature and quality of the totality of the data and for weighing the evidence in order to allow regulators to judge and make risk management decisions about the acceptability and veracity of a health claim submitted by an applicant. The development of a scientific framework for weighing the totality of the available data and the determination of the extent to which a cause and effect relationship is demonstrated are both scientifically justified and valid, and they can help to identify gaps in research.

As described in Section 5.5, organisations like WHO and WCRF have already used various systems to assess the level of evidence from different types of studies, and in the recent EFSA Scientific Opinion (2010) on establishing food-based dietary guidelines (FBDG), the identification of diet-health relationships was described using the same terminology, namely convincing evidence, probable evidence, possible evidence and insufficient evidence. Likewise, the EFSA consultation paper (2010) on guidance on human health risk-benefit assessment of foods defines ‘benefit’ as the probability of a positive health effect and/or the probability of a reduction of an adverse health effect.

Clearly, the concepts developed by PASSCLAIM, WHO, WCRF and EFSA could be used further to underpin the regulatory approaches to assessing the totality of the available data and, in particular, the weight of the evidence. Other researchers have also proposed scientific criteria to assess the (i) strength, (ii) consistency, (iii) temporality and (iv) coherence of evidence from cohort studies on diet and health relationships, and have examined the consistency of these findings with results from randomised trials (Mente et al. 2009).

Mente *et al.* applied the Bradford Hill guidelines (Hill, 1965) for causality and a modified set of criteria for assessing the associations between diet and coronary heart disease. A causation score was based on whether the four criteria were met or not. If all four criteria were met, a score of four was assigned (i.e. strong evidence), whereas if only one or two criteria were met, a score of one or two (i.e. weak evidence), respectively, was assigned (see Table 7). The evidence for each food/health relationship was then tabulated to show whether it was judged to be ‘strong’, ‘moderate’ or ‘weak’. Although this judgemental classification could be criticised for being arbitrary, the framework illustrates that it is possible to assess the extent of the evidence of causation and to compare the consistency of relative risks from well designed epidemiological cohort studies with outcomes from randomised controlled trials (RCTs). The findings of Mente et al. (2009) support the strategy of investigating dietary patterns in cohort studies and RCTs, especially for common and complex chronic diseases such as CHD.

Grading the strength of the body of evidence is an accepted scientific practice that allows the assessment of the quality, consistency and quantity of evidence, and the use of such grading is needed for elaborating not only dietary guidelines but also a regulatory framework for the use of health claims. Rarely are there cases where there is only a single piece of evidence for a causal claim. When assessing whether an association is causal, it is necessary to consider *all* the relevant studies: this is the powerful idea underlying the importance of systematic reviews (Howick *et al.* 2009).

In conclusion, in evidence-based nutrition there is a need to examine critically and scientifically the current hierarchies of evidence and evidence-based grading systems that can be applied in the area of human nutrition. Assessing the strength, consistency and biological plausibility of the evidence is a prerequisite to the determination of the strength of recommendations for regulatory use by risk managers, and for the wording of the claim to reflect the extent to which, or probability that, a particular food/constituent health benefit is true and will likely be refined (not reversed) by subsequent scientific research.

It is now critical from a global perspective to identify a suitable scientific framework for the weighing of evidence in order to embrace the 'state of the art' nutrition science, to stimulate future academic research, to promote product innovation and to communicate accurate and truthful nutrition and health messages to the public.

6. Consumer understanding and communication of nutrition and health messages

Nutrition and health claims are potentially powerful tools in communication to consumers as they convey information on food characteristics (e.g. a 'source of calcium') and health benefits that might otherwise remain unknown to the consumer (e.g. 'calcium is needed for the maintenance of normal bones and teeth', 'calcium is needed for normal growth and development of bone in children' and 'calcium may reduce the loss of bone mineral in post-menopausal women'. Low bone mineral density is a risk factor in the development of osteoporotic bone fractures). As such, nutrition and health claims may influence consumer preferences and facilitate well informed food choices. The use of validated claims on foods and food supplements has become widespread and, applied correctly, they present an opportunity to improve consumers' nutritional knowledge and healthy eating patterns, as well as contribute to public health more generally (Leathwood *et al.* 2007; van Trijp, 2009). Not surprisingly, consumer understanding as well as scientific substantiation are cornerstones of global legislation on nutrition and health claims.

6.1 Existing knowledge about consumers' use of nutrition information

Reviews of consumer science (Cowburn and Stockley, 2005; Grunert and Wills, 2007) indicate a consistent finding is that consumer interest in nutrition and health claims is high, as shown by the fact that health has become a key driver in the world's fasting growing food and beverage categories (van Trijp, 2009). As a result of the advancement of the nutritional sciences and public health communication efforts, the associations between diet and health generate high awareness.

Nutrition information on pack and in advertising is widely available, although it varies considerably between product categories and countries. Back of pack nutrition panels appear on many packaged foods and food supplements, consistent with the prevailing legislation. In addition, there are several consumer-orientated food labelling initiatives such as the use of Guidance Daily Amounts (GDAs) and the traffic light system in the UK, the Green Keyhole in Sweden, and front of pack calorie labelling etc. A potential problem is not so much information shortage, but an overabundance of information.

In store, consumers spend very limited time on food selection, and another consistent finding is that across all cultures, taste, price, naturalness and absence of pesticides etc. are considered by consumers to be of greater importance than health information. Although interest in and motivation by nutrition and health information tends to be higher among women, parents and older consumers, many consumers simply do not attend to the information provided. There is a clear need for more research on consumer attitudes towards and perceptions of nutrition information (van Trijp, 2009).

6.2 Consumer understanding

Currently, there is no precise or agreed definition of what understanding is in the context of nutrition and health information. Unfortunately, nutrition knowledge is often lacking, and although consumers seem to have a basic awareness of calories, for other nutrients knowledge is much lower (Grunert and Wills, 2007). Consumers are easily confused by detail and scientific wording of nutrition and health information. In addition, many consumers seem sceptical about commercial claims.

As consumers process information, the meaning assigned to nutrition information may easily go beyond the literal (or even intended) meaning conveyed in the nutrition or health claim (Hasler, 2008; Leathwood *et al.* 2007). This is largely due to the fact that the human memory is organised as an 'associative network' of interlinked information items. Much of this information can be accessed spontaneously with little mental effort, a process known as 'spreading activation'. In the context of nutrition information, it implies that simple nutrition messages such as a vitamin C content claim or 'with extra dietary fibre' may automatically trigger other (subjective) knowledge, e.g. helps colds and flu and reduces risk of cancer, respectively.

Consistent findings indicate that the presence of a claim, a logo or an endorsement can itself lead to a more positive interpretation of the product carrying the claim, but the presence of a health claim on front of pack may obstruct consumers' further search for other information on back of pack. Another consistent finding is that consumers prefer simple and easy to understand information on front of pack, with more detail provided on back of pack (Roe *et al.* 1999, Williams, 2005).

Methodologically, the field of consumer understanding of nutrition and health claims is in great need of further development. Leathwood *et al.* (2007) reviewed the type of data and information that could be needed to provide evidence of consumer understanding. After exploring several different approaches, the review proposes a case-specific, stepwise procedure for assessing consumer understanding of health claims:

- Identify the intended consumers (i.e. those to be targeted specifically).
- Define the food, claim and presentation to be tested (i.e. the nature and appropriateness of the food vehicle, the wording of the claim, logos, packaging, advertising, endorsements etc.).
- Identify the range of consumer interpretations of the claim using qualitative market research techniques such as in-depth interviews with individuals or focus groups.
- Quantify the accuracy of consumers' understanding of the benefit claim where the tested consumer is able to outline in his or her own words the beneficial effects expressed in the claim without significantly embellishing or exaggerating them.

Currently, there are practically no precedents from earlier research on the proportion of the average consumer's understanding of nutrition and health claims. This area of consumer research is ripe for development in order to establish expected plausible benchmark proportions and to determine what constitutes 'adequate understanding' (Leathwood *et al.* 2007).

6.3 The wording of claims

Consumers prefer simple and trustworthy information over scientific detail, although such detail is welcomed on back of pack and product endorsements by competent authorities and recognised charities can provide a means of verification and reassurance. The wording of health claims is determined by the totality of the scientific data and by weighing the evidence. However, a key question is: can the scientific judgements on the strength, consistency and biological plausibility of the evidence be communicated to consumers? Clearly, the health benefits must not go beyond the scope of the evidence, or confuse or mislead the consumer. Research from the USA has indicated that consumers had difficulty in distinguishing between the four levels of claims proposed by the FDA, categorised as A, B, C and D, to reflect scientific evidence, which was graded as 'high', 'moderate/good', 'low' and 'lowest', respectively (International Food Information Council, 2007). The FDA also concluded that consumers could not recognise the difference between a nutrient mentioned in a food-specific claim, a structure-function claim or a dietary guidance claim. Similar findings were reported in The Netherlands (van Trijp, 2005) and Australia (Williams, 2006).

Owing to lack of knowledge, misinterpretation and over-generalisation of nutrition and health claims by consumers in the USA and the limited research on consumer understanding in Europe and other parts of the world, the concept of using qualified health claims has been treated cautiously by some regulatory bodies. In the PASSCLAIM report of the Second Plenary Meeting (Howlett and Shortt, 2004), there was support for the idea that a structured approach to characterising the quality of the data would enable assessors to weigh the evidence, but caution was expressed by participants that this should not lead to a weighted characterisation of the claim itself. Participants also expressed opposition to the idea of 'qualified claims' on the grounds that a claim should either be judged as substantiated or not. This 'yes' versus 'no' approach to the assessment of outcomes for the scientific substantiation of health claims in Europe has been influenced by the low comprehensibility of claims to consumers. These aspects of consumer understanding were not part of the PASSCLAIM initiatives and are considered to be outside the scope of the scientific assessors of health claims.

Nevertheless, the Codex guidelines and the regulation in the EU requires an assessment of the weight of the evidence and the extent to which a cause and effect diet/health relationship is demonstrated. Hence, any assessment of the evidence for a health claim should have a scientific framework and give a clear statement of potential wording or graphics to reflect the strength of the evidence.

The approach for scientific assessors to give a yes or no response is likely to stifle the desire of both industry and governments to capitalise on promising research opportunities in food biosciences and technology. Equally, consumers may be deprived of authoritative information about, and access to, food products with health benefits. The final decision on whether or not a claim should be allowed rests with the regulators and policy managers, taking into account the scientific assessments of the strength, consistency and biological plausibility of the evidence and other societal and policy considerations including the broader purposes of food labelling to educate and improve public understanding of nutrition.

A scientific assessment that considers the strength and consistency of the totality of the evidence should also be sufficient to permit policymakers to draw conclusions about the probability that a change in the dietary intake of a food or food constituent will result in a health benefit. Unfortunately, there is a surprising lack of systematic research in the area of 'qualified' health claims that are understandable to the average consumer. In EC Regulation 1924/2006, Recital 16 provides an interesting definition of the average consumer: "average consumer means the consumer who is reasonable well informed and reasonably observant and circumspect, taking into account social, cultural and linguistic factors".

7. Conclusion

The clear aims of global legislation on the scientific substantiation of health claims are to achieve a high degree of consumer protection, to ensure confidence in claims on foods and food supplements, and to promote and protect innovation.

Developing the scientific criteria and the legislation for the substantiation of health claims has already involved extensive collaboration and discussion amongst the different stakeholders, including scientists from academia and research institutes, industry, consumer organisations and regulatory bodies. Further work is necessary to elaborate a robust and pragmatic scientific framework for weighing the totality of available data and for expressing the strength, consistency and biological plausibility of the evidence. To provide conclusive proof of a diet and health relationship represents an aspirational scientific standard that most health claims and indeed, most nutritional public health recommendations and dietary goals cannot achieve. To weigh the evidence involves value judgements, but it needs a credible scientific structure that captures the existing knowledge in such a way that policymakers can draw conclusions about the probability that a change in the dietary intake of a food or food constituent will result in a health benefit.

Global approaches to scientific substantiation specifically state that it is the extent to which a cause and effect of a diet/health relationship is demonstrated. Hence, the scientific assessments should reflect the strength of the evidence to allow researchers and innovative manufacturers supporting research to know where they stand on the continuum of research investigation. The determination of the strength of the evidence should draw on best practice around the world, e.g. WHO/FAO, 2003; Mente et al. 2009) to describe the evidence as convincing, probable, possible or insufficient or as strong, moderate or weak. Further research is also needed to develop a transparent process for creating well defined consensus standards and guidelines for the development of biomarkers, their validation and qualification (Elwood *et al*. 2009).

Much of the available nutrition scientific data are derived from the state-of-the-art published literature, where the onus has been, and still is, on the peer-review system to ensure that an appropriate standard of rigour is applied in the assessment of the quality of the studies. There is ample nutrition science available, but it was not necessarily designed to fit the purpose of substantiating health claims and providing conclusive evidence of cause and effect. A major issue relates to the appropriateness of a drug-based standard of proof. The field of nutrition needs to reflect on alternative experimental designs and endpoints. Nutrition policy decisions need to be based on the totality of the available data and on evidence that is less persuasive than that provided by a RCT. In the future, heightened scrutiny of the design, execution and interpretation of the data from human studies before publication will improve the overall credibility within the nutrition area, particularly in the context of the potential use of these data to establish and sustain food-related

health claims (Jones et al. 2008). Likewise, researchers exploring the benefits of particular foods, food ingredients and food constituents will have to pay greater attention to the relevant legislation, to available guidance documents and to the scientific quality of their data, both proprietary and in the public domain.

Health claims should assist consumers to make informed choices and help consumers identify particular foods and food constituents as well as encouraging greater consumption of such foods as part of a balanced diet. From an industry perspective, claims are used to identify, market and promote products. The challenge is to translate accurately the scientific wording of the nutritional benefit into consumer language. The wording of a claim involves a careful balance between keeping it simple and understandable versus keeping it serious and scientific. In Europe, a key issue relates to the move from the current use of more generalised claims to more specific, substantiated claimed effects describing discrete physiological functions. The initial research on consumer understanding of health claims reinforces the need to develop new, and refine existing, methods of consumer research, and to conduct academic and market research on the intended consumers in order to ascertain the extent to which the claims are understood in the context of the total diet, and to establish whether consumers can understand the relative strength of the evidence that exists to support the claim.

The ultimate objectives are to stimulate innovative developments in food technology and consumer science and to create a renaissance for food biosciences in order to:

- Identify beneficial interactions between the presence or absence of a food component and a specific function or functions in the body.
- Improve understanding of role of food and food components in maintaining and improving human health and in reducing the risk of major diseases.
- Establish science/evidence-based approaches to underpin regulatory developments on nutrition and health claims around the world.
- Stimulate multidisciplinary research and development between biochemists, nutrition scientists, medical and health professionals, food scientists and technologists.
- Reinvigorate efforts to process and preserve raw materials from agriculture, horticulture, fisheries and aquaculture into a diverse range of foods and food supplements.

Table 1

PASSCLAIM Criteria for the scientific substantiation of claims (Aggett et al. 2005)

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

Table 2

Ranking of studies in the assessment of the totality of the available scientific datain descending order of persuasiveness (based on FDA/CFSAN, 2005)

Randomized, controlled clinical trial
Cohort (longitudinal) studies
Case-control studies
Cross-sectional studies
Uncontrolled case series or cohort studies
Time-series studies
Ecological (cross-population) studies
Descriptive epidemiology
Case reports

Table 3

Key questions considered by the FDA to determine whether scientific conclusions can be drawn from an intervention or an observational study about the substance/disease relationship (FDA/CFSAN, 2007; Elwood et al. 2009)

Intervention studies
Were the study subjects healthy or did they have the disease that is the subject of the health claim?
Did the study include an appropriate control group?
Was the study designed to measure the independent role of the substance in reducing the risk of disease?
Were the relevant baseline data (e.g. on the surrogate endpoint) significantly different between the control and intervention group?
How were the results from the intervention and control groups statistically analysed?
What type of biomarker was measured?
How long was the study conducted?
If the intervention involved dietary advice, was there proper follow-up to ascertain whether the advice resulted in altered intake of the substance?
Where were the studies conducted?
Were the studies randomised and blinded and was a placebo provided?
Were inclusion/exclusion criteria and key information on the characterisation of the study population provided?
Was subject attrition (subjects leaving the study before the study was completed) assessed and explained in the report of the study?

Observational studies
What type of information was collected?
Were scientifically acceptable and validated dietary assessment methods used to estimate intake of the substance?
Did the observational study evaluate the relationship between a disease and a food or a food component?
Was there an adequate adjustment for confounders of disease risk?

Table 4

Permitted health claims in China (Yang)

Function	
1) Enhance immunity	13) Increase bone density
2) Antioxidative	14) Improve nutritional anaemia
3) Assist in memory improvement	15) Assist in protecting against chemical injury to the liver
4) Alleviate eye fatigue	16) Eliminate acne
5) Facilitate lead excretion	17) Eliminate skin cholasma
6) Moisten and clean throat	18) Improve skin water content
7) Improve sleep	19) Improve skin oil content
8) Facilitate milk secretion	20) Regulate gastrointestinal tract flora
9) Alleviate physical fatigue	21) Facilitate digestion
10) Enhance anoxia endurance	22) Facilitate faeces excretion
11) Assist in irradiation hazard protection	23) Assist in protecting against gastric mucosa damage
12) Improve child growth and development	

Reduction of disease risk	
24) Weight loss	26) Assist in blood sugar reduction
25) Assist in blood lipids reduction	27) Assist in blood pressure reduction

Table 5

Contrasts between parameters for drugs (evidence-based medicine, EBM) and nutrients (evidence-based nutrition, EBN). Adapted from Shao (2009)

Parameter	Drugs	Nutrients
Those human subjects with disease at baseline	100%	0%
Essentiality	None	Essential
Homeostatically controlled by the body	No	Yes
True placebo group	Yes	No
Dose-response	Relatively easy	Difficult in context of varied, balanced diet and healthy lifestyle
Biomarkers	Validated biomarkers of disease (few)	Research needed to identify adaptive responses in healthy individuals
Targets	Single organ/tissue	All cells/tissues
Systematic function	Isolated	Complex network
Baseline 'status' effects response to intervention	No	Yes
Effect size	Large	Small
Side effects	Large	Small
Nature of effect	Therapeutic	Contribution to, and/or role in growth development or functions of the body; maintenance/improvement of health reduction of risk of disease

Table 6

Summary of strength of evidence on foods and food components that give a health benefit (adapted from WHO, 2003)

Condition	Factor	Grade of evidence
OBESITY/WEIGHT GAIN	Regular physical activity	Convincing
	High dietary fibre intake	Convincing
	Low GI foods	Possible
DIABETES (TYPE 2)	Weight loss; regular	
Healthy blood sugar levels	physical activity	Convincing
Increases insulin action	High fibre intake (NSP)	Probable
	Low saturated fat	Probable
	n-3 fatty acids	Possible
	Low GI foods	Possible
	Vit E, Cr, Mg	Insufficient
CARDIOVASCULAR DISEASE	Regular physical activity	Convincing
Heart health	Linoleic acid, EPA/DHA	Convincing
	Fruit and vegetables	Convincing
	Potassium	Convincing
	Low Na intake, TFA	Convincing
	α-linolenic acid; oleic acid	Probable
	NSP/dietary fibre	Probable
	VWhole grain cereals	Probable
	Nuts (unsalted)	Probable
	Plant sterols/stanols	Probable
	Folate	Probable
	Flavonoids/Soy products	Possible
	Ca, Mg, vitamins C, E	Insufficient
CANCER	Fruit and vegetables	Probable
(oral cavity, oesophagus, stomach, colorectum)	Fibre, soya, n-3 fatty acids, carotenoids, vitamins B_2, (B_6, folate, B_{12}, C, D and E, Ca, Zn, Se, allium compounds, flavonoids, isoflavones, lignans)	Possible/Insufficient

Table 6 continued

Summary of strength of evidence on foods and food components that give a health benefit (adapted from WHO, 2003)

Condition	Factor	Grade of evidence
DENTAL HEALTH	Good oral hygiene	Convincing
	Fluoride, Vitamin D (enamel defects);	Convincing
	Hard cheese, sugar-free chewing gum;	Probable
	Milk, dietary fibre, xylitol	Possible
BONE HEALTH	Regular physical activity	Convincing
	Vitamin D, calcium	Convincing

Table 7

Summary of the evidence of a causal association between diet and coronary heart disease, as determined from examination of prospective cohort studies using the Bradford Hill guidelines and consistency with findings from RCTs[a] (Mente et al. 2009)

Evidence of a causal association from cohort studies	Cohort data only	Supported by RCTs
STRONG		
"Mediterranean" diet[b]		Yes
High-quality diet	✔	
Vegetables	✔	
Nuts	✔	
Trans-fatty acids	✔	
Glycaemic index or load	✔	
“Prudent” diet[c,d]	✔	
“Western” diet[d,e]	✔	
Monounsaturated fatty acids	✔	
MODERATE		
Fish		No
Marine ω-3 fatty acids		Yes
Dietary folate	✔	
Supplementary folate	✔	RCT Data only
Whole grains	✔	
Dietary vitamin E	✔	
Dietary beta carotene		
Supplementary beta carotene		RCT Data only
Dietary vitamin C	✔	
Alcohol, light/moderate consumption	✔	
Alcohol, heavy consumption	✔	
Fruits	✔	
Fiber	✔	
WEAK		
Supplementary vitamin E		Yes
Supplementary ascorbic acid		Yes
Total fat		Yes
Saturated fatty acids	✔	
Polyunsaturated fatty acids		Yes
ω-3 fatty acids, total	✔	
Meat	✔	
Eggs	✔	
Milk	✔	

Abbreviation: RCT - randomised controlled trial

(a) The analysis of the results from RCTs is not meant to override the results from cohort studies, but rather to indicate whether the evidence from RCTs is concordant with that of cohort studies.

(b) The "Mediterranean" dietary pattern emphasises a higher intake of vegetables, legumes, fruits, nuts, whole grains, cheese or yogurt, fish, and monounsaturated relative to saturated fatty acids.

(c) The "prudent" dietary pattern is characterised by a high intake of vegetables, fruit, legumes, whole grains, and fish and other seafood.

(d) Strong evidence was found when analysis was restricted to cohort studies of high methodological quality (low risk of bias).

(e) The "Western" pattern is characterised by a high intake of processed meat, red meat, butter, high-fat dairy products, eggs and refined grains.

(f) Cohort studies have assessed plant (α-linolenic acid) and marine (eicosapentaenoic acid and docosahexaenoic acid) sources of ω-3 fatty acids; RCTs have assessed predominantly marine sources.

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IADSA

International Alliance of Dietary/
Food Supplement Associations

International Alliance of Dietary/Food Supplement Associations
50, Rue de l'Association, B-1000 Brussels - Belgium
Telephone: +322 209 11 55
Facsimile: +322 223 30 64
Email: secretariat@iadsa.be
Website: www.iadsa.org

Designed by The Bubblegate Company Limited
Tel: +44 (0)1303 863800