ILSI Europe
Report Series

Beyond PASSCLAIM – Guidance to Substantiate Health Claims on Foods

Summary Report of a Workshop held in December 2009

Organised by the ILSI Europe Functional Foods Task Force

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BEYOND PASSCLAIM – GUIDANCE TO SUBSTANTIATE HEALTH CLAIMS ON FOODS

SUMMARY REPORT OF A WORKSHOP HELD IN DECEMBER 2009 IN NICE, FRANCE
ORGANISED BY THE ILSI EUROPE FUNCTIONAL FOODS TASK FORCE

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INTRODUCTION

The workshop "Beyond PASSCLAIM – Guidance to substantiate health claims on foods" was held in Nice, France from 14-16 December 2009 and brought together over 70 experts from industry, academia and public bodies to discuss guidelines to establish beneficial effects of functional foods. The event was commissioned by the ILSI Europe Functional Foods Task Force, and organised as a joint effort of four different expert groups it currently supports. The aim was to discuss two draft guidelines related to health claim substantiation, guidance for design and reporting of human intervention studies and for a standardised approach to prove the efficacy of foods and food constituents. In addition, expert group work evaluating the PASSCLAIM criteria using polyphenols and antioxidant activity as an example was presented. The workshop also initiated a discussion on guidelines for quality standards to apply in nutrition research involving human subjects.

The main activities of the workshop took place in parallel sessions of working groups of approximately 15 persons each. This design allowed all participants to visit all sessions – staying approximately one hour in each. The outcomes of the sessions were combined and summed up in a plenary session. Participants had received relevant literature and draft manuscripts prior to the event.

The purpose of this summary report is to share the comments that were made during the parallel sessions. The views expressed in this publication do not represent the views of the authors or institutions or companies, nor a consensus of the workshop. It should be considered as a summary of the feedback provided by the workshop participants. The feedback will enable the ILSI Europe expert groups to complete their work, resulting eventually in scientific articles in peer-reviewed journals.

FOREWORD

Prof. Peter Aggett, Lancaster University, UK
Dr. Jan de Vries, CSM, The Netherlands

The increased appreciation of the role of nutrition in preventative medicine and public health led, in the last two decades of the 20th century, to the development of many foods, food ingredients and novel products with claimed beneficial effects internationally. These claims were usually made on the basis of traditional use and of epidemiological associations of variable quality. In the context of demonstrating causal relationships and substantiating such claims, and although most national regulatory authorities had processes to assess the safety of novel foods and processes, there were no mechanisms for the critical evaluation and approval of any evidence base for claims on benefits from the products. Amongst others, ILSI Europe realised that food producers, and anyone else, who wished to make a functional claim for any product or ingredient should provide and, if necessary, develop evidence to justify any claim. The Functional Food Task Force (FF TF) of ILSI Europe initiated the Concerted Action "Functional Food Science in Europe" (FUFOSE) that was funded by the European Commission (EC). FUFOSE was followed by the EC-funded project PASSCLAIM (Process for the Assessment of Scientific Support for Claims on Foods). The workshop "Beyond PASSCLAIM" needs to be placed in the perspective of both prior projects.

FUFOSE blended two concepts that were emerging at that time: the concept of "Evidence Based Nutrition" and that of "Functional Foods". The activity developed a rationale for the intelligent and strategic use of markers of intake or exposure, internal dose or systemic burden, intermediate markers of effect and markers of the expected functional endpoint. Thus FUFOSE epitomised the essence of evidence based nutrition, and the principles involved could clearly be seen as relevant to the development of validated and quality assured markers for any food or food component. In this respect FUFOSE served an important purpose, and in doing so embraced and tested the key elements of validating markers. It is important to note that FUFOSE used the term "markers" rather than "biomarkers". This was done in part to emphasise the breadth of available markers other than biomarkers.

FUFOSE enabled the conceptualisation of a structured approach to existing evidence for the health effects of foods and food components. FUFOSE clearly intended to endorse Evidence Based Nutrition in order to encourage the quality of nutritional sciences in Europe. It did not, however, consider the confounders, uncertainties and variabilities associated with such evidence. These are clearly important in the confident attribution of outcomes in evidence based approaches, and FUFOSE did not explore the likelihoods that more than one food or ingredient could have a similar health effect nor that single foods or ingredients could have multiple outcomes.

The PASSCLAIM project has evaluated existing schemes, like the FUFOSE outcomes, that assess scientific substantiation of claims. PASSCLAIM proposed criteria that can be used to explore links between diet and health. The process resulted in a generic guidance tool for assessing the scientific support for health claims on foods. It was envisaged that the PASSCLAIM guidance tool would set a gold standard for the appraisal of evidence. Additionally, the PASSCLAIM tool was seen as providing a structure for the intelligent handling of ambiguities and uncertainties in the evidence, for the responsible extrapolation of the data between genders and age groups and for ensuring transparency, objectivity and integrity for the process, thereby improving the efficiency of the regulatory review.

However, PASSCLAIM did not review or comment on the process for allowing or disallowing health claims, and it did not consider qualifying the evidence in the context of generating qualified health claims. Establishing qualified health claims is essentially a Policy Makers' or Risk Managers' exercise. PASSCLAIM informed the process for the Risk Assessors. There are concerns that opportunities for relaying to the Commission the quality and strength of evidence for claims are being missed, with the result that opportunities for qualified claims for use in public health nutrition are similarly being missed. However, approaches to enable these aspects of Risk Analysis to work effectively would probably need to be explored with Policy Makers and the Commission.

After finalising the PASSCLAIM project the Task Force assigned an expert group to apply the criteria to provide scientific substantiation of a polyphenol claim as a case study. In this exercise the applicability of the PASSCLAIM criteria had to be critically reviewed. In addition to this process the Task Force recognised a further need for guidance on how to establish a sound scientific substantiation of health claims. Regulatory frameworks are increasingly requiring a high level of scientific evidence to support health claims on foods. Although the PASSCLAIM project provided clear criteria for the scientific substantiation of claims, a need for more detailed guidance on how to best conduct and report human intervention trials was identified.

In assessing the benefit of functional foods and food ingredients, the need was identified to find consensus on how to address complex small effects on health, both in relation to functions or risk factors. A dedicated expert group focused on developing a standardised approach to build a body of scientific evidence to establish food-health relationships.

The limited success of applications being submitted to EFSA for evaluation against criteria that match closely those of PASSCLAIM is a challenging audit or commentary on the quality of the portfolios of evidence, and, one fears, of the quality of nutritional science behind the proposals. It is thus expected that the output of these expert groups may help to improve the quality of nutritional sciences and create societal confidence in the food industry.

DESIGNING AND REPORTING OF HUMAN INTERVENTION STUDIES SUPPORTING FUNCTIONAL FOODS

The first two working sessions of the workshop were held based on a draft document "Guidelines for design and reporting of human intervention studies to evaluate Functional Foods". The draft had been developed by an expert group of Dr. Jean Michel Antoine (Danone), Prof. Arne Astrup (University of Copenhagen), Dr. Jean-Louis Berta (consultant), Dr. Achim Bub (Max-Rubner-Institut), Dr. Jan de Vries (CSM), Dr. Francisco Guarner (Hospital General Vall d'Hebron), Dr. Oliver Hasselwander (Danisco), Dr. Henk Hendriks (TNO Quality of Life), Dr. Martin Jäkel (Unilever), Prof. Berthold Kolezko (University of Munich), Dr. Myriam Richelle (Nestlé), Dr. Stephan Theis (Südzucker/BENEO Group), Prof. Robert Welch (University of Ulster) and Dr. Jayne Woodside (Queens University). The objective for the group was to provide 'best practice' guidance on how to conduct intervention studies to scientifically substantiate health benefits of foods. This was addressed by analysing and extracting learnings from published studies, taking into consideration various aspects, including:

- Definition of appropriate control products – lack of perfect controls, and the type required depends on the nature of tested ingredients or foods;
- Responder selection and status, including how to deal with 'low', 'normal' and 'high' responders;
- Criteria for validation of markers – rationale for supporting substantiated and valid markers;
- Design(s) of studies – what is the rationale?

The workshop sessions included an inventory of discussion points. A generalised overview of topics and remarks has been integrated in a mind-map in Figure 1 (page 9). Several specific topics in the draft document were commented on; also several topics to be included in the document were suggested. In addition, the experts commented on study design, single arm studies, study product characterisation, selection of subjects, adverse events reporting and trial registration.

Study design

Dr. Henk Hendriks, TNO Quality of Life, The Netherlands
Prof. Rob Welch, University of Ulster, UK

The group discussions clearly indicated the notion that when a clinical study is designed with the purpose to substantiate a health claim, the design may strongly benefit from a predefined claim. Such a definition will not only help formulate the null hypothesis, it will also indicate the markers of choice, the power of the study etc. A clear distinction should always be made between primary and secondary hypotheses. Secondary hypotheses should always be reconfirmed in independent studies. The experts indicated that the choice between cross-over and parallel designs strongly depends on the research topic. Whereas a cross-over design will allow comparison within an individual, because each individual is its own control, it will lengthen study duration and may suffer from learning effects.

Other important issues that deserve special attention when designing intervention studies are the effects of potentially confounding lifestyle and other factors, such as physical activity level, and the background diet. Also, acceptable levels of compliance need to be specified. In general, it was agreed that single arm studies were only appropriate in a very limited number of specific cases and were, in general, considered not useful. Single arm studies may be applied as a first preliminary orientation, but they are not publishable. These studies will also not contribute to an EFSA dossier, since they will not be taken into account. Single arm studies may even form a danger for smaller companies; they may seem a reasonable alternative, but are scientifically unacceptable.

Study product characterisation

The group stressed the importance of study product characterisation. Not only the composition of the background diet, but also information on intended habitual intake should be given. Advice on how to use a product should to be considered and described in study protocols. Also the minimal dose for an effect needs to be specified.

Safety aspects of the study product should be known, possibly also related to the highest potential dose without side effects. In general, specifying previous knowledge, including outdated studies, in protocols would help prevent superfluous studies. Some guidance is needed on how to design the correct control for a food usually consisting of a mixture. Studies using mixtures may need more than one control arm in a study. The eventual guideline should contain recommendations or refer to examples on background diet and how to deal with control products.

Selection of subjects

The experts discussed the pros and cons of different study populations. On the one hand extreme groups, like patients, may be used to show a beneficial effect, but on the other hand studies on patients should not form the basis for substantiation of a claim. Using slightly compromised persons may offer an alternative. Such a study population should always be representative of the targeted consumer group.

In general, it was considered to be very difficult to show that healthy people will become healthier when consuming a specific product with a health benefit. The difficulty of defining an effect may be overcome by challenging the subjects; the recovery from a challenge may better define health as using one specific health indicator being affected. However, ethical issues may arise when the challenge concept is applied.

Inclusion and exclusion criteria should be focused on the central hypothesis and their choice should be justified. Selection of "super healthy" subjects should be avoided. Genotyping may help explain variability and may help recognise specific subgroups, but was not considered generally relevant for consumers. It was also considered difficult to show health benefits for the general population. The general feeling was that the use of well-defined subgroups might offer a reasonable alternative. The document should provide more guidance on inclusion and exclusion criteria.

Adverse events reporting

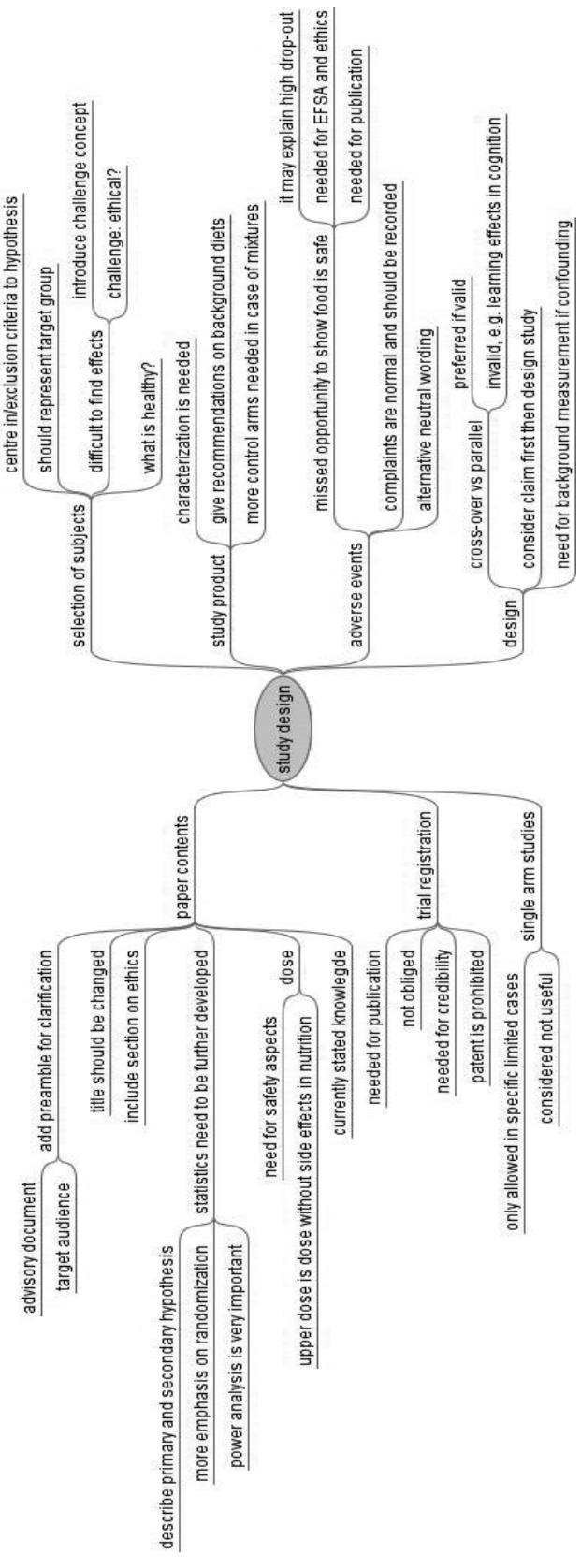
There was an overall consensus among the participants at the workshop that adverse events should be registered, since complaints occur on a daily life basis. It may be appealing to use a different terminology, because nutrition trials may be considered as essentially different in their purpose and risk, as compared to drug trials. For that purpose, alternative, more neutral terms such as co-effects, co-events, side effects, unfavourable effects or other observed effects were suggested. However, the overall consensus was that recording of these events is needed, not only for ethical committees and EFSA, but also to facilitate publication in high-ranking journals and to further show that the food is safe, and in some cases to explain high incidence of dropouts.

Trial registration

Trial registration was considered as an ethical need and as a contribution to the credibility of nutrition research. Such registrations have been indicated in the Declaration of Helsinki. However, registration may form a problem in case new findings need to be patented, as it obviously publicly discloses the idea.

Also, registration will better provide insight into the totality of evidence; all trials will contribute to meta-analyses and as such help to prevent publication bias. The ILSI Europe document should provide guidance on this topic and therefore indicate that trial registration is the preferred option. Patenting of new findings may prohibit publishing the outcomes of a limited number of initial studies.

Figure 1. Mind-map of discussion points covered in the "Study-design" session.



Markers

Dr. Jonas Wittwer, DSM, Switzerland
Dr. Jean-Michel Antoine, Danone, France

An integral part of a proper human nutritional study design is the choice of the right markers to be measured in order to describe a certain (intermediate) effect of a nutritional product on a certain condition. Depending on the conditions of interest different kinds of markers can be chosen, e.g. markers to measure efficacy (show benefits of the nutritional product), or a certain risk (risk markers to evaluate safety properties), or a certain function (to investigate the mechanistic function of a nutritional compound), or compliance of the study participants. In addition to these known kinds of markers, also markers for an early prediction of improvement (as early as possible) and special markers for demonstration of a claimed effect (validated markers to demonstrate a claimed effect of a substance) were suggested. Also a ranking of the markers into "light" and "hard" markers was proposed. The "light" markers (e.g., new markers which lack full validation) could be used for exploratory studies while the "hard" markers (e.g., markers with a long history of use) could be used for confirmatory studies. Further, it might be a good suggestion to not only use markers describing a definite status (e.g. oxidised low-density lipoprotein (LDL) or LDL-cholesterol plasma levels as a recognised marker for cardiovascular disease risk) but to use a marker describing a dynamic effect (e.g. Flow Mediated Dilation as a descriptor for coronary artery (cardiovascular) health).

Often, multiple markers are used to describe a benefit of a nutritional substance. This can be of advantage if it is not clear on which parameter the substance has most impact (e.g., in explorative studies or in studies with different endpoints describing several aspects of a health condition). An example would be the field of cognitive performance: several cognitive aspects can be tested in the same study, like memory, attention etc. Multiple markers can also be used to explore different independent mechanisms integrated in (modulating) a global effect, or to explore different dependent mechanisms (cascades). For instance, anti-oxidative capacity of a substance can be measured in various ways, such as lipid peroxidation, DNA oxidative damage by COMET assay, or by determining the expression of detoxification enzymes.. The use of an "index" integrating several endpoints to an indicator of a substance's benefit was discussed and was rated as being possible, but statistical analyses and rating of different endpoints will have to be carefully considered.

In general, the markers taken in a human trial should follow the definition given by PASSCLAIM: a marker should be both technologically (analytically) valid as well as biologically valid. Changes of markers will become convincing, when they are statistically significant and biologically relevant. The biological relevance can be based on objective (e.g., body weight) or subjective (e.g., mood, appetite) measurements. All markers should be proxy measures that reflect a functional, physiological or biochemical characteristic associated with the underlying condition.

"New" markers, having either not yet being validated, or derived from emerging technologies, are being explored, and will be able to be used in human trials. However, special attention will have to be given so that they are analytically (e.g., accuracy, precision) and scientifically robust (e.g., already being used commonly by experts and described in several peer reviewed journals). In addition, especially with new emerging technologies like "-omics" and imaging technologies, the physiological relevance of the marker changes is of importance in order not to just measure numbers/patterns or changes in activity that cannot be biologically interpreted. Therefore, an objective significant and biological relevant change associated with a subjective (experienced) benefit is essential for claim substantiation.

As only very few markers have been validated for specificity, variability, limitations and applicability to various subject groups, a need has been identified to create a database of validated markers. This database could be set up by either ILSI Europe and its respective consensus groups, or by another party. The database would have to be regularly updated. As only validated markers would appear in this database, a validation procedure (e.g., rating/scale of existing evidence) should be established. This would explain minimal levels of information needed to define a certain marker as validated. In addition, information about claims can be inserted into the database and can help to choose the right marker for assessing a certain effect or health benefit. For practical reasons, the database could be based on the already existing paper by Griffiths *et al.* (Mol Aspects Med 2002 23: 101-208), which reviewed the usefulness of markers in the scope of the EC-funded ESCODD program.

A STANDARDISED APPROACH TOWARDS PROVING THE EFFICACY OF FOODS AND FOOD CONSTITUENTS: PROVIDING GUIDELINES

Dr. Gert Meijer, Unilever, The Netherlands

There is consensus that solid scientific evidence is needed to substantiate claims on food products with a specific function. The PASSCLAIM process is generally accepted for the assessment of scientific support for claims for foods. However, it is not clear what is required for health claims substantiation, with a concurrent risk that foods will be evaluated and/or classified like drugs.

This expert group should deliver a peer-reviewed publication on the scientific guidelines for a structured framework of scientific studies that are needed to generate aligned and sufficient scientific evidence to substantiate the relationship between a food (constituent) and a physiological effect (typically expressed as a "health claim", i.e. a function or disease risk reduction (DRR) claim), taking into account efficacy, tolerability and safety of a food (constituent). The structured framework will need to provide criteria for the assessment of the scientific substantiation of a relationship between a food (constituent) and a physiological effect, and will clearly delineate nutritional practice from drug practice, while applying similar scientific standards.

The approach that has been taken is to work with an expert group (Dr. Alison Gallagher (University of Ulster), Dr. Gunhild Kozianowski (Südzucker / BENEO Group), Dr. Gert Meijer (Unilever), Prof. David Richardson (DPR Nutrition), Dr. Virginie Rondeau (INSERM / Université Victor Segalen Bordeaux 2), Dr. Marianne Stasse-Wolthuis (Stasse Consultancy), Dr. Guy Tweedie (Danone) and Ms. Maria Skarp (ILSI Europe)) to propose draft guidelines. The input from the workshop will be integrated in the guidelines, which will be published.

In preparation for the workshop a draft paper was produced by the expert group, which was discussed by the working groups, focusing on three specific interest areas:

1. Implications of "beneficial to health":
   - How to assess whether a claimed effect would qualify as "beneficial to health"?
   - How should body function claims be assessed for the general population?
2. Assessment of strength and consistency of evidence – what are the requirements?
   - Assessment of evidence vs. existing systems?
   - Minimum level to demonstrate effectiveness?
   - Different requirements for different claim types / active ingredients?
   - Less studies required when surrogate markers available?
   - Weighing the evidence for different amounts / quality of data?
   - Mechanistic understanding always / not a prerequisite?
   - Role of animal and *in vitro* studies? How do these weigh versus human intervention studies?
3. Disease risk reduction claims:
   - Qualified health claims – Are more strict criteria needed for certain claims (e.g. disease risk/ children's claims) than for other (function) claims?
   - Does a "representative sample" of the population go beyond healthy volunteers?
   - Are there ways to communicate on promising, but not yet conclusive, evidence?
   - Evidence may be based directly on a true outcome of a disease, without a reduced surrogate marker?
   - Confusion between risk factor and surrogate marker and risk of disease?

The purpose of this summary report is to share the comments that have been made during the workshop. It is important to note that this paper does not reflect consensus and can therefore not be seen as a consensus report.

What does "beneficial to health" entail?

Dr. Alison Gallagher, University of Ulster, UK
Dr. Gunhild Kozianowski, Südzucker/BENEO Group, Germany

This session considered questions inherent and initial to any evaluation of a body function claim, i.e. whether the claimed effect can be considered"beneficial to health". A body function in accordance with the Regulation was considered as a health claim for a relationship between a food/constituent and a body function and/or growth and development of the organism. Body functions can also include mental and physical functions.

The key elements for discussion comprised how to assess whether a claimed effect would qualify for "beneficial to human health" and how could body function claims be assessed for the "general population".

The discussions comprised general aspects as well as specific examples for extrapolation. They were based on scientific understandings of the individual participants and thus not limited to any regulatory restrictions for other legitimate factors. The following key points that have been summarised represent those for which a sense of general agreement was achieved. However, since it was not the aim of the discussion to reach consensus these key points should not be interpreted as such, but there was major agreement on these.

Definition of health

There was a general feeling that a definition of health is lacking/needed. The WHO definition of 1946 'Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity' was considered as a starting point, but would need to be further elaborated.

It was emphasised that health should also include well-being and quality of life when quality of life is meant/linked to physical states ("health-related") and measured with acceptable questionnaires. "Well-being" in the context of a health/nutrition claim perspective, however, should not include mere psychological states such as "feel good because of sunshine" or sensorial delight. In contrast, other sensory impacts such as pain reduction could be considered.

As an example, well-being in relation to gut (dis)comfort of subjects suffering from irritable bowel syndrome (IBS) was seen as acceptable for a benefit for the general population.

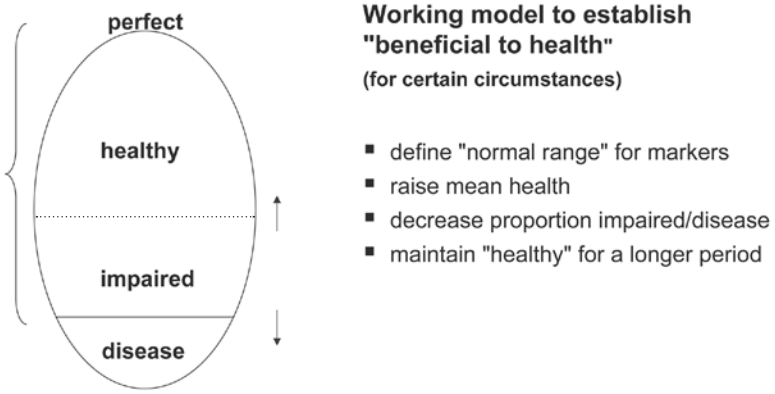
How to assess benefits to health?

Clinical markers such as cholesterol for cardiovascular disease or fasting blood glucose for blood glucose regulation can be regarded as sufficiently relevant for health but their applicability to the various body functions that are subject to dietary modulation is limited.

For health targets for which markers are not yet established a model was drafted (Figure 2, see page 14). It is based on the fact that the general population consists of only a few individuals with 'perfect health', the majority being healthy/impaired between the overt disease status and the 'perfect health' upper end. The proposed model considers health as a dynamic process and a continuum, which includes suboptimum functions that can be improved. For health targets without established markers this model could be applied and evidence of preventing a decline would be considered as reducing the risk of disease.

The distribution of markers in such a population could be shown and health aims achieved by raising the mean level, decreasing the proportion of impaired/diseased or maintain the healthy status for longer.

Figure 2. Body function in relation to general population: continuum.



The Figure describes health as a continuum between perfect health (top) and disease (bottom) and reflects the population at large. It shall provide guidance on what to consider when addressing novel effects/markers with food/constituents. While usually the cut-off to disease is by convention set (full line), the arrowed line between healthy and disease shall demonstrate its arbitrary setting. The "perfect" stage is a theoretical ideal that cannot be reached. The distribution of the effect/marker needs to be defined in the population at large, shifts of the arrow line towards the top, lowering the disease proportion or keeping the healthy part for longer and the aims for claims for the general population. For health claims fitting this model efficacy studies may use subjects with disease as a model rather than the target population only.

Examples for benefit (marker) assessment and their substantiation

There was essential agreement that evidence from diseased individuals could be used when there is a continuum from healthy to impaired status (e.g. data from diabetic people to healthy population).

Frequent borderline clinical states such as IBS were seen as acceptable for the general population.

Dilemma between precise markers/end points and general claims

Discussions were more faltering when considering specific markers/end points and general health claims. In principle, a claimed benefit should be precise and measurable. However, this is difficult when markers for the intended health effect are not yet conclusive or very disease-specific, in particular for "broad" or "diffuse" health targets, e.g. "natural defence" and lower/less infections/cold/flu. For one part of the participants such outcomes would qualify for risk of disease reduction claims rather than the intended body function claim. Some other participants would prefer: "supports natural defence" together with mechanistic data. For specific groups markers for general immune claims were seen as feasible, e.g. lower decline of immune defence in elderly or athletes.

Similarly, a healthy gut function was addressed in some groups. Classical markers such as bowel movement and gut comfort were seen as relevant, whereas other markers should be related to health end points (e.g. butyrate with aberrant crypt foci). Validation using animal models was mentioned as an option. The approach of the above scheme to define the normal range of the overall physiology and the flora including saccharolytic fermentation, butyrate, putrefactants, faecal water toxicity etc. might be another useful option.

Further major points raised

The inclusion of mental functions in health was generally seen as important. Generally, the relevance of the claimed effects is easier to assess than physiological functions as outlined above. However, causal-effect relationship needs to be established and made more target-group specific.

Opinions on satiety as a stand-alone benefit or together with body weight regulation were divided. Different "-omics" were considered promising, but not yet ripe for application in the field of health claim substantiation.

Outlook

For not yet established markers/benefits the discrepancy between scientific accuracy/precision of a study vs. the translation into meaningful consumer language became clear. The example to link a claim directly to a prescribed method such as used for tooth-friendly candies/chewing gums and pH-telemetry was seen as an interesting possibility. Generally, it was felt that it is up to the risk manager to deal with communication, and possible claims from proof-of-concept studies would need to be negotiated.

The discussions reflected an open exchange and mutual understanding among the stakeholders. However, how to assess benefits to health using advanced nutritional targets/markers still needs to be solved.

Disease Risk Reduction (DRR) claims

Dr. Gert Meijer, Unilever, The Netherlands
Dr. Virginie Rondeau, Université Victor Segalen Bordeaux, France

Are different criteria needed for DRR claims than for other (function) claims?

Generally, it was noted that different criteria are not needed, in terms of quality of the science, but that the evidence needs to be specific for the claimed benefit (disease risk or health). However, markers that can be applied may be different between DRR claims and other (function) claims.

There was also discussion on differences between types of studies. Randomised Controlled Trials (RCT) are seen as at the top of the pyramid. Epidemiological studies may be more relevant for DRR claims than for function claims, but it was also brought forward that epidemiological studies alone might not be enough. The number of studies required depends on the status of the risk factor / marker. Ideally a meta-analysis of good quality RCT (with a minimum of two independent studies, in which 1 multi-centre study = 1 study) should be done to substantiate a claim.

Are different criteria needed for children's claims than for other (function) claims?

According to the PASSCLAIM criteria, the claim has to refer to the target population. Thus, from a substantiation perspective there is a need for data in children.

However, for studies in children there are high requirements for ethics (age, informed consent, etc.) and safety (e.g. GCP). The risk that nutrition intervention studies in children will be perceived as drug treatment is high. As much as possible, for children's claims there should be less reliance on intervention studies and more on, for example, observational studies (e.g. with vitamins / minerals).

Animal studies can be used for safety reasons, and it is important not to go directly from animal studies to studies in children. When adults are biologically relevant models for children, for ethical reason, adults data should be accepted as surrogate. As a rule, if a study in adults is possible then it is not allowed to do that study in children. For animal studies as well as studies in adults the issue is how to validate the study outcomes in children. However, for such validation, studies in children seem to be inevitable.

Can a "representative sample" of the population consist of only healthy volunteers?

The study sample of the population has to be representative for the (claim) target group in terms of demographics (age, gender, etc.), genetic predisposition, responders vs. non-responders, etc. For studies it is important to have clarity on inclusion and exclusion criteria, especially on the inclusion of people treated with drugs (but not diseased), as there may be interactions between the food and the drug(s).

It is difficult to differentiate between healthy and unhealthy. A representative sample should not be diseased, but the presence of the risk factor in the study subjects is a prerequisite (i.e., the sample should include people at risk). A challenging concept is the question how changes in risk factors in people at a low risk, changes their actual risk.

If nutrition intervention studies are targeted at a disease, or performed with diseased people, then there is a risk that the claim substantiated with such studies will be perceived as a medical claim. Also the physiology in diseased people may be different than in healthy people, which is an issue in secondary prevention vs. primary prevention.

Is "promising, but not yet conclusive evidence" sufficient evidence to substantiate a DRR claim?

Generally, the opinion was expressed that claims should only be allowed at a sufficient ("probable" or "convincing") evidence level. Evidence at a "promising" level means that the claim is not yet substantiated.

Whereas scientist can "grade" evidence, with practical issues such as how to weigh different risk factors and how to combine risk factors, consumer understanding of "graded" claims is required before applying such claims.

Should we not consider true outcomes to substantiate a DRR claim?

From a scientific point of view, it is possible to use true outcomes or endpoints to substantiate a DRR claim. A practical disadvantage of outcome data is that these are typically limited to observational studies, and expressed in terms of incidence, occurrence and severity. Another practical disadvantage is that for some diseases the study duration to determine true outcomes would be too long.

A risk factor is related to disease risk (prediction) and more than one (of multiple) risk factor can contribute to the same disease risk. Thus, a true outcome has more scientific weight than a risk factor. Typically risk factors are not either present or absent but rather are positioned somewhere on the continuum between health and disease. Risk factors or markers should be validated against the disease, i.e. a change in a risk factor should be associated with a change in the disease risk, also taking genetic predisposition into account.

It was noted that using true outcomes would create an issue with the EU legislation. In addition, there is an increased risk that a claim based on true outcomes will be perceived as a medical claim, whereas risk factors are more likely to be linked to foods and not to drugs. Interestingly, PASSCLAIM prefers endpoints and only if there are no endpoint data, then risk factors should be considered.

How do we deal with surrogate endpoints to substantiate a DRR claim?

The number of validated markers for disease risk is limited. For surrogate endpoints, it is necessary to demonstrate and validate the (causal) relationship to the true endpoint (cf. PASSCLAIM criteria), with respect to relevance, biological validity, technological validity and statistical significance.

Assessment of strength and consistency of evidence – what are the requirements?

Dr. Guy Tweedie, Danone, Spain
Prof. David Richardson, Consultant, UK

Two questions were posed. Do researchers, industry and policy makers need a scientific framework for weighing the evidence so that it can be applied across the wide range of functional and disease risk reduction claims? Or a clear statement about the strength, consistency and plausibility of the evidence that indicates the extent to which one can be confident that the claimed effect is correct?

There was general support for these. However, there were reservations regarding the grading of scientific evidence.

Assessing the levels of evidence

There were basic questions around how to assess the level of scientific evidence supporting a specific area. For example, should a stepwise approach of different levels of evidence be considered? There were also questions on whether evidence based nutrition could be used to conclude whether cause and effect is established.

How can researchers present data in such a way that prevents different conclusions being drawn? There were references to different methods used to assess evidence. Methods cited were Cochrane and the World Cancer Research Foundation.

Types of studies

Randomised clinical trials (RCTs) can be conclusive in certain cases but it may not be possible to carry out such a study type for all targets or all situations. In addition, there may be ethical reasons why RCTs are not applicable for certain nutritional interventions. It is also of note that some of the "most conclusive" thinking in food functionality (e.g. for vitamins) is coming from observational data and associations, rather than RCTs which are required for evidence that is only being established.

A number of workshop participants expressed concern that scientific on nutrition related issues studies are designed too much with the model of pharmaceutical research. Do we overstate the simplicity of pharmaceutical research regarding food research? Controls used in pharmaceutical studies appear to be much more straightforward than for food. In addition, detecting a response in an intervention study for the normal population can be very challenging. The duration of studies is also highly variable in different areas of research.

In general, there is currently a lack of discussion of how studies should be set up in the food industry. A review of existing models to assess strength and consistency of evidence is needed. We need to be able to address what are the limitations and strengths of the data from different sources of evidence as well as exploring the distinction between evidence based medicine and evidence based nutrition.

Weighing and grading the evidence

The dossier format required by EFSA was questioned (i.e. should the format be adapted to allow gradation of scientific evidence?). The need for more transparency and objectivity in the weighing of scientific evidence was expressed. It was commented that the quality of the studies is very important compared to numbers of studies carried out in a particular field.

The current EFSA framework was questioned. Specifically, whether the health benefits related to fruit would be judged positively using this framework. If not, why not, and what would need to change in this framework to allow this? Is there a need to revise the current hierarchies of evidence through evidence based nutrition?

The European legislation refers specifically to the weighing of evidence. However, to what extent does the EFSA dossier framework lend itself to the weighing of scientific evidence? Therefore, should we (re-) introduce the notion? Within the "grading" of evidence, a framework could be worked out on how to weigh different data.

There are two considerations to be taken into account for grading the evidence. First, the scientific assessment and secondly, how risk managers express this.

In the workshops, some participants were supportive of a scientific grading system. There were comments expressing concern that the grading of scientific evidence could lead to opinions being changed as more studies emerge in a particular area. Examples were brought for and against this question (e.g. folic acid).

There were question marks on whether a "conclusive" level of evidence is ever truly achievable in food research. It was apparent during the workshops that an issue exists regarding the understanding of the language of the regulation.

There was also reiteration that RCTs are not realistic in situations where the likelihood of response to a test product is low.

Key questions and comments to address comprise the following. How would a grading system be constructed? What can be learnt from the United States? Do qualified claims mean anything from the consumers´ point of view? If we have different strengths of scientific evidence, can we reflect this in the wording of the claim? The methodologies used in Japan and the US should be reviewed.

PASSCLAIM quote:

> " …but caution was expressed that should not lead to weighted characterisation of the claim itself. In this context participants expressed opposition to the idea of "qualified claims" on the grounds that a claim should either be judged substantiated or not".
> Ref: Howlett & Short (2004). Report of second plenary meeting. *Eur J Nutr* Vol 43.2 page 179.

Several concerns were expressed. Grading of the evidence is linked with Qualified Health Claims and qualified claims are not for Europe. 1924/2006 speaks about " the average consumer to understand…" There is probable/convincing scientific evidence from the USA that consumers cannot distinguish between "significant scientific agreement" and qualified health claims. Equally, there is scientific data that consumers do not make a distinction between nutrition claims, function claims and DRR claims (e.g. Williams, *Nutr Rev* 63:256-264; Van Trijp *et al., Eur Rev Agric Econ* 32:347-268).

With respect to qualified claims being permitted in the context of PASSCLAIM, yes or no, should be determined on the basis of the PASSCLAIM CONSENSUS document (*Eur J Nutr* Vol 44.1), not on the basis of pre- or post discussions (in other phases of the process, such as during the 2nd Plenary Meeting) that do not form part of the consensus.

The weighing of the evidence is EFSA-NDA´s responsibility on the basis of the scientific substantiation. Allowing, yes or no, a qualified claim is the responsibility of the EU Commission, on the basis of the reworded (consumer oriented) version of the underlying scientific claim. EFSA must not pre-empt the Commission`s work by making decisions concerning qualified claims.

There was general consensus for development of a scientific framework for weighing the evidence. There was general consensus to give direction on undertaking new science and the level of proof required to support a claim. There should be a distinction between state of the art science and further scientific guidance on design, execution and interpretation of new studies.

Number of studies

It was stated that the number of scientific studies cannot be prescribed and should be decided on a case-by-case basis. Human intervention studies should be recognised as a "minimum" input. To substantiate a claim, the need for two RCTs have been quoted or an RCT plus animal studies as sufficient evidence. There was an observation that there are no positive EFSA opinions with less than five pertinent studies.

Members of the workshops from EFSA stated that the quality of studies is key and not the number of studies. Also, whether a study is pertinent or not does not address the quality of the study. The need to know the requirements of study reproducibility was expressed.

Target population

Studies should be targeted. Study populations should be representative of the intended target. However, there were questions on how this could be achieved and how a representative sample could be conclusive versus the general population.

Remaining questions concerned whether data could be extrapolated in scientific investigation? Is there a framework for this? How do broad studies fit with personalised nutrition? Better definition of the target population is needed (general vs. personalised).

Markers

Multivariate statistics are important to reflect a number of markers. The word "biomarker" was not incorporated into PASSCLAIM. "Bio" was dropped to allow the inclusion of any parameter that could be measured and tested. Is a biomarker requirement correct scientifically? Is there is a case for a number of small markers as opposed to one major marker?

Mechanistic data

Mechanistic knowledge should not be essential in claim substantiation (e.g. questions still remain around the mechanism of sterols and penicillin). However, there were opinions expressed that if no mechanistic data existed in a particular scientific area, human intervention data are critical.

Mechanistic data were seen to bring credibility to sustaining cause and effect. In addition, animal studies may help reduce the number of human studies required in research. Two fundamental questions were raised. First, what should be the role of mechanistic studies? Secondly, if mechanistic data are supplied, are strong RCTs still necessary?

Dose dependency

Is it realistic for regulators to require dose dependency data? How can RCTs be constructed to account for prolonged habitual intake? Some investigators may construct studies incorporating high doses of test product. However, this may not reflect the real life situation.

Process for the evaluation of claims

Should there be a pre-approval process for a dossier submission? Do we need overall guidance on each application? One possible outcome in the evaluation of a dossier from EFSA is known as "insufficient". Applicants expect in this instance, very clear feedback so that appropriate actions can be implemented. This should include feedback on the biological plausibility of the application. There were concerns that the current guidelines are not sufficient regarding the characterisation of food.

In addition, there were concerns that the current evaluation process is too subjective and the system needs to be more transparent. Specifically, the process of evaluation should be more interactive and the applicant should feel more informed in terms of progress of specific applications. (N.B. EFSA only evaluates scientific information).

A framework would help to support this; for example a rating system indicating the level of achievement.

CONCLUSION

As mentioned before, the workshop was organised to gather feedback on the preliminary work of ILSI Europe's Functional Foods Expert Groups. Likewise, the workshop report aims to illustrate the discussions that took place, and to highlight areas that need to be further elaborated, rather than providing a definitive point of view.

Following the workshop the expert groups will finalise their publications, taking into account the input derived from the workshop as the authors see fit. As usual, the publications will be freely distributed through the ILSI Europe website.

ABBREVATIONS

COMET assay	also known as "Single cell gel electrophoresis" assay, measures DNA damage in individual eukaryotic cells. Cells with extensive DNA damage produce a comet-shaped signal.
DRR	Disease risk reduction claim
EFSA NDA	European Food Safety Authority's panel on Dietetic Products, Nutrition and Allergies
ESCODD	European Standards Committee on Oxidative DNA Damage
FUFOSE	Functional Food Science in Europe
GCP	Good Clinical Practice
IBS	Irritable Bowel Syndrome
LDL	Low-density lipoprotein
PASSCLAIM	Process for the Assessment of Scientific Support for Claims on Foods
QHC	Qualified health claims
RCT	Randomised Controlled Trial
WHO	World Health Organization

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