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PASSCLAIM[1] – Report of the Second Plenary Meeting: review of a wider set of interim criteria for the scientific substantiation of health claims

Background

Over the past decade or so there has been a growing recognition in the scientific community that foods may offer beneficial physiological and psychological effects beyond basic nutrition. In order for consumers to benefit from this growing awareness, legislation must provide for information relating to the communication of beneficial effects and attention is focussing on how the links between diet and beneficial effects can be characterised and substantiated. The EU has previously funded a concerted action under the title "Functional Food Science in Europe (FUFOSE)" with the purpose of developing and establishing a science-based approach to characterising beneficial effects of foods beyond basic nutrition (the concept of "functional foods"). That concerted action resulted in a consensus document [1] which concluded that the development of functional foods should be based on a sound scientific knowledge of the target function in the body and the demonstration of effects relevant to improved health or reduction of disease risk. It identified evidence from human studies based on markers relating to biological response or on intermediate endpoint markers of disease as being capable of providing a sound scientific basis for messages and claims about functional food products. Building on the conclusions of FUFOSE, the EU funded a second concerted action "Process for the Assessment of Scientific Support for Claims on Foods (PASSCLAIM)" with the objective of developing a generic tool for assessing the scientific support underpinning health-related claims for foods and food components.

The approach adopted by PASSCLAIM, which has been more fully described elsewhere [2, 3], involved three phases, the first of which established four expert groups (Individual Theme Groups, "ITGs") to review and report on the scientific basis supporting links between diet and:

- Cardiovascular disease (ITG A);
- Bone health and osteoporosis (ITG B);
- Physical performance and fitness (ITG C);
- and on Existing regulatory and other frameworks for claims worldwide (ITG D).

The first phase culminated in a First Plenary Meeting at which the findings of the four ITGs were discussed and used as the basis for the agreement of a first draft set of interim criteria for the assessment of scientific support for claims [4].

During the second phase of PASSCLAIM, the interim criteria agreed at the First Plenary Meeting have been further developed under the guidance of the PASSCLAIM Steering Committee (Table 1) and a further four expert groups (ITGs) have reviewed the scientific basis supporting links between diet and:

- Body weight regulation, insulin sensitivity and diabetes risk (ITG E);
- Cancer (ITG F);
- Mental state and performance (ITG G);
- Gut health and immunity (ITG H).

During the Second Plenary Meeting, which is the subject of the present report, these reviews were used to test and critically evaluate the wider set of interim criteria developed by the PASSCLAIM Steering Committee.

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[1] Process for the Assessment of Scientific Support for Claims on Foods.

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Table 1 Draft wider set of interim criteria proposed by the PASSCLAIM Steering Committee: the basis of discussion at the Second Plenary Meeting

Preamble

1) **Foods and food components for which a claim is made should comply with existing legislation.** ***If an effect on a function can be scientifically substantiated, regulations should allow a health claim, thereby taking into account new scientific developments as appropriate.***

2) ***A*** **health claim should be scientifically substantiated by taking into account the totality** ***of available data and weighing*** **of evidence.** ~~***A scientifically substantiated mechanism is valuable but not essential.***~~

Notes for discussion:
- *Available data refers to accessibility of the data to the authority that will assess the dossier and is thus a regulatory issue not for debate here.*
- *Weighing the evidence includes taking into account the quality of the data in both positive and negative studies. Reference could be made to the qualitative classification of evidence used in the recent World Health Organization report 916 (e. g. convincing, probable, possible, insufficient).*
- *The second part of the sentence on the mechanism was transferred after point 4 as point 4 bis.*

3) **When a claim is made, it should be specified who may benefit from the effect, e. g. the entire population, a subgroup or an at risk group**

Note for discussion:
- *This point is not a prerequisite and is basically not scientific so it was included in the preamble. It could be discussed in the light of the ITG E-H reports.*

Criteria

4) ***Substantiation of a*** **claim should be based primarily on human intervention** ***data*** ~~***studies***~~ **that show demonstrable effects consistent with the claim. They should have a scientifically valid design compatible with the purpose of the study, including the following:**

Notes for discussion:
- *Human intervention data is the gold standard, but consideration of epidemiological and animal data is possible. Some types of claims will be based on a host of published reports, whereas other types of claims will have a few intervention studies with the food in question as primary documentation. Could claims be based solely on epidemiological data?*
- *Some claims cannot be demonstrated using human intervention data with the real endpoint, e. g. a claim on reduced risk of bone fracture.*

4a) **Study groups that are representative of the target group**

Notes for discussion:
- *Study groups should be biologically representative of the target group.*
- *As social-economical factors can interfere with the study results, study groups should be chosen taking into account these factors.*
- *It is sometimes not possible to define the target group at the moment when the study is carried out.*

4b) ***Appropriate*** **controls both for the intervention itself, and for the subject groups**

Notes for discussion:
- *The intervention should be controlled, e. g. treatment versus non-treatment.*
- *The subject groups should be controlled, i. e. test and control groups.*
- *For some food studies, proper placebo products can be made (e. g. yoghurt with and without Lactobacilli, or with live/dead Lactobacilli) . In other cases, where no true placebo is possible, appropriate controls have to be made – which criteria should then be applied? For example a group testing fat replacer versus a group testing fat.*
- *What will be an appropriate control group for testing the effect of a recommendation such as doubling the intake of fruit and vegetables?*

4c) **An appropriate duration to demonstrate the intended effect**

Note for discussion:
- The appropriate duration needs to be discussed in the light of ITG E-H papers, e. g. short-term and long-term effects, down slopes of effect, habituation, attenuation of effects.

4d) **Characterisation of the target groups' background diet, which should be controlled for where necessary**

Note for discussion:
- *The importance of characterisation of the background diet, the amounts of the components in a full diet and specification of food ingredients needs to be discussed in the light of ITG E-H papers.*

4e) **The amount** ***(*****of the food or food components*****)*** **being evaluated should be consistent with its intended use and the expected consumption pattern**

Note for discussion:
- *The amount, specification and matrix of other food ingredients should also be taken into account when performing a study. The bio-equivalence of an ingredient in a new matrix should be shown prior to claiming the efficacy of an ingredient in a new food product.*

4f) **Ideally, an intake-**~~***exposure***~~**-response relationship should be determined to identify optimum effective intake**

Note for discussion:
- *The necessity of a known intake-response relationship needs to be discussed in the light of ITG E-H papers.*

4g) **Dietary compliance, which should be monitored**

Note for discussion:
- *Monitoring of dietary compliance needs to be discussed in the light of the ITG E-H papers.*

4h) **The statistical power to test the hypothesis**

Notes for discussion:
- *The hypothesis has not yet been discussed at this stage. It is mentioned as new point 4 bis (see below).*
- *Statistical power to test the hypothesis needs to be discussed in the light of the ITG E-H papers.*

4 bis) **A scientifically substantiated mechanism is valuable but not essential**

Note for discussion:
- *It is more important to demonstrate a consistent effect than to have a scientifically substantiated mechanism. A hypothesis could be needed (see point 4 h) but a mechanism would be better.*

5) **If the claimed enhancement of function or reduction of risk cannot be measured** ***directly*****, studies should use** ***(batteries of)*** **markers of effect that have been scientifically validated**

Notes for discussion:
- *In the physiological area of gut health and immunity, a full battery of markers will be needed to describe the effect.*

Table 1 *Continued*

	– *FUFOSE defined 3 types of markers:* • *Markers of exposure to food component* • *Markers of target function/biological response* • *Markers of intermediate endpoint* *Is this classification of markers valid for the areas reviewed by ITG E-H.*
6)	**Markers should be validated:** **Methodologically to include their** **• precision and accuracy** **• specificity and sensitivity** **• reproducibility and repeatability** **Biologically so that** **• they reflect closely the process leading to the claimed health benefit** **• respond ~~quickly~~ in line with changing events** *Notes for discussion:* – *The methodological and the biological validation of markers need to be discussed and tested against the ITG E-H papers.* – *Points 5 and 6 could be combined.*
7)	**Within a study the marker should change in a biologically relevant way and be statistically significant for the target group consistent with the claim to be supported** *Note for discussion:* The question 'what is a biologically relevant change' needs to be discussed in the light of ITG E-H papers.

It is planned that during the third phase of the concerted action, the wider set of interim criteria and the discussion which they have received in the context of the findings of the ITGs during this Second Plenary Meeting will be examined by a consensus group. The task of the consensus group will be to propose a draft final set of criteria for consideration during a third and final Plenary Meeting.

Second Plenary Meeting – objectives and structure

The Second Plenary Meeting had the following objectives:

- To present the reports of ITGs E – H;
- To evaluate the applicability of a draft set of interim criteria for the assessment of the scientific support for claims in the light of the ITG reports presented;
- To develop a further set of wider interim criteria for consideration by a Consensus Group prior to finalisation.

The meeting took place over the three days 29–31 October 2003 in Bordeaux, France, and was attended by about 70 participants, approximately half of whom came from industry and the remainder from academia and government. The overall Chairman was Professor Nils-Georg Asp of the Swedish Nutrition Foundation. During the course of the three days, approximately 30 % of the time was assigned to formal presentation of ITG reports and other topics. The remaining 70 % of the time was assigned to discussion and development of the interim criteria, with the participants either distributed amongst six groups working in parallel or discussing together in plenary session.

Proceedings – Day 1

After a brief welcome to participants by Professor Asp and introductory presentations by Dr Nico van Belzen (Executive Director, ILSI Europe, Belgium) concerning the role of ILSI Europe, and by Dr Laura Contor (Deputy Director, ILSI Europe, Belgium) and Dr France Bellisle (National Institute for Agronomic Research, France) concerning the history and objectives of the PASSCLAIM project, the chairman of each of the ITGs E – H presented the findings of their respective Theme Groups.

Body weight regulation, insulin sensitivity and diabetes risk (ITG E)

In presenting the findings of ITG E, Professor Riccardi (University of Naples, Italy) explained that the biological functions underlying the three diseases characterised separately as overweight, metabolic syndrome and diabetes are related inter-dependently. The complex inter-dependency of their underlying biological functions (body fat deposition, insulin sensitivity and regulation of blood glucose respectively) does not always allow a clear sequence of events in the causality of the diseases to be identified. Nevertheless, it is clear that these are key target functions in relation to a spectrum of diseases of growing importance in the context of contemporary diet and lifestyle. And each key target function has a range of associated functions, modulation of which provides a basis for possible claims. In each case, ITG E had been able to identify markers and reliable methods for their measurement. The Group had con-

cluded that there is scope for the establishment of links between diet, quantifiable biological responses and disease risk factors in this field which fit well with the basic principles identified by the FUFOSE project and which could be used for the scientific substantiation of both enhanced function and disease risk reduction claims.

During subsequent discussion of the presentation it was pointed out that the effectiveness of interventions relating to changes in diet and lifestyle would vary with the genotype and life stage (child or adult) of the individual. Likewise, the applicability of methods for assessing, for example, deposition of body fat by morphometric parameters such as body mass index, waist circumference and waist-hip ratio are not universally applicable without adjustment for regional differences in the physical characteristics of the population. Nevertheless, there was general agreement that with appropriate attention to defining the normal ranges for local populations, these markers could provide an adequate means of assessing the relevant target functions for the purpose of generating data in support of claims.

Diet-related cancer (ITG F)

Professor Joseph Rafter (Karolinska Institute, Sweden) presented the report from ITG F. Several reports suggest that about 35 % of cancer deaths are diet-related and also that the risks attributable to some other cancers (for example lung cancer from exposure to tobacco) can be reduced by dietary measures (the consumption of fruits and vegetables). In attempting to fulfil its task of assessing the potential for claims and their substantiation, the Group had focussed on tumours of the colon, lung, breast and prostate. As a general observation, since the true marker of disease in this field, the malignant tumour, is for practical reasons not usually accessible to intervention studies in support of claims, the ITG considered disease risk reduction claims were rarely likely to be capable of substantiation by intervention studies based on this endpoint. Where claims of this nature had been made, the supporting evidence was usually taken from epidemiological observational studies. As an alternative parameter for study, intermediate markers could be used but these provide less compelling evidence which the ITG considered applicable only in support of enhanced function claims.

The Group had identified 18 targets or markers suitable for study in support of claims concerning diet-related cancer. With the exception of polyp recurrence, all of these should be considered as intermediate markers. While the majority of them reflect well established events in the disease process, they lack validation with respect to the true marker of disease, the tumour. The Group therefore considered future research effort should be focussed on the difficult task of their validation. It had also considered it important that in making any claims in this area, the target group should be specified and that where reliance was made on intermediate markers, a scientifically substantiated mechanism is essential.

Mental state and performance (ITG G)

The report from ITG G was presented by Professor Joachim Westenhoefer (Hamburg University of Applied Sciences, Germany). The Group had considered mental state and performance in terms of the attributes mood, arousal (including activation, vigilance, attention and sleep), motivation and effort, perception, memory and intelligence. In addressing these attributes it is important that any claims are stated with sufficient specificity to be capable of meaningful assessment. Only where they are stated in terms of functions which are both measurable and quantifiable, can claims be scientifically substantiated. Likewise, particular attention must be paid to the application of investigative methods based on verbal scales because they may perform differently when applied across different linguistic and cultural groups. A further area of potential concern signalled by the ITG related to the magnitude of the effect claimed. For the claim to be meaningful it would not be sufficient merely for the effect to achieve statistical significance. For a claim to be truly meaningful and not misleading it must relate to a magnitude of effect which has both statistical and functional significance for the intended target group.

Taking all these factors into account, the ITG concluded that the attributes of mental state and performance studied are adequately defined and understood in scientific terms and that reliable methods exist or can be developed for their measurement and quantification. In the view of the ITG, claims relating to the enhancement of specific mental functions are as susceptible to substantiation and validation as claims relating to other biological functions.

Gut health and immunity (ITG H)

In presenting the report of ITG H, Professor John Cummings (University of Dundee, United Kingdom) explained that while it is possible to measure many of the attributes of the gut and immune system, their functions exhibit such a wide range of variation within what is considered to be normal that the concept of "benefit" cannot easily be defined. Nevertheless, many products currently on the market do make claims for gut health and/or immune system benefits. Therefore the challenge the ITG had was to define norms for gut and immune system functions and then to identify methods for the measure-

ment of these functions. The Group considered many functions of the gut (for example bowel habit and transit time, gut flora, gastric emptying and motility) which are accessible to measurement and for which norms can be determined. An attempt was also made to describe gut health in terms of gastrointestinal well-being. This concept is important for claims but the group considered it less well characterised. In the case of the immune system, while there are many components which can be measured, the Group considered that there is no single test which adequately defines status or functional capacity. Nevertheless the ITG has been able to identify approaches and methods, which if used in conjunction with each other, were considered adequate to assess immune function. The availability of suitable markers of gut and immune function and methods for their measurement, taken together with information on normal values, in principle makes substantiation of claims in this area possible, although much work remains to validate possible markers in relation to true endpoints.

The presentations of the work of the ITGs were generally well received by the Meeting participants. Publication of the papers in full will make the findings accessible to a wide audience.

Proceedings – Day 2

At the opening of the second session Dr Hans Verhagen (Unilever Health Institute, Vlaardingen, The Netherlands) presented a draft set of wider interim criteria for the assessment of scientific support for claims which had been drawn up by the PASSCLAIM Steering Committee on the basis of the interim criteria agreed at the First Plenary Meeting. Following this introduction, participants dispersed into six working groups for a detailed discussion of the draft with a view to its further development in the light of the input received from ITGs E – H. The working group discussions continued throughout the morning of Day 2 and the participants reconvened in plenary session at the beginning of the afternoon.

The EU Sixth Framework Programme – Food Quality and Safety

Professor Gérard Pascal (National Institute for Agronomic Research, France) presented an outline of those aspects of the EU Sixth Framework Programme relating to food quality and safety on behalf of Dr Jürgen Lucas (EU Commission, DG Research) who had been unable to attend. Food Quality and Safety has been identified as a Priority Thematic Area under the programme heading Integrating European Research for which a budget of €685 million has been foreseen. The Thematic Area is defined in terms of a two-way interpretation of the farm-to-fork approach in which research aimed at improving the linkage between food production and processing systems and consumer health and well-being is to be complemented and informed by research in the latter area through feedback in the mode "fork-to-farm". Emphasis is being placed on traceability and the total food chain. The first call for proposals for projects to start at the beginning of 2004 was issued in December 2002 and is now closed. A second call is to be issued in November 2003 with a closing date of 5 February, and third and fourth calls are foreseen for July 2004 and September 2005 respectively. Further information is to be found on the CORDIS web site [5].

Proceedings – remainder of Day 2, Day 3

During the remainder of Day 2, rapporteurs gave an account in plenary session of the discussions which had taken place in the six working groups during the morning. Discussion of the points raised provided an initial cross fertilisation of ideas between the working groups in the plenary. The output of this session was used by the rapporteurs to refine and consolidate their accounts in preparation for discussion of the wider set of interim criteria in the final session on Day 3. The final session on Day 3 also included a presentation by Professor David Richardson (University of Reading, United Kingdom) providing an update with respect to the present regulatory situation in the EU.

Recent developments in EU legislation on nutrition and health claims

Professor Richardson explained that discussion of the initial draft proposal for a Regulation on Nutrition, Functional and Health Claims made of Foods circulated by the EU Commission in June 2002 had led to a further draft proposal in June 2003 and then finally in July 2003 to a formal proposal for a European Parliament and Council Regulation on the subject [6]. Since the first draft proposal, the concept of "functional claim" has been abandoned. In addition, the concept of "nutrient profile" has been added. According to the proposal, nutrition and health claims would only be permissible for foods meeting an acceptable nutrient profile, as yet to be defined, with respect to fats, sugars and salt and/or sodium. Health claims relating to overall good health and well-being, psychological and behavioural functions would be prohibited, and to these had been added prohibitions on claims relating to slimming, weight control, satiety and reduction of available energy from the diet, and the endorsement of health professionals and their associations.

Both the initial draft and the final proposal stressed that scientific substantiation should be the main aspect to be taken into account for the use of health claims, that substantiation should be based on generally accepted scientific data and that the European Food Safety Authority (EFSA) should be responsible for verifying that the requirement for scientific substantiation is met before a health claim can be used. The proposal would require the EFSA to publish detailed guidance to applicants on the presentation of applications before the regulation enters into effect. The proposal has now to be discussed in the Parliament and the Council of Ministers.

In presenting his summary, Professor Richardson reminded participants of the main conclusions regarding scientific substantiation reached by ITG D during the first phase of the PASSCLAIM project [7].

Discussion of the draft wider set of interim criteria – Day 3

The discussions which had taken place first in the six working groups and then in plenary on Day 2 were summarised and further discussed under the chairmanship of Professor Aggett on Day 3. In the account which follows, the headings reflect the draft wider set of interim criteria as proposed by the Steering Committee based on the outcome of the First Plenary Meeting of PASSCLAIM (see [3] and Table 1). The underlining or striking out reflects the extent of the initial modifications proposed by the Steering Committee. These headings provided the basis for all discussions during the Second Plenary Meeting.

Preamble

There was general agreement with the inclusion and extension of the proposed preamble into which general aspects should be gathered to distinguish them from the strictly scientific criteria which would follow.

1. *Foods and food components for which a claim is made should comply with existing legislation. If an effect on a function can be scientifically substantiated, regulations should allow a health claim, thereby taking into account new scientific developments as appropriate.*

There was general agreement with the intent of the statement. It was, however, suggested that "existing legislation" be replaced by "applicable legislation" and that the scope of PASSCLAIM should be more closely reflected by including reference to "health claim" rather than just "claim" in the first sentence. Reservations were expressed about including the recommendation that regulations "should allow a health claim" on the grounds that it was inappropriate to make this a requirement in the context of a scientific discussion and there was sympathy for the suggestion that this criterion be split into two in order to distinguish between the message relating to compliance and that implying mandatory regulatory access to a claim once the scientific data merited it.

2. *A health claim should be scientifically substantiated by taking into account the totality of available data and weighing of evidence. ~~A scientifically substantiated mechanism is valuable but not essential.~~*

Again there was general agreement that all the elements of the criterion are appropriate. The concept of a hierarchy of evidence in which studies are valued according to whether they are conducted in humans, animals and *in vitro* experimental systems was discussed without agreement being reached. There was support for the idea that a structured approach to characterising the quality of data would assist assessors in weighing the evidence but caution was expressed that this should not lead to a 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. A question was also raised about whether different types and/or quality of data could be admitted for generic as opposed to product specific claims. Comment was made that active dialogue between all parties (regulators, industry, academia and consumers) would facilitate the application of this criterion.

3. *When a claim is made, it should be specified who may benefit from the effect, e. g. the entire population, a subgroup or an at risk group.*

Opinions varied as to whether this criterion should be retained or deleted. A number of participants expressed reservations about the inclusion of the phrase "at risk group" and others pointed out that difficulties were associated with generating study data in relation to some population subgroups such as children. Although the view was expressed that extrapolation between subgroups was not always scientifically valid, it was pointed out that human populations are essentially heterogeneous certainly with respect, for example, to metabolic capacity and genotype, so the possibility of extrapolation should be retained and its validity judged on a case-by-case basis.

Additional aspects for the Preamble

It was suggested that reference to consumers' perceptions of claims should be included but it was pointed out that this was not a scientific matter and so was not within the remit of PASSCLAIM. On the other hand, if the purpose of the "preamble" was to bring attention also to related issues then it could be appropriate to include it in order to acknowledge its relationship to claim validity in the broader sense and then to exclude it from further discussion within PASSCLAIM.

It was suggested in view of the conclusion from ITG G (mental state and performance) that valid concepts and methodologies are available, it might be appropriate to state that there was no scientific justification for excluding claims relating to enhancement of psychological and behavioural functions from the scope of any framework on the grounds that they could not be substantiated.

4. Substantiation of a claim should be based primarily on human intervention data ~~studies~~ that show demonstrable effects consistent with the claim. They should have a scientifically valid design compatible with the purpose of the study, including the following:

There was divergence of opinion on whether human intervention data were an absolute requirement for the establishment of any claim. There was agreement that human intervention data represented the "gold standard" but also a recognition that studies demonstrating disease risk reduction would not always be obtainable for practical or ethical reasons. Some participants felt that human observational data would be sufficient in certain cases, but this issue remained unresolved. The cautionary view was also expressed that studies should not be done simply because they could be conducted – the issue was that data should be required because they are necessary to substantiate a claim, not merely because they are desirable. During the course of discussion the question of whether animal data could substitute for human data in some circumstances arose, given that the substantiation of a claim should be determined by the totality and weight of evidence. The role of animal data was discussed and it was agreed that they could provide indirect support for a claim (for example by elucidating mechanisms) but could not provide definitive justification.

As might be expected, there was agreement that study design should be scientifically valid and compatible with the purpose but it was pointed out that statistical elements could only be designed in for anticipated effects. If the study design and data quality otherwise permit, the retrospective evaluation of studies for unanticipated effects should not be ruled out simply on the grounds that the effects were not foreseen and planned for.

4a) study groups that are representative of the target group

Generally there was agreement that the study group should be representative of the target group for which the effect is claimed. Some reservations were however expressed that an element of judgement should be retained ("… representative of the target group where appropriate…") to allow for case-by-case assessment.

4b) appropriate controls both for the intervention itself, and for the subject groups

During discussion of appropriate controls, the practicality of applying a placebo in all circumstances arose. Where manipulation of major components of the diet is involved (for example, increased consumption of fruits or vegetables) the possibility of applying a placebo is problematic. It was agreed that studies should in all cases be adequately controlled and the use of a placebo would need to be judged according to the circumstances of the study.

4c) an appropriate duration to demonstrate the intended effect

It was agreed that the study duration should be appropriate to demonstrate the effect but that this would normally be taken into account during the consideration of appropriate study design.

4d) characterisation of the target groups' background diet, which should be controlled for where necessary

It was agreed that supporting data should include a characterisation of the target groups' background diet and that anything that might affect the outcome of the study (background diet and any other lifestyle factors) should be controlled for.

4e) the amount (of the food or food components) being evaluated should be consistent with its intended use and the expected consumption pattern

It was agreed that the amount of the active component used should be consistent with the use and pattern of

consumption of the food/food component which is the subject of the claim. It was also agreed that the presence of other ingredients being studied and/or in background diets should be controlled for and that where the active component was proposed for use in a new food matrix, the bioequivalence in the new matrix should be demonstrated and the potential effects of the matrix controlled for.

4f) ideally, an intake-~~exposure~~-response relationship should be determined to identify optimum effective intake

Participants agreed that determination of an intake response relationship reflected the ideal situation but recognised that it would often not be practicable to achieve it. There was a strong element of opinion which considered that an intake response relationship is not essential and that determination of minimum effective amount is more important. It was pointed out that, in any event, the validity of any claim would be limited to the data on intake and the effects demonstrated in its support.

4g) dietary compliance, which should be monitored

Opinion on the necessity of establishing dietary compliance was divided. Some participants felt that it should be a requirement while others judged that it was too laborious to be practicable. It was more realistic to think in terms of monitoring markers of exposure to the active component where they were available and placing emphasis on good scientific study design and practice.

4h) the statistical power to test the hypothesis

Some participants felt that statistical power was chiefly of importance in establishing absence of effect and as such was likely to contribute little to the process of evaluating support for claims. It is however an important element in scientific study design and should be taken account in the design of studies if not in their evaluation. Again, the point made in relation to overall considerations of study design (criterion 4 above) was made – where unforeseen events arose in a study, the lack of statistical planning for them should not preclude retrospective re-evaluation of the study for the unforeseen events where other aspects of quality of study design and data permit.

4bis) a scientifically substantiated mechanism is valuable but not essential.

There was general agreement with the principle that a substantiated mechanism is not essential although some participants considered that it is necessary where studies are based on markers of intermediate effect and not directly on true endpoints in order to validate the link to the endpoint. There was discussion about whether to delete the criterion (on the grounds that it is not essential), to keep as-is, to expand by way of explanation or to reserve the point for discussion and expansion with examples in the consensus document. This was not resolved.

5. If the claimed enhancement of function or reduction of risk cannot be measured <u>directly</u>, studies should use (<u>batteries of</u>) markers of effect that have been scientifically validated

There was support for maintaining the original wording of the criterion (i. e., delete "directly" and "batteries of"). Participants felt it was particularly relevant to apply the concept of a hierarchy of evidence in assigning value to the use of markers and to discuss the relevance of markers of intermediate effect as opposed to endpoint. It should be made clear that establishment of an association between intermediate markers, or where appropriate combinations of markers, and their respective health endpoints is an essential part of the case supporting any claim. Absence of validation of a marker should preclude its use as supportive evidence of a claim.

6. Markers should be validated:
Methodologically to include their
– precision and accuracy
– specificity and sensitivity
– reproducibility and repeatability
Biologically so that
– they reflect closely the process leading to the claimed health benefit
– respond ~~quickly~~ in line with changing events

It was agreed that the validation of markers should be in compliance with the application of standard "GLP" principles and some thought should be given to establishing a code of GLP for markers. In assessing methodological validation it is important to recognise that, as with all biological parameters, markers are subject to natural variation. Their value in studies in support of health claims is dependent on the establishment of their biological relevance to the function/pathogenic process and an understanding of their relevance to the final outcome. Ideally, there should be a scientific consensus supporting the relevance of any marker used.

7. *Within a study the marker should change in a biologically relevant way and be statistically significant for the target group consistent with the claim to be supported*

Emphasis was placed on the fact that any change observed in a marker should not only be statistically significant from an experimental point of view, but also biologically relevant from the point of view of the consumer. To make this point more forcefully it was suggested that this criterion be re-drafted accordingly: "Within a study the marker should change in a statistically significant manner. The change should be confirmed to be biologically relevant". It should be understood that "biological" in this context includes "physiological" and "psychological". It was further suggested that the sentiment of this criterion applies equally to any target functions and endpoints studied and so the term "marker" could be broadened to "target variable" to encompass all three.

In concluding the discussion of the wider set of interim criteria, the meeting stressed that the objective should be presented as the provision of guidance on the scientific elements which dossiers submitted in support of claims should contain; they should not be presented as establishing regulatory requirements.

Closure of the Meeting

In closing the Meeting, Professor Asp commented on the high quality of the work of the ITGs presented and on the productive nature of the discussion of the interim criteria. On behalf of the Steering Committee, he thanked participants for their input. He reminded participants that the content of the discussion and its conclusions would go forward into the third phase of PASSCLAIM where they would be taken into account by the Consensus Group in the further development of the criteria in the last stage prior to their finalisation.

List of participants

Prof. Peter Aggett	University of Central Lancashire (UK)
Dr. Jean-Michel Antoine	Groupe Danone (F)
Dr. Margaret Ashwell	(UK)
Prof. Nils Asp	Swedish Nutrition Foundation (S)
Dr. France Bellisle	National Institute of Agronomic Research (INRA) (F)
Prof. Jacques Bindels	Numico (NL)
Dr. Nino Binns	McNeil Consumer Nutritionals Europe (UK)
Dr. Richard Black	ILSI N. A. (USA)
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Dr. Max Blum	Roche Vitamins Europe (CH)
Prof. John Blundell	University of Leeds (UK)
Dr. Francesco Branca	Istituto Nazionale di Ricerca degli Alimenti e la Nutrizione (INRAN) (I)
Prof. Per Brandtzaeg	University of Oslo (N)
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