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GUIDANCE NOTES FOR COMPILING THE LIST OF HEALTH CLAIMS UNDER ARTICLE 13 OF THE NUTRITION AND HEALTH CLAIMS PROPOSAL

EXPLANATORY NOTES

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These explanatory notes have been developed to assist companies and other interested parties to compile a list with health claims, based on generally accepted scientific data/knowledge, well understood by the average consumer, describing or referring to

(a) The role of a nutrient or other substance in growth, development and the functions of the body, or

(b) Psychological and behavioural functions, or

(c) Without prejudice to Directive 96/8/EC, slimming or weight-control or a reduction in the sense of hunger or an increase in the sense of satiety or to the reduction of the available energy from the diet,

and the necessary conditions applying to them, as laid down in Article 13 of the proposed Nutrition and Health Claims Regulation.

PROPOSED LIST FORMAT

The nutrition and health claims regulation does not provide for a format of the list under Article 13. It only specifies that the list should contain the claims, the conditions applying to them and the references to the relevant scientific justification.

Based on this and in order to be able to collate the scientific information relating to the claims, the following format is proposed:

Food or Food Component	Health Relationship	Conditions (if any)	Nature of evidence	Grade of evidence	References	Example of wording

Entry 1: Food or Food Component

Article 2.5 defines a health claim as any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health. Article 13 refers to 'the role of nutrients' and 'other substances' in growth, development and the functions of the body. However, health claims are often linked to more complex entities, e.g. a combination of nutrients or substances, a food as a whole or even a combination of foods in a specific diet. In all cases, the effect will be linked to the nutrients or other substances contained in such entities. Therefore, for the purposes of assembling the list of claims, the broadest interpretation of food or food component will be used:

A diet		e.g. a diet low in saturated fat or high in fruit and vegetables, high in fibre, low in salt etc
A food category		e.g. fruit and vegetables, whole grain cereals, nuts, oily fish
A food		e.g. whole oats, salmon, almonds, cranberry juice, tomatoes, fermented dairy products
A constituent:	**Nutrient**	e.g. macronutrient such as a protein sources, a carbohydrate source; micronutrients such as a vitamin or mineral
	A component/ a substance	e.g. whey protein, Soya protein, inulin, other fibre materials like oat bran, beta-glucan soluble fibre, omega-3 fatty acid, L-lysine, sterols and stanols, lycopene, lutein, glucosamine, probiotics, prebiotics like fructo-oligosaccharide (FOS), conjugated linoleic acid (CLA) etc
	A botanical	e.g. garlic, ginseng, bilberry, ginger, etc

The diet, food, food component, nutrient, other substance, botanical, ... that is the subject of the health relationship and the claim should be sufficiently specified.

In case of botanicals: the Latin (botanical) and English name, the origin, the plant part used, characteristics of the isolate or extract, including where relevant minimal or maximal limits of active components and specifications on the amount to be used in relation to the relationship and claims listed, etc.

Entry 2: Health Relationship

Article 13 refers to:

a) The role of a nutrient or other substance in growth, development and the functions of the body.
b) Psychological and behavioural functions, or
c) Without prejudice to Directive 96/8/EC, slimming or weight control or a reduction in the sense of hunger or an increase in the sense of satiety or to the reduction of the available energy from the diet.

For example, nutrients and other substances can be necessary for and/or contribute to the structure and functions of particular organs and several physiological states, e.g. reproduction, conception, growth and development, body maintenance. The well-established functions of nutrients and other substances are documented extensively in the scientific literature.

Nutrients and other substances, foods or food components can have specific beneficial effects on physiological, psychological, cognitive functions or biological activities. Ingredients and a whole range of substances can be included as long as they have well-established physiological or biological functions in the body. For example, a function of a food or food component can apply to constituents that have cholesterol-lowering effects, calcium-absorption effects, prebiotic or probiotic effects. Specific physical or chemical properties of a food or food component may influence a particular function, e.g. a low glycaemic index due to specific structural or starch properties.

Specific diets may also have specific effects on health in general. These may be listed in so far as the effect of such diets can be attributed to the foods, food components, nutrients or other substances that characterise the specific diet (e.g. high in fibre, low in fat, etc)

Article 13 refers to 'health claims other than those referring to the reduction of disease risk'. Hence, the health benefit under Article 13 must **not** refer to any food or food component (including a nutrient) that has the property of treating, preventing or curing human disease or make any reference to such a property, i.e. medicinal claims. Nor must a reduction of a disease risk relationship or claim be listed. Hence, the health relationship under Article 13 must relate to the maintenance of healthy body functions, organs of the body or health in general, and refer only to maintenance of the healthy state of those body functions or processes (body metabolism, cholesterol, metabolism, digestion etc).

The health relationship should therefore be listed as precisely as possible, in line with the scientific supportive evidence.

Entry 3: Conditions for the Claim to be Valid

The general requirements of the Nutrition and Health Claims Regulation as laid down in chapter II (articles 3-7) apply to all health claims, including those included in the article 13 list. It may be appropriate however to indicate next to the health-relationship any specific conditions of use for a specific nutrient/other substance/food-health relationship. This should be done in line with the general requirements of art 5 of the Regulation.

- Quantity:

  Any food or food component should be consumed in realistic amounts in the daily diet, and the claim must always be made in the context of the total diet. The health benefit must be fulfilled by the amount of the food or food component and the frequency of consumption to produce the nutritional or physiological effect claimed. The quantity of the nutrient, other substance, food or food component to which the claimed effect is attributed should be sufficiently characterised and described to allow an assessment of the validity of the scientific case made in support of the claim.

Some examples:

Plant sterols and stanols and their esters	2g/day as free stanols/sterol
Soya protein	25 g/day
Oat beta-glucan	3 g/day
Oily fish	2 portions/week
Fruits and vegetables	At least 5 servings/day
Vitamins/minerals	Conditions set in Annex of nutrition and health claims proposal
Botanicals	Indication of the amount of the botanical and/or active components

- Quality aspects, where relevant:

  Where relevant, an indication should be given on the specificity of the substance (origin, form, etc) and the validity of the claim for a specific food or substance, e.g. by indication of specific analytical methods in the case of botanicals.

Entry 4: Nature of Evidence

It is clear from all the existing international laws, codes of practice and guidelines that the claimed effect must be supported by scientifically valid evidence that demonstrates the effect of the nutrient, other substances, food or food component in humans and under conditions that reflect the actual conditions of use and exposure. The relationship between a nutrient, other substances, food or food component and health can be demonstrated by a number of different types of studies and designs. Methodological soundness is critical, given that the validity of the study type depends on the quality of design, execution and analysis. In brief, studies on humans are accorded greater weight than animal and *in vitro* studies, and human intervention studies have greater weight than observational or epidemiological studies.

Article 13 claims must be based on generally accepted scientific data/knowledge. Hence, it is necessary to evaluate the totality of the available evidence and weigh up the evidence on a case-by-case basis. In some cases this process of evaluation has already been carried out by expert panels and organisations. This is e.g. the case with the knowledge usually found in recognised textbooks, monographs, scientific opinions by officials scientific bodies (e.g. SCF, EFSA, NAS, etc) and claims already approved by national authorities (e.g. USA FDA, etc).

The terminology to be used in completing the template is:

- Authoritative body
- Textbook
- Meta-analysis
- Monographs
- Critical Reviews
- Individual studies

Entry 5: Grade of Evidence

Science is a continuous process where one finding provides the basis for further research, gradually building up evidence for a certain fact with each further step. It is therefore important to reflect the concept of grades of evidence, the contribution of emerging as well as consensus science, and the balance of probabilities that an association between a food or a food component and a health benefit will be refined (not reversed) by subsequent scientific research.

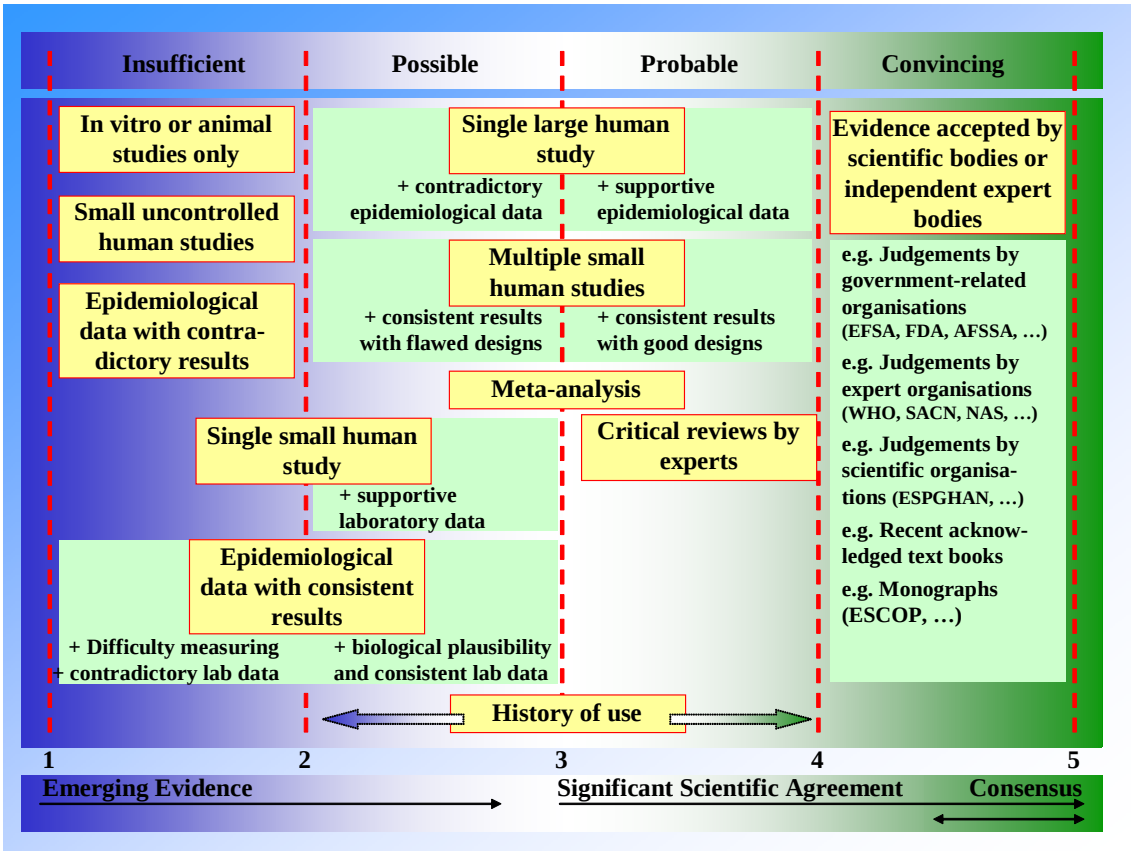
The table below represents the grading of different sources of evidence in support of a health claim.

Insufficient	
Categories 1 and 2	insufficient substantiation; more data needed
Probable/Possible	
Category 3	'Positive outweighs the negative', one publication of meta-analysis or peer-reviewed article' moves a relationship towards the category 'probable'
Convincing	
Category 4	Meta-analysis; peer-reviewed critical reviews move the relationship towards the category 'convincing'
Category 5	Text books, monographs, judgements by government-related organisations, scientific groups or expert organisations (e.g. World Health Organisation (WHO), US National Academy of Sciences (NAS), European Food Safety Authority (EFSA), UK Scientific Advisory Committee on Nutrition (SACN)

It is important that the relationships included in the list are underpinned by the best evidence available. Authoritative statements on well established function claims, e.g. those identified by the UK JHCI, Swedish Nutrition Foundation, those already approved by other independent expert bodies and committees, those found in recognised textbooks and monographs, would be sufficient for underpinning a specific relationship and are classified as category 5.

For specific foods and food components, the underlying supporting evidence can come from a number of scientific reviews, meta-analysis or individual studies. Such evidence should be analysed and graded as described below and graphically represented in figure 1. In this analysis, all available evidence can be used, but the value of human intervention studies rank higher than observational/epidemiologic studies and supporting evidence. History of use can be a factor that may be taken into consideration in the judgement of the amount of recognition that exists for a certain relationship, but the validity itself must be based on scientific data.

Figure 1.



Entry 6: References

The references should be complete and allow an expert committee to find the information quickly and efficiently. It is recommended that, for claims that are not underwritten by recognised text books and monographs or groups of independent experts, the key hard copy or electronic version of the individual scientific paper(s) is identified and assessed as set out below. This is essential to enable companies and other interested parties to grade the evidence. It also indicates that the company or other interested party is ready to provide the supporting data if required by the European Commission, the Member States or EFSA.

1. Evidence accepted by independent expert bodies and national and international committees can include the following sources (non-exhaustive list)

ANZFA: Permitted health claims by Food Standards Australia and New Zealand
CEDAP: Commission d'étude des denrées alimentaires destinées à une alimentation particulière (Fr).
FDA: Food and Drug Administration (USA)
FNFC: Ministry of Health and Welfare (Foshu, Japan)
FSB: Federal Scientific Bodies (USA)
JHCI: Joint Health Claims Initiative (UK)
NFA: National Food Agency (Fin)
SNF: Swedish Nutrition Foundation

VC: Voedingscentrum (Nl)
WCRF: World Cancer research Fund
WHO: World Health Organisation
Etc.

2. Evidence from recognised text books and monographs

e.g.:
Encyclopedia of Human Nutrition 2E. Editor-in-chief, Michele J. Sadler, editors, J.J. Strain, Benjamin Caballero. San Diego : Academic Press, c1999.

Handbook of Nutrition and Food. Edited by Carolyn D Berdanier...[et al.]. Boca Raton, Fla.: CRC Press, 2002.

Introduction to Human Nutrition. Edited on behalf of The Nutrition Society by Michael J. Gibney, Hester H. Vorster and Frans J. Kok. Blackwell Science, September 2002.

Etc.

3. Evidence from individual references (see also annex 1 and annex 2)

The relevant data should be extracted objectively from peer-reviewed publications in the scientific literature and presented in a clear, concise manner (see table below).

Example for a synopsis protocol
1. Title of the study
2. Authors (and their affiliation)
3. Journal or book reference
4. Objective of the study
5. Study type/design *If the study type/design is a pooled analysis (systematic review or meta-analysis) of many studies, then include* (i) inclusion/exclusion criteria for the studies, and (ii) data extraction from the studies
6. Study population (inclusion/exclusion criteria)
7. Baseline characteristics of study subjects and controls
8. Duration of the study
9. Location of the study
10. Methodology (including quality of the active component)
11. Dietary assessment technique
12. Outcome measurement and other relevant measurements
13. Statistics
14. Results
15. Conclusion
16. Points to note/further comments

<u>Entry 7: Examples of Claims Wording</u>

Examples of wordings of the health claims made on product labels and in advertising and other promotions should be included in the list. A copy of product labels and advertising materials is also advisable as back up, should it be required.

Examples of wording of the claims should be consistent with:
- The nutrient, other substance, food or food component – health relationship
- The level or grading of the available underlying evidence (use of modal verbs, qualifying language (see examples in table below))
- The context of the nutrient, other substance, food or food component in relation to their role in the daily diet and their content in the food
- Consumer understanding
- The scope of the list (i.e. not being a reduction of disease risk claim)

Some examples of wording of claims:

Food or food component	Health relationship	Example claim
Calcium	Necessary for normal structure of bones and teeth, normal nerve and muscle function	Maintains strong and healthy bones and teeth
Glucosamine	Joint health	May help to maintain healthy joints; improves mobility; helps keep joints supple and flexible
Ginseng	Enhancement of mental and physical capacities in cases of weakness, exhaustion, tiredness and loss of concentration	Helps maintain optimal stamina, feelings of energy and vitality, physical and mental well-being
Wholegrain cereals	Maintenance/promotion of a healthy heart	People with a healthy heart tend to eat more wholegrain foods as part of a healthy lifestyle
Oats (whole oats, flour, oat bran and rolled oats as sources of soluble fibre, beta-glucan)	Reduces total and LDL cholesterol	The inclusion of oats as part of a diet low in saturated fat and a healthy lifestyle can help reduce blood cholesterol; proven to naturally reduce cholesterol as part of a healthy lifestyle; oats can actively reduce cholesterol levels, which in turn helps to maintain a healthy heart; reduce cholesterol with soluble oat fibre
Oily fish (omega-3 PUFA)	Maintenance and promotion of a healthy heart	Two a week helps heart health; Everyone knows that fish is good for you and that's why we're supporting the (UK) Food Standards Agency recommendation that everyone should eat at least two portions of fish per week, one of which should be an oily fish such as salmon or mackerel to provide approx. 3 g of long chain omega-3 per week

Below are examples of wording that could reflect the grade of the evidence

Health Claim	**Grade (based on WHO/WCR grading system)**	**Qualifying language**
Yes	Convincing	Scientific evidence supports [function in the body] [Substance x] is necessary for [function in the body]; This product contains ... of the substance. The function of [Substance x] in the body is ...; Intake of [the substance] will promote ... Modal verbs: 'will'; show; demonstrate
Yes	Probable	Although there is scientific evidence supporting ..., evidence is not conclusive A diet rich in [substance] has been shown to ...; This product contains ... of the substance. Scientific findings indicate that [substance x] Based on current evidence it is likely / plausible that [substance x] ... Modal verbs 'can'; indicate
Yes	Possible	Some scientific evidence suggests ... However the evidence is limited and not conclusive. Regular consumption of [Substance x] may help [...]. [Substance x] has traditionally been used for [...]. These effects have not been scientifically proven. Based on current evidence, it is possible that [substance x] ... These findings are subject to further research. Modal verbs 'may'; suggest Disclaimer present
No	Insufficient	There is little scientific evidence supporting the claim

REFERENCES

1) Aggett, P.H., Antoine, J-M., Asp, N-G., Bellisle, F., Contor, L., Cummings, J.H., Howlett, J., Müller, D.J.G., Persin, C., Pijls, L.T.J., Rechkemmer, G., Tuijtelaars S., Verhagen, H. 2005. PASSCLAIM – Process for the assessment of scientific support for claims on foods. Consensus on criteria. European Journal of Nutrition **44** (Suppl 1): 1/5–1/30.
2) Asp, N-G., Cummings, J.H., Howlett, J., Rafter, J., Riccardi, G., Westenhoefer, J. 2004. PASSCLAIM – Process for the assessment of scientific support for claims on foods. Phase II: moving forward. *European Journal of Nutrition* **43** (Suppl 2): 1–183.
3) Asp, N-G., Cummings, J.H., Mensink, R.P. *et al*. 2003. PASSCLAIM – Process for the assessment of scientific support for claims on foods. Phase I: Preparing the way. *European Journal of Nutrition* **42** (Suppl 1): 1–119.
4) Richardson, D.P. 2005. The scientific substantiation of health claims with particular reference to the grading of evidence. *European Journal of Nutrition* **44** (5): 319–324.
5) Richardson, D. P. 2005. The scientific substantiation of health claims with particular reference to the grading of evidence and consumer understanding. *IFIS Food Science and Technology Bulletin: Functional Foods* **2** (4): 39–48.

6) Richardson, D.P., Affertsholt, T., Asp, N-G. *et al*. 2003. PASSCLAIM – synthesis and review of existing processes. *European Journal of Nutrition* **42** (1): 96–111.
7) Truswell, A.S. 2001. Levels and kinds of evidence for public health nutrition. *Lancet* **357**: 1061–1062.
8) US Food and Drug Administration, Centre for Food Safety and Applied Nutrition (1999–2003)http://www.cfsan.fda.gov/~dms/fig-6c.html; **http://www.cfsan.fda.gov/~dms/ssaguide.html**; **http://www.cfsan.fda.gov/~dms/hclmguid.html**; **http://www.cfsan.fda.gov/~dms/hclmgui3.html**.

Annex 1:

Brief and concise synopsis of individual references.

1. Title of study
   Ensure full title is presented.

2. Authors
   Complete list of **all** the authors' names and initials. *Et al.* is not sufficient. Also list the author's affiliation (e.g. University, company, ...).

3. Journal or book reference
   The reference must be complete, stating the full name of the journal/book, the date of publication, volume number and page numbers. It should be clearly stated if the reference is a supplement to a journal or special edition. For books, the name of the book and editors, the chapter heading and authors, the pages, the publishers and ISBN number should be mentioned.

4. Objective of the study
   The abstract or summary together with the introduction to the scientific paper usually state the objective(s) of the research work.

5. Study type/design
   Studies can be broadly classified as follows:

   Human intervention studies
   - randomised, controlled trials (RCT)
   - clinical trials
   - physiological/psychological trials

   Observational/epidemiological
   - prospective (cohort)
   - cross-sectional (analytical)
   - case-control

   Supporting
   - animal
   - *in vitro* cellular and molecular
   - studies of genotype
   - modelling (of a mechanism)

   Note, if the study type/design is a pooled analysis (systematic review or meta-analysis) of many studies, then include:
   - inclusion/exclusion criteria for the studies, and
   - data extraction from each of the studies

6. Study population
   Study groups should match as far as possible the target group, considering as is appropriate, for the food or food component. Typically, age, gender, ethnic origin, body weight and height, usual or background diet and intervention, level of physical activity, smoking habits, alcohol consumption, location and other relevant lifestyle and environmental factors should be stated. The study results

could relate to the whole population or a specific subgroup (e.g. elderly, obese, smokers, runners, students, pregnant women).

7. Baseline characteristics of study subjects and appropriate controls
There needs to be an adequate description of the study population as stated above, but it is also important to state inclusion/exclusion criteria for subjects in the study, recruitment procedures to minimise selection bias, and for a controlled intervention, the matching and randomisation procedures employed to assign the subjects to the control and test groups.

An appropriate design and randomisation is required including, in cross-over studies, adequate wash-out periods, and the control food or diet should, as far as possible, provide similar nutrients/energy intakes. Many foods cannot be studied in a 'blinded' way. However, with food supplements or components that can be hidden in a product, the use of a control product without the component is recommended. Wherever possible, a control product should be used. The test and control materials should be the same as, or be as close as possible to the food or food component as it is intended to be marketed and purchased.

7. Duration of the study
There are two aspects to this criterion:
- the period of intake should be suitable, and
- the duration of observation should be long enough for the expected benefit to occur and, if necessary, to show that a health benefit is sustained.

For example, the effect of a food on glycaemic index or satiety, or a carbohydrate source on cognitive performance may be measured in hours, whereas changes in blood cholesterol may take weeks or months. Any human intervention study design should ensure that the product is ingested long enough to allow the claimed effect.

8. Location of the study
Environmental and climatic factors may influence the study outcome as well as typical background diets and lifestyles. The location should be stated as precisely as possible. The evidence can also be assessed based on the consistency of results among different population groups and within them.

9. Methodology
   - **Characterisation of study groups' background diet and other relevant aspects of lifestyle** are needed as they might affect the outcome of the study, e.g. the effect of a cholesterol-lowering component will be influenced by the amount of energy in the diet from saturated fat.
   - **The amount of the food or food component should be consistent with its intended use and the way and frequency with which it will be consumed.** Where dose-response studies are reported, the range of doses must be clearly stated.
   - **The influence of the food matrix and dietary context on the functional effect of the component.** This criterion relates to the physico-chemical properties of the food or food component and its bioavailability or 'nutritional equivalence'. The food matrix, both in the raw state, after

storage and during culinary preparation can have a significant influence on the bioactive component.

- **Monitoring the subjects' compliance concerning the intake of the food or food component under test**
  It is essential to know the **actual** dietary intake of the subjects and to confirm that they have taken the food or food component in the right amount at the right time over the specified period. Monitoring compliance is essential for assurance that the study is valid. Compliance measures can include biomarkers in blood, urine or breath. Studies of dietary compliance have shown that adherence to the experimental diets is often much less than expected. Exclusion of non-compliant subjects can make a major difference to interpretation of results.

10. Dietary assessment technique
    The baseline or habitual diet of the target population and the study group must be taken into account when planning and evaluating an intervention. If the baseline diet is not described, the scientific justification for inclusion or exclusion of the reference would need to be presented. For example, a bioactive component may already be present in the diets of populations or subgroups of interest, and there may be potential interactions between a substance provided by the diet and the test substance. The difficulties in determining dietary intake are frequently underestimated and dietary assessment needs as vigorous approach as possible. Methodological challenges exist for both the collection of information on foods consumed, the composition of the foods and the amount of intake. Various methods of dietary assessment have been used, and their strengths and limitations need to be stated. Independent markers of intake are helpful for assuring the validity of dietary intake data.

11. Outcome measurement and other relevant measurements
    Wherever possible, the claimed benefit, i.e. the true endpoint, should be measured directly, e.g. a disease outcome or mortality rate. In many cases, the period between an intervention and an outcome may be long, such as a reduced incidence of a disease. Alternatively, it may be possible to measure changes in metabolism relating to, for example, energy balance, protein turnover, cholesterol metabolism, glucose kinetics etc; in other words, by the use of biomarkers. The FUFOSE and PASSCLAIM projects classify markers of relevant functional outcomes as to whether they relate to:
    - Exposure to the food or food component
    - The target function or biological response
    - An endpoint of an improved state of health or reduction of disease risk

    The 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

12. Statistics
    Studies providing evidence for a claimed effect of a food or food component should indicate the statistical criteria that were used in the design of the study. This assessment includes an estimate of the power (study size) needed to achieve a particular level of statistical significance, estimates of the size of the effect and

the validity of the conclusions. In cases where the results fall short of statistical significance, the data will not, on their own, be sufficient to substantiate a claim. In comparing studies that differ in their outcomes, greater weight should be given to those trials that have the best design and adequate numbers of subjects.

13. Results

The results must be stated and scrutinised in detail to ensure their biological and methodological validity. The target variable or biomarker should have changed in a statistically significant way and the change should be biologically meaningful for the target group consistent with the claim to be supported. When assessing the validity of a claim, any reviewing body will need access to, and consider on their scientific merit, all relevant data. Selective presentation of data depending on whether or not they support the claim is not acceptable.

14. Conclusion

The results should be analysed in such a way as to describe the validity of the dietary methods, the use of particular biomarkers and/or outcomes, and the consistency of the results with evidence from other sources. The conclusion should state clearly the contribution that the publication makes to the process of scientific discovery, new information and the strengths and limitations of the data. The results and conclusions must have been subject to peer review. The abstract or summary of the published paper may help guide the assessor, but an analysis of the data and an evaluation of the quality of the results is essential.

15. Points to note/further comments

An evaluation of the data may leave some questions unanswered. In such cases, the strengths and weaknesses should be set out clearly and questions raised as to whether or not the evidence supports the proposed claim. The quality and results of individual papers may differ and the study may be incomplete. The assessment should set out clearly how the individual study fits into the totality of the available data and the persuasiveness and relevance to the claim.

The final scientific assessment of a claim will be on a case-by-case basis and will involve the judgement from independent assessors that the diet/health relationship is valid, and that the evidence in support of the relationship outweighs the evidence against. The assessment of the totality of the available data and weighing of the evidence should be sufficient to permit the conclusion that a change in the dietary intake of a food or food component will result in a health benefit and/or health outcome, including a change in disease endpoint.

Examples of how data can be extracted and presented are shown in Annex I. The individual studies have been analysed in accordance with the protocol described in Table 1 as far as possible to ensure ease of comparability.

Annex 2

Examples of Individual Summaries of Evidence

WHOLE GRAIN

Reduced mortality among whole grain bread eaters in men and women in the Norwegian County Study

Jacobs DR Jr, Meyer HE and Solvoll K

Eur J Clin Nutr, 2001; 55: 137-143.

Objective of the study:

To study whether mortality and death from CHD and total CVD is reduced among whole grain bread eaters in Norway.

Study design:

A prospective cohort study

Study population:

16 933 men and 16 915 women, aged 35-56 years at baseline, not disabled and free from CVD.

Duration of the study:

A follow-up period from 1977-1983 to 1994, i.e. from 11 to 17 years.

Location of the study:

Norway, three different counties.

Methodology:

Dietary assessment: A validated (against 24 hour recall) semi-quantitative, 66-item food frequency questionnaire was used to measure dietary intake. The questionnaire focused strongly on the intake of bread, meat, fish, milk, coffee, oranges, potatoes, cakes and fat, with no other information on fruit and vegetables. Although the questionnaire was relatively brief, and energy intake is probably underestimated, it is likely that the ranking of individuals by energy intake is reasonable.

The FFQ included four questions about bread intake:

1. how many slices of bread do you usually eat per day? (6 categories ranging from < 2 to >13)
2. what kind of bread do you eat most often? (bought or home made)
3. if you buy, what type most often? (white, light or whole grain)
4. if you bake at home, what proportion of the flour is whole grain? (4 categories from none to more than half)

A whole grain bread score was formed to evaluate the intake of whole grain. The score is defined as the product of the number of slices eaten per day times the proportion of whole grain flour. Given the tendency for those who ate mostly bought bread to overestimate the coarseness of the flour used, the answer to question 4 was downgraded one category for those who bought their bread in order to calculate the whole grain bread score.

Outcome measurement:

Cause of death was assigned based on ICD 8 and 9 codes by nosologists at Statistics Norway. In addition to total mortality, underlying causes of CHD and total CVD among other causes were studied as well.

Statistics: Participants were divided in five categories according to their whole grain bread score. Characteristics of male and female study populations are presented in table 2 p.139 and table 3 p. 140, respectively. Proportional hazards regression analysis was used to study the relationship between total mortality and each cause of death as dependent variable and category of whole grain score. Minimally adjusted (age, energy intake and sex) and multivariate adjusted (all the variables mentioned in the tables 2 p.139 and 3 p.140 except fat) hazard rate ratios (HRR) were calculated for men and women separately in each of the whole grain intake category and then combined. All analyses were done using the Statistical Package for the Social Sciences (SPSS, 1999).

Results:

- Men reported eating 6.3 ± 2.0 slices of bread per day with the energy intake of 7847 ± 2242 kJ/day. Women reported eating 3.9 ± 1.6 slices per day with the energy intake of 5211 ± 1531 kJ/day. Men used 22.8 ± 13.9% whole grain flour in their bread, compared to 25.6 ± 14.2% among women.
- The mean whole grain bread score was 1.43 ± 1.00 among men and 1.00 ± 0.71 among women. After adjustment for age and energy intake, the mean whole grain bread score was virtually identical between sexes, 1.21 among men and 1.22 among women.

- All in all, whole grain bread eaters had a more favorable profile of health behaviors and diet than the non-eaters (table 2 p.139 and table 3 p.140).
- During 488 500 person-years of follow-up, 587 men and 146 women died of CVD (in total 733), death was attributed to CHD in 456 of these men and 79 of these women (in total 535). Obs. According to the table 4 p.141 total number of CVD deaths was 758 and the total number of CHD deaths 553. Why the discrepancy?
- Comparing the highest vs. the lowest category of the whole grain bread score the minimally adjusted HRR for CVD, for men and women combined, was 0.64 (95% CI, 0.50 - 0.82) and the multivariate adjusted HRR 0.77 (95% CI, 0.60 – 0.98). Minimally adjusted HRR for CHD, for men and women combined, was 0.63 (95%CI, 0.47 – 0.85) and the multivariate adjusted HRR 0.76 (95% CI, 0.56 – 1.02) (table 4 p.141)

Points to note:

- This study finds reduced death rates in healthy, middle-aged, Norwegian, whole grain eaters in several disease categories. The association of whole grain bread intake with mortality was most consistently graded for CVD. However, the reduction in mortality rate was greatest for noncardiovascular, noncancer causes, about 35%, even in those with a relatively low whole grain bread score (table 4 p.141).
- The findings of this study is of particular interest because it extends the findings from the US for differential risk according to amount of whole grain intake to the higher intake levels customarily consumed by Norwegians.
- All dietary surveys, including this one, suffer from high within-person error in self-reported diet. This error tends to flatten the association of dietary factors such as whole grain intake with disease endpoints.
- It is a major limitation that the survey contains very little information about the intake of other plant products besides bread, potatoes and oranges. Therefore, it needs to be kept in mind that the findings for whole grain in this study may in part reflect the influence of fruit and vegetable intake.

OATS

Oat products and lipid lowering. A meta-analysis.
Ripsin CM, Keenan JM, Jacobs DR Jr, Elmer PJ, Welch RR, Van Horn L, Liu K, Turnbull WH, Thye FW, Kestin M, et al.
JAMA (1992, Jun 24)267(24):3317-25.

Meta-analysis
of trials investigating the relationship between consumption of oats and total blood cholesterol levels in free-living subjects. Trials published by March 1991 were identified by computerized literature search in MEDLINE and checking the unpublished trials relating to lipid-oat association supplied by the Quaker Oats Co, Barrington, Ill. 19 trials were identified, reviewed and summarized.

Inclusion criteria:

- Trials had to have been controlled and randomized.
- If a product was used for comparison, it had to have been one with very low or no soluble fibre.
- If a trial tested the intervention against a special background diet (low-fat and low-cholesterol), there had to have been a sufficient lead-in period—a minimum of 4 weeks.
- All trials had to have made a formal assessment of dietary behaviour and body weight changes in treated and control subjects.
- If investigators did not submit their raw data for analysis, the published report had to provide the necessary information to calculate the appropriate size of the effect and associated standard error.
- Cross-over trials were analysed in the primary analysis as parallel design trials when the raw data were available, using the information from just the first phase.

Extended inclusion criteria:

- Applying all other criteria as above but not number 3. The extended inclusion criteria did not assume a lead-in period with low fat and low cholesterol background diet.

Study population:
A total of 10 trials met the a priori inclusion criteria and 12 trials met the extended inclusion criteria. The 10 trials generated 19 and 12 trials 22 individual sizes of effect, because some single trials included multiple treatment groups. From 10 to 137 subjects were enrolled in each treatment or control group, with an age range from 20 to 73 years. The mean blood total cholesterol levels in the trials ranged from 4.6 to 7.1 mmol/L.

Study design and follow-up period:
8 trials used a parallel design, 3 used a 2 x 2 oat bran and wheat bran crossover design and one used a 3

x 3 design that tested oat bran, rice bran and wheat bran. The duration of treatment phases ranged from18 days to 8 weeks and the majority of the trials assessed diet by use of a 3- or 4-day written food record.

Location of the study:
University of Minnesota, Minneapolis

Background diet:
Six trials used an AHA (low fat, <30% energy from fat and low cholesterol, <300 mg/d) diet, 4 a normal, free-living diet, 1 a low-fibre diet and 1 a low-fat diet.

Control diet:
In 6 trials wheat fibre and in 4 trials diet only was used as a control.

Intervention diet:
Oat bran or oatmeal, oat bran dosage ranging from 28 g to 100 g per day, providing oat soluble fibre from 1.1 to 6.1 g per day, according to Table 2, pp.3320–3321. OBSERVATION: Soluble fibre values are estimates in many trials and are based on the assumption that 28 g of oat bran provides 2 g of soluble fibre.

Statistically significant ($p \leq 0.05$) effects on blood lipids:

- Total cholesterol: A summary size of effect for change (a decrease) in total blood cholesterol level of -0.15 ± 0.03 mmol/L (95% CI, -0.22 to-0.09) was calculated for the 10 trials meeting the inclusion criteria when a dose of at least 3 g of soluble oat fibre has been used.
- When the initial blood total cholesterol was < 5.9 mmol/L and the intervention dose of beta-glucan ≥ 3 g/d, there was a decrease of -0.13 ± 0.12 mmol/L in total cholesterol; and when the initial blood total cholesterol was ≥ 5.9 mmol/L and the intervention dose of beta-glucan ≥ 3 g/d, a decrease of -0.41 ± 0.21 mmol/L was observed, representing a decrease of 2.2-6.9% from the initial total blood cholesterol (table 4, p.3323).
- Applying the extended inclusion criteria a summary size of effect for change (a decrease) in total blood cholesterol level of –0.13 ± 0.03 mmol/L (95% CI, -0.19 to –0.07) was calculated for the 12 trials with the average dose of 3.2 g of soluble fibre. This data is presented in the forest plot of the meta-analysis by Ripsin *et al*, 1992.

OMEGA-3: PRIMARY PREVENTION – COHORT STUDIES

Fish consumption and coronary heart disease mortality. A systematic review of prospective cohort studies.
Marckmann P, Gronbaek M.
Eur J Clin Nutr. 1999 Aug;53(8):585-90

Study design:
A systematic review of prospective cohort studies examining the relationship between fish intake and coronary heart disease mortality.

Inclusion and exclusion criteria for the studies:

- Prospective cohort studies reporting fish or very long chain n-3 fatty acid consumption and CHD death, with the minimum duration of 5 years and more than 95% completeness of follow-up.
- MEDLINE was search for the studies between 1996 and January 9th 1998 using indexing terms: fish, coronary heart disease, journal article, total number of hits was 324. Reference lists of retrieved articles were also checked for relevant articles.

Study population and follow-up time:
In total 11 studies were identified. The cohorts counted a total of 116 764 individuals. Individual study populations ranged from 272 to 44 895 and only 3 studies included females. Follow-up time among these studies varied from 5 years to 30 years.

Evaluating the study quality:
Each study was scored for its scientific quality on a scale from 0-6 points. Points were scored according to dietary assessment method, CHD death ascertainment, number of CHD deaths and statistical presentation. Studies scoring 5-6 points were considered of high quality, those scoring 3-4 points intermediate, and those scoring 2 points or less of insufficient quality to draw conclusions.

Results:

- Four studies were judged of high scientific quality and four of intermediate scientific quality. The lower scoring of intermediate studies was caused either by their use of less valid dietary assessment methods, small number of CHD deaths, or less rigid ascertainment of CHD deaths. The key characteristics and scientific quality scores of the studies are presented in table 1 and table 2, p. 586. Results and conclusions reported below are based on these 8 studies ranked being of high and intermediate quality.

- Among the high quality studies an inverse and graded relationship between fish intake and CHD death was observed by Kromhout et al (1985) and Daviglus et al (1997), but it was absent in the other two high quality studies of much larger cohorts, Ascherio et al (1995), and Albert et al (1998), p(trend) = 0.14 and 0.49 respectively), figure 1, p. 587. However, Ascherio et al (1995) observed that eating any amount of fish compared with eating no fish was associated with an insignificant lowered risk of CHD death (RR = 0.74, 95% CI, 0.44-1.23). The incidence of myocardial infarction was unrelated to fish consumption in the studies by Ascherio et al (1995) and Albert et al (1998).
- The conclusions reached in the four studies of intermediate scientific quality also diverged. Roderiguez et al (1996) and Mann et al (1997) were unable to demonstrate any association between fish consumption and CHD death in their studies. In contrast, Doleck & Grandits (1991) reported an inverse relationship between quintiles of dietary intake of very long chain n-3 fatty acids and CHD mortality, and Kromhout et al (1995) observed that fish consumers with average fish intake of 24 g/d had an adjusted relative risk of CHD death of 0.51 (95% CI, 0.29-0.89) as compared with those not eating fish.
- The two high-quality studies that were both negative included American health professionals with healthy lifestyles (Ascherio et al, 1995 and Albert et al, 1998). Among these individuals there were few current smokers (8-13%), they had low saturated fat intakes of < 10% of total energy intake, desirable total cholesterol concentrations around 5 mmol/L and low CHD death rates (1.0 and 1.4 CHD deaths for every 1000 person-years of follow-up. In contrast, the two high-quality studies showing a protective effect of fish comprised participants at a much higher absolute risk of CHD and with unhealthy lifestyles. The CHD death rate was 4.6 for every 1000 person-years in the study by Kromhout et al (1985), and 7.9 in the Western Electric Study by Daviglus et al (1997). Participants also had average saturated fat intakes of 16-18% of total energy. In the latter study average cholesterol concentration were close to 6 mmol/L, and almost 60% were smokers. A similar pattern of differences between studies showing or not showing an association between fish and CHD death applies to the four intermediate-quality studies.
- The overall conclusion on the basis of these studies is that individuals at low risk of CHD with healthy lifestyles do not gain any additional protection against CHD from eating fish. On the other hand, high-risk individuals appear to benefit in a dose-dependent manner from increasing their fish consumption up to an optimum of 40-60 g/d. At the optimal fish intake, risk of CHD death may only be around half the risk of individuals not eating fish at all.