ATTACHMENT 8

SUBSTANTIATION FRAMEWORK

SUBSTANTIATING NUTRITION, HEALTH AND RELATED CLAIMS ON FOODS

A draft framework
September 2005

Acknowledgement
The content of this paper has been developed drawing on a number of sources including Aggett et al. (2005), the Australian National Health and Medical Research Council (1998, 1999, 2000), the Australian Therapeutic Goods Administration (2001), Health Canada (2000), Hennekens & Buring (1987), Khan et al. (2001), Mann & Truswell (1997), Mann (2002), Rychetnik & Frommer (2002), Truswell (2001a and 2001b, 2002), the United States Food and Drug Administration (1999), the World Cancer Research Fund (1997 and 2004), and the World Health Organisation (2003), together with other sources identified in the bibliography. The framework has been prepared with input from a group of New Zealand and Australian scientists who are experts in assessing scientific evidence relating to public health and diet.

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CHAPTER 1: Introduction

This document sets out the principles for the scientific substantiation of diet-health relationships that are proposed to form the subject of nutrition and health claims on foods supplied in Australia and New Zealand. It is not intended to serve as a guide to applicants, which is proposed for development towards the finalisation of the proposal.

In the context of this document, a 'diet-health relationship' is any relationship between intake of individual food constituents, a food itself, a diet or dietary pattern, and any physiological function, health effect or disease outcome. A 'diet-disease' relationship however, is a subset of 'diet-health' relationship specifically in relation to high level claims. These relationships may subsequently be expressed in the form of a claim appearing on a food label. For the purposes of this framework, the term 'health effect' encompasses biomarker and disease outcomes.

Further refinement of the content of this document may occur as FSANZ undertakes the process of developing the Standard on nutrition, health and related claims.

1.1 General principles for considering evidence to substantiate diet-disease relationships for high level claims

Substantiation is the process of deciding whether the body of scientific evidence supports a claimed relationship between a food, property of a food (including a nutrient or other bioactive substance or other defined property of the food) and a specific health effect. This decision is made on the basis of an assessment of all available scientific evidence of appropriate quality, on a claim-by-claim basis.

The evaluation process used in determining whether or not a diet-disease relationship is substantiated must be rigorous, to determine with confidence that the evidence shows consistent associations that are likely to stand the test of time. The general principles that apply to substantiation are:

- A structured approach should be used to ensure all relevant evidence is considered and the conclusions are justified based on the totality of evidence.
- The evidence must be of a suitable quality and level and include appropriate human studies.
- The evidence should show a causal relationship (actual or inferred with reasonable certainty) between consumption of the diet, food or food component and the claimed effect.
- The evidence should substantiate the relationship for the population group/s that are the intended target of a claim.
- The required intake of the food or food component should be achievable in the context of the total diet of the intended population group/s.

These principles can be applied in two ways – where a comprehensive review of all available evidence is undertaken, and where an existing authoritative and relevant review of the evidence is already available.

1.2 Substantiating a diet-disease relationship for a high level claim based on a comprehensive review of all available evidence

Except in the circumstances set out in Section 1.3 below, a comprehensive and rigorous review of all available, relevant evidence will be undertaken when determining whether or not a diet-disease relationship proposed to support a high level claim is substantiated.

This review should be undertaken in three key steps that take into account the general principles for substantiation (refer Section 1.1):

1. identifying and categorising all the evidence
2. assessing and interpreting the evidence, study-by-study
3. evaluating the totality of the evidence across studies and determining if, and under what circumstances, a claimed relationship is substantiated.

Because high level claims must be substantiated on a claim-by-claim basis, the detailed application of these steps may vary.

More detail on this process is provided in Chapter 2 of this document.

1.3 Substantiating a diet-disease relationship for a high level claim based on existing Reviews conducted by authoritative bodies

In many cases an authoritative body will have already reviewed the evidence about a diet-disease relationship proposed as the basis of a claim, to standards comparable to those set out in Chapter 2 of this document. These authoritative bodies may include the governments or research agencies of other countries.

When these reviews are to be used as the basis for substantiating relationships that will form the basis of high level claims, the following steps will be undertaken:

1. a critical analysis of the authoritative review will be undertaken, including re-assessment of some key evidence sources cited in the review;
2. relevant evidence released since the review was completed will be considered in detail and the review's conclusions re-assessed in the light of this new evidence; and
3. the relevance of the review to the diet and health status of Australians and New Zealanders will be assessed.

More detail on this process is provided in Chapter 3 of this document.

1.4 Preparing a claim based on a substantiated diet-disease relationship

Once a diet-disease relationship has been substantiated, the relationship can be described in the form of a claim. Requirements in relation to the use of claims are established in draft Standard 1.2.7 – Nutrition, Health and Related Claims

1.5 Safety of foods carrying health and related claims

The purpose of the substantiation process is not to assess the safety of foods carrying claims. Other FSANZ processes exist to assess food safety, such as the assessment of novel foods. Nevertheless, information on undesirable effects associated with studies of the efficacy and effectiveness of diet, food or components will not be ignored.

1.6 Reviewing approved claims

Despite health claims being based on a rigorous substantiation process that aims to stand the test of time, evidence relating to the relationship between diet and health emerges continually. It is anticipated, therefore, that approved claims will be subject to review (possibly every 5 – 10 years, or if significant new evidence emerges) to ensure they continue to be based on the best available evidence.

CHAPTER 2: Substantiating a diet-disease relationship for a proposed high level claim, based on a comprehensive review of all available evidence

The proposed processes reflect standards established by overseas governments and recognised scientific bodies that have undertaken comprehensive and rigorous reviews of the relationships between diets, foods or components and health or disease. A comprehensive review of evidence is, of necessity, a detailed and time-consuming process that requires considerable scientific skills across a range of disciplines.

For simplicity, the process that will be used can be divided into three key steps:

1. identifying and categorising all the evidence
2. assessing and interpreting the evidence, study-by-study
3. evaluating the totality of the evidence across studies to determine if, and under what circumstances, a claimed relationship is substantiated.

Each of these key steps is covered in detail in the remainder of this chapter. Chapter 3 sets out a process that can be used when an existing comprehensive review about a claimed relationship is already available.

2.1 Identifying and categorising the evidence – Step 1

Identifying all relevant studies, whether or not they support a proposed diet-disease relationship, is a critical first step in the substantiation process. It is not possible to later evaluate the totality of evidence in relation to a relationship unless the evidence is drawn from a structured and thorough search of the scientific literature. In order to guide the identification process, it is vital that a clearly formulated research topic is identified at the beginning of the substantiation process.

Evidence to substantiate a diet-disease relationship could be drawn from a variety of study types, including reports of human experimental studies, human observational (cohort and case control) studies and systematic reviews of relevant randomised, controlled trials, supported by other evidence types such as animal studies, studies examining biological mechanisms and some other types of observational studies.

However, as a minimum, substantiation of a relationship that will form the basis of a high level claim requires evidence derived from well-designed studies (experimental and/or cohort/case control observational) of humans, to ensure a high degree of certainty that a proposed claim is relevant to the dietary and health context of Australians and New Zealanders.

It is not possible to offer guidance on the number of studies and reports that need to be considered in substantiating a diet-disease relationship. Each relationship will be considered individually and the amount and quality of information available will vary with each case. However, it is highly unlikely a claim would be approved based on the findings of a single human study or a very small number of such studies. On the other hand, a large number of poor quality studies would also be insufficient to substantiate a relationship that will form the basis of a high level claim.

Useful resources for those preparing to identify and categorise evidence are the Australian National Health and Medical Research Council's 1999 publication *How to review the evidence: systematic identification and review of the scientific literature* and the World Cancer Research Fund's *Systematic literature review specification manual* (2004).

2.1.1 Identifying the evidence

Before the search for scientific evidence begins, a search strategy should be developed that reflects the research topic being addressed. The strategy should document the key search words or terms that will be used, excluded terms, search limits, the time period searched, the databases searched and the inclusion and exclusion criteria used to select studies for subsequent detailed review. The strategy should allow inclusion of studies where findings appear to support the diet-disease relationship, as well as studies where the findings appear to show little or no effect, or to refuting evidence. At this stage, studies should not be excluded on the basis of design or assumed quality, but on their relevance to the review topic.

Identifying studies will generally involve searching electronic databases (such as MEDLINE, EMBASE, FSTA, Science Citation Index, CINAHL, BIOSIS, Cochrane Library, Australian Medical Index and others). Several databases should be searched as different databases cover different publications and topics. Searching scientific literature can be a complex task and may require assistance from an experienced information manager.

The time frame of the search needs to be determined on a case by case basis. Some areas of research may be relatively recent, while others may have been underway for several decades.

The task may also include manual searching, such as checking the bibliographies of review articles or research reports to identify important studies not identified through electronic searches, and scanning research registers and conference proceedings. It may be useful to consult one or more experts in the area who are familiar with the subject matter and may be able to identify any key evidence sources that have been missed in the literature search. Unpublished studies may be identified during the search process as well as published studies that have not been peer-reviewed.

Some scientific journals publish letters or comments from researchers critiquing the findings of previously-published reports. Where this is the case, these critiques should accompany the report of the study and should be taken into account when assessing study quality.

Attention should be paid to the potential for publication of the same study findings in more than one journal paper, or of the inclusion of previously published data in the results of a follow-up study. Where this occurs the results should not be recorded as entirely separate studies.

The initial search will identify many studies that may not be useful for determining if a diet-disease relationship is substantiated. The search strategy may need to be refined and/or the results reviewed to select those studies that will be subject to detailed evaluation.

It is preferable to have two people apply the stated search criteria independently.

Once all potentially relevant studies have been identified, reports of all these studies should be obtained for detailed evaluation; abstracts are insufficient for evaluation purposes.

2.1.2 Categorising the evidence

Categorising studies into broad types is a helpful first step as it provides an indication of the range of available evidence.

For the purposes of substantiating diet-disease relationships that will form the basis of proposed high level claims, evidence can be divided into four main categories: experimental studies of humans, observational studies of humans, systematic reviews and supporting evidence.

Experimental (interventional) studies

These are individual studies that involve a conscious intervention in the diet of humans in order to examine a diet/food/component and health relationship. Experimental studies include randomised and non-randomised, blinded and non-blinded controlled trials of either healthy participants ('primary prevention' trials) or diseased participants ('secondary prevention' trials). Depending on the number of experimental studies identified in the search stage, it may be useful to divide the studies into separate sub-categories based on whether or not studies were randomised and/or blinded, and on the nature of the intervention and the group studied (e.g. by age, gender or health status).

Observational studies

Observational studies are individual studies where humans are observed without a direct treatment intervention. The observational study designs that are most likely to be useful in substantiating claims are prospective cohort studies and, to a lesser extent, case control studies. Other observational studies are most likely to be considered to form supporting evidence.

Systematic reviews

Systematic reviews are comprehensive analyses of all the available information (generally all available and relevant randomised controlled trials) relevant to a review question. Examples of such reviews are publications of the Cochrane Collaboration, which now has a health promotion and public health field that incorporates evidence in addition to clinical trial data (see http://www.vichealth.vic.gov.au/cochrane/welcome/index.htm). The International Agency for Research on Cancer also publishes systematic reviews; see http://www.iarc.fr/ for details. Meta analyses, where data from different primary studies are integrated to achieve quantitative assessment of the overall evidence base, and pooled data analyses form part of the systematic review process.

Supporting evidence

This category includes a diverse range of studies that may add weight to an assessment but are not sufficient on their own to substantiate a diet-disease relationship. It includes data from studies involving chemical, cellular or animal models, data from human biological experiments investigating possible mechanisms of action of foods or components, and some observational studies such as case series, population monitoring statistics and cross-population studies.

Minimum evidence requirements

In order to substantiate a diet-disease relationship proposed as the basis of a high level claim, there must be relevant experimental and/or observational evidence. In general, well-designed experimental studies such as blinded, randomised, placebo controlled trials represent the highest level of evidence available from individual studies. Such studies are likely to be given the greatest weight in the subsequent assessment of the totality of the evidence, where they are available.

In practice, there are likely to be many instances where high quality experimental studies are not available to assist in the evaluation of diet-disease relationships. In this case, it is possible that the quantity and quality of observational evidence may be sufficient to substantiate a relationship, particularly where this evidence is drawn from prospective cohort observational studies. It is unlikely that a claim could be substantiated solely on case control observational studies.

In some cases, relevant experimental and observational evidence may have been integrated into a systematic review such as a Cochrane review. Under certain circumstances, these reviews may be able to be used as the basis for claim substantiation; these circumstances are set out in Chapter 3.

Supporting evidence alone is insufficient to substantiate a diet-disease relationship for a proposed high level claim.

2.1.3 Example of the process of study identification and categorisation

Table 1 provides an example of the results of a structured process used to retrieve relevant evidence relating to the assessment of the diet-disease relationship that will form the basis of a proposed health claim:

'Consumption of fruits and vegetables may be associated with a reduced risk of cancer'. The example covers the process from an initial thorough literature search, to selection of studies for detailed review based on pre-defined inclusion and exclusion criteria, to initial categorisation into study type. It does not, at this stage, include assessment of study quality.

Table 1: Example of a search and categorisation strategy used to identify evidence to substantiate the diet-disease relationship between consumption of fruits and vegetables and reduced risk of cancer*

Databases searched	**Cancerlit, Medline, Medline Biol, Medline Psych, Medline Sociol, current titles**
Search key words (search words refined after other search words such as 'Diet' and 'Cancer' retrieved a very large number of references, many with little relevance)	'Fruit and vegetables' and 'Cancer prevention' 'Fruit' and 'Cancer prevention' or 'Vegetables' and 'Cancer prevention' 'Diet' and 'Cancer prevention' 'Diet' and 'Cancer risk reduction' 'Diet' and 'Behaviour change' and 'Cancer' 'Food Group and Cancer' As above for specific vegetables or fruits. Keywords were mapped to subject headings, for example 'Cancer prevention' was mapped to the subject heading 'Neoplasms' and then to the subheading: 'Prevention and Control'
Search key words not used	'Nutrients'/'Phytoestrogens'/'Antioxidants' and 'Cancer prevention' 'Diet' and 'Cancer treatment'
Search dates	1989 to present, because systematic reviews were identified early in the planning process that reviewed literature prior to 1989
Other information sources checked	International Agency for Research on Cancer Directory of Ongoing Research in Cancer Prevention <http://www-dep.iarc.fr/direct/projects.htm> Personal discussions with two New Zealand experts on this area
Total references retrieved from all sources	228 (number of papers retrieved would have been much greater if an earlier search date had been used)
Method of determining if references should be reviewed	Results from the search were printed by title and abstract Inclusion: if studies were directly related to the subject of the review, involved humans, if the intervention was not a component extracted from fruits and vegetables. Abstract scanned for relevance and abstracts provisionally classified as Experimental, Observational or Review Full text of relevant abstracts obtained
Number of references to be subject to further review	50 studies met the inclusion criteria
Category of studies retrieved	No experimental studies identified 46 observational studies identified (listed in attachment) 3 review articles identified (listed in attachment) 1 report of an assessment of a health claim conducted in an overseas country (listed in attachment)

* This table is provided as an example only and does not imply that alternative search and selection strategies may not be appropriate

2.2 Assessing and interpreting the evidence – Step 2

Once all relevant evidence has been identified and categorised in step 1, the next step is to assess the quality of individual studies that comprise the evidence and to interpret the findings of these studies. In the subsequent assessment of totality of the evidence (step 3), greater weight will be placed on higher quality studies.

2.2.1 Assessment of individual study quality

Study quality is difficult to define and factors that need to be considered in assessing study quality will vary with the study design being evaluated. This section provides some general information on the issues that may be considered when assessing the quality of evidence. Because high level claims will be assessed on a claim-by-claim basis, FSANZ may also consider issues that are not identified below, where appropriate.

A useful resource for those preparing to assess the quality of evidence is the Australian National Health and Medical Research Council's 2000 publication *How to use the evidence: assessment and application of scientific evidence*.

Study purpose, overall design and reporting

Studies should have a clearly stated hypothesis that can be addressed by the chosen study design. The report of the study should fully describe the study aims, the methodology used (including its limitations) and the results achieved. Quality control procedures used should be described.

Participants' age, gender, health status, body weight, socioeconomic status, family history, lifestyle practices and ethnicity should be reported. Other factors such as genotype may be relevant in some cases.

Identification and description of the diet, food or food component ('exposure') being measured

Studies should clearly identify and characterise the dietary pattern, the specific food consumed or the specific component (the 'exposure') that is the subject of the study. The exposure studied should be directly related to the diet, food or component that is proposed as the subject of the diet-disease claim.

For example, if fruit and vegetable consumption is being measured the study should identify which specific fruits and vegetables are being studied and whether this includes processed fruits and vegetables such as potato crisps or fruit juices, or related foods such as nuts. If a claim in relation to apples were being considered, then studies used as evidence should include apples as the exposure being investigated. Processing or cooking methods should be specified where this may be relevant.

Where a specific food component is the subject of a study, the study report should define the particular chemical forms of the component being studied. For example, a study of the effect of consuming vitamin E on a health effect should describe the particular stereoisomers of alpha tocopherol that are measured and whether other tocopherols are included in the study's definition of vitamin E.

Measuring consumption of a food or food group

All techniques for measuring food consumption have significant limitations and it is important that these limitations are taken into account. Dietary recording techniques used in studies should have been validated before use and attention paid to the potential for bias in self-reported food intakes, with under-reporting of intakes a particular issue for foods perceived as having undesirable attributes.

In experimental studies, consideration should be given to whether the study participants adhered to the intervention throughout the trial. Therefore for studies of dietary patterns or intakes of specific foods, dietary compliance may need to be measured at several different stages in the study. This is particularly important in longer-term studies where dietary patterns may change from those at the commencement of the study. Information should also be available on intake of key foods or nutrients other than those that are the subject of the intervention.

In an observational study, measurement of consumption can be more difficult in retrospective studies because these studies rely on participants recalling what they have eaten in the past.

Measuring intakes of a food component

Studies should assess intake of the component in question from all foods consumed and from non-food sources such as dietary supplements. For example, a study of the relationship between vitamin C intake and a health effect would need to consider vitamin C intake from all foods consumed, both from naturally occurring vitamin C and from its use as a food additive. Intake of vitamin supplements containing vitamin C should also be recorded. Where a set amount of a component is added to a food as an intervention, the level of the component in the food should be verified by analysis to ensure participants actually receive the stated amount throughout the trial duration. This is particularly important when the component is potentially unstable.

When laboratory determination of levels of a component is required, measurements should be conducted at laboratories experienced, and preferably quality certified, in that particular method of analysis. Ideally, methods of analysis should be chosen that are well-accepted and have previously been validated and published. The method chosen should quantify the actual component that is being investigated. For example, components such as dietary fibre are not a single chemical entity and different analytical methods will be required depending on the chemical form of the fibre being studied.

If nutrient data are drawn from published food composition tables rather than analysis it is important that close consideration be given to selection of appropriate food matches, to the origin of the data (ideally Australian or New Zealand data should be used in Australian or New Zealand studies) and to the limitations of the data (for example, if values were determined using outdated methods of analysis or on foods no longer available). It should also be recognised that levels of components, such as nutrients, vary considerably within a single type of food.

Reliable assessment of the intake of a particular component is generally more difficult in an observational study because these studies do not involve a direct intervention with a controlled amount of the component. Quantification of intake is likely to be by indirect techniques such as the use of food composition tables.

Some studies may have included measurement of one or more physiological markers of exposure to a particular component as an objective method for quantifying intake or validating other dietary measurement techniques. Where markers of intake or exposure are used, they should be specific to the dietary intervention being measured, measure responses across the range of intakes being studied, be measurable with precision and sufficient sensitivity and be applicable to the population group being studied.

Measurement of the exposure needs to be the same in the groups being compared and done blinded to any outcomes.

Bioavailability of food components

The form of a component used in experimental studies to substantiate a claim should be clearly recorded. If the chemical form of a component used in studies is different to that used in foods, or if studies have been conducted using a different matrix to the food matrix in which the component will be found, then it will be necessary to consider whether or not the bioavailability of the component remains unchanged.

Bioavailability of specific food components can be affected by factors such as:

- the chemical form of the component;
- the individual's physiological need or nutritional status (for example, if body stores are lacking, more of the material may be absorbed from the diet);
- interactions between substances in the food, the meal or the total diet (matrix effects).

Relevance of studies of components administered in therapeutic form

In some cases, evidence about the relationship between ingestion of a food component and a health effect will be derived from studies where the component was administered in therapeutic form, for example in a vitamin or mineral supplement. Such studies are not automatically suitable for use in substantiating a diet-disease relationship. For example, the bioavailability of the component may be altered compared to its bioavailability in foods (see above). Daily dosage administered in therapeutic form may be higher than can be achieved through the diet and/or may be administered at a different frequency than through the diet. Such studies must be carefully interpreted in order for them to be useful for the substantiation of diet-disease relationships.

Measuring the health related effect

Outcomes measured in a study may be a health effect or disease outcome (e.g. incidence of myocardial infarcts) or a surrogate outcome (e.g. serum LDL cholesterol levels).
Where the health effect is assessment of disease initiation or progression, consistent diagnostic and assessment criteria must be used. The assessors of these effects should be trained in applying these criteria and should be unaware of the exposure status of the participant.
Anthropometric measurements, such as of body mass or height, must be conducted using consistent techniques and equipment to overcome the considerable variation in these measurements that can result from different measurement techniques.

All assessment techniques should have been validated before the study commenced. In addition, outcomes must be assessed blinded to the participants' exposure status.

Surrogate health outcomes or endpoints are often used, particularly in experimental studies, because they may be easier to measure objectively and may develop in a shorter time than disease outcomes. These surrogate outcomes are commonly referred to as biomarkers.

Studies using surrogate outcomes are only useful in the substantiation process where there is a well-accepted, predictive and dynamic relationship between the surrogate and the health outcome or effect under investigation. Where studies with surrogate outcomes are used as evidence, the validity of the surrogate should be demonstrated.

Where a biochemical parameter is measured, analyses should be conducted in accredited laboratories with experience in the required method of analysis. Analytical methods must be sufficiently sensitive that small changes in levels can be accurately measured and reported.

More information on the use of biomarkers in substantiating diet-disease relationships is in Appendix 1.

Sample and measurement bias

Bias in study design and conduct is a major determinant of study quality and therefore it is vital that any assessment of study quality considers the presence and extent of bias. There are three major types of bias that need to be considered when evaluating primary evidence sources for health claims. These are:

- **Selection or allocation bias**. Issues that may be relevant to consider, depending on the study design, include the appropriateness of the randomisation technique used and the similarity of test and control groups in factors such as age, gender, socioeconomic status, ethnicity, exercise status, disease or risk factor progression. Study reports should fully describe the participant inclusion or exclusion criteria.

- **Performance and measurement bias**. Issues to consider may include whether the test and control groups were reviewed at the same time intervals and using the same assessment procedures, whether they experienced similar confounding variables, and the 'blinding' technique used (where appropriate). In studies of whole foods or diets it is rarely possible to conceal the intervention from participants or assessors. In retrospective studies, recall bias may be a particular issue as assessment is based on events that took place in the past.

- **Attrition or exclusion bias**. Study reports should identify the completion rate in both test and control groups and reasons for non-completion. Loss to follow-up is likely to be a greater issue in long-term studies.

Potential confounding variables

Confounders are factors associated with a disease, disorder or condition, or with an intervention, which prevent researchers from being able to unequivocally attribute an intervention to an outcome. Studies should attempt to control, as far as possible, potential confounders or to take them into account when analysing and interpreting the study results using appropriate statistical techniques.

Common confounders in studies of diet and health include changes in body mass, exercise level, alcohol intake and smoking cessation. In addition, when one component of a food or diet is altered (for example, total fat content), the levels of other components are also likely to be altered (for example, protein and carbohydrate levels may change). It can therefore be difficult to separate the contribution of one dietary change from that of another.

Inclusion of appropriate controls

Controls are used in experimental or observational studies to take into account the effect of chance or other non-intervention factors on the study outcome. The most common control used in experimental studies is the placebo. However, when the intervention being studied is a food or dietary change, it is difficult to disguise this change with a placebo, because the sensory properties of the diet or food also change. In observational studies the control may be a matched group of participants who do not receive the food in question or who follow a different dietary pattern. Because of the difficulty in developing appropriate controls for food and/or diet studies, the results of these studies may have a greater degree of uncertainty than experimental studies of, say, a new medicine.

Study duration

Study duration should be sufficient to allow development of whatever health effect is being measured and therefore to enable conclusions to be drawn about the significance and sustainability of this outcome. If disease, rather than changes in the level of a biomarker, is the study outcome, studies will need to be of much longer duration.

In experimental studies, time should be allowed at the beginning of the study ('lead-in period'), and between any separate interventions in a crossover trial ('wash out period'), to allow biochemical parameters to stabilise.

The health status of participants in experimental studies should be followed up some time after the study finishes to monitor long-term health effects.

Sample size and statistical analysis

Studies must include sufficient participants, in both the test and control groups, to be able to reach confident conclusions about the outcome, particularly where the magnitude of the outcome is likely to be small or the rate of occurrence of the outcome is expected to be low. However, if there are a number of related studies available for assessment, their results may be able to be pooled in a meta-analysis to obtain a more precise estimate. Sample size calculators are available to aid assessment of the sample size needed to reach a conclusion at a given level of statistical significance; see for example, <www.sch.abs.gov.au>.

All experimental and observational studies should be subjected to rigorous statistical analysis. Without this it is rarely possible to conclude with confidence that a health effect measured in a study has been affected by the study treatment. The statistical analysis should enable some judgement to be made about the significance and magnitude of the outcome measured. Common ways in which the outcome is analysed include use of a P-value, confidence intervals, odds ratios, relative risk, attributable risk, number needed to treat, standardised mean difference or weighted mean difference. Definitions of these terms are provided in the glossary at the end of this paper.

Statistically significant results may be observed in a study that are of no health significance, either for an individual or for the population as a whole. Therefore, the finding of statistical significance in a diet-disease relationship does not automatically imply that a health claim based on this relationship is appropriate.

In addition, the health effect measured may be significant at a population level but not at an individual level; this does not negate the value of the study in substantiating a relationship.

Assessing animal and cellular studies

It is not intended to provide detail in this document about the assessment of the quality of animal and cellular studies, as these will form supporting evidence only and are inadequate on their own to substantiate a diet-disease relationship in humans. Some key issues to consider are:

- In the case of **animal studies**, what was the species studied and is this species a suitable model for the particular relationship under review? Were the doses and form of the component comparable to those used in human studies (animal studies often involve administration of doses in excess of what could be achieved through the diet)? Was the intervention administered at a comparable developmental stage to that at which humans would consume it or at which human disease might be expected?

- In the case of **cellular studies**, was the cell model chosen relevant to the health effect being investigated in terms of diet-disease relationships substantiation? Were the levels of the component studied likely to be comparable to physiological levels that would be achieved through consumption of the component in a food?

2.2.2 Interpreting the evidence – individual studies

As part of the assessment of study quality, or immediately after, it is then necessary to consider the findings of the individual studies. Issues to consider include:

- Does the study demonstrate a relationship between the exposure and the outcome?

- If so, what is the specific relationship? Issues to consider in relation to exposure include identifying the foods or food components associated with the outcome, the required intake and/or frequency of intake and, in the case of components, the specific chemical form and food matrix in which it was administered. Issues to consider in relation to the outcome include the particular outcome (e.g. disease or biomarker change), the magnitude of the outcome, and the relevant population group (consider age, gender, race, socioeconomic status, geographic location and health status of the population studied).

- Under what circumstances does the relationship exist? Any additional dietary or lifestyle factors associated with the outcome should also be identified. For example, the intervention may have only been studied in association with a specific dietary pattern such as a diet containing no more than 30% of energy from fat, or may have been associated with a specific food matrix or with an exercise program.

- Is the study relevant to the proposed claim and can its findings be generalised to the broader population? Was the study conducted in a high risk population that does not reflect the broader population health patterns of New Zealanders and Australians? If the study related to a food or dietary pattern that is unusual in New Zealand or Australia, the study findings are unlikely to be broadly applicable in the context of the total diet in our countries. Consideration of the dietary patterns of Australians and New Zealanders may show that it is unlikely that such an intake could be achieved in practice. In considering applicability to dietary patterns, FSANZ will take account of information on the most recent national nutrition surveys held in New Zealand and Australia and, where necessary, from other available information such as company-specific market research.

- How does the study type and quality affect the weight that can be placed on the study findings in the subsequent assessment of totality? Well-designed experimental studies are likely to carry the greatest weight.

2.2.3 Identify undesirable effects

Undesirable effects associated with an exposure in a study should be identified. These may include adverse health effects, changes in key biomarkers that may predict adverse health effects, or undesirable changes in nutrient intakes as a result of the intervention.

2.2.4 Assessing systematic reviews

Systematic reviews selected to aid substantiation of a diet-disease relationship should be directly relevant to the subject of the proposed high level claim. If a review has been identified that is relevant, some specific aspects of the quality that should be considered include:

- The review should have a clearly stated aim.

- The review should be based on a comprehensive search for evidence that used clearly stated inclusion and exclusion criteria relating to the purpose of the evaluation. The search strategy should be fully described (see Section 2.1 for more detail on literature searches).

- The reviewers should have assessed the effect of publication bias (such as many small studies that have a positive effect compared to only a few well-designed experimental studies that have a negative effect).

- The quality and validity of each cited study should have been reviewed, using a process at least comparable to that outlined in this document. The use of more than one assessor may help to overcome assessment bias.

- The results should be presented clearly and effectively.

- Conclusions reached should be supported by the data and the analysis presented.

Where a meta-analysis is included in a systematic review, the following additional points should be considered:

- Individual studies included in the analysis should have closely related outcomes and measurement techniques so it is reasonable to combine the results.
- Appropriate statistical techniques should have been used to analyse the results.

2.2.5 Example of an assessment of the quality and findings of a study

Table 2 provides an example of a template that can be used to facilitate assessment of the quality and findings of studies available to substantiate a diet-disease relationship proposed as the basis for a high level claim. A range of such templates can be used depending on the claim under evaluation and the type of study being evaluated.
When a large number of studies are available for review, it can be helpful to group studies by study design, by the type of exposure and/or by the outcome being measured.
Please note that the study described in Table 2 is fictitious.

Table 2: Example of a template that can be used to evaluate the quality and interpret the findings of available studies, using a randomised, controlled, unblinded study

Study	Study design and hypothesis	Quantification of intervention and outcome	Subjects, inclusion criteria, duration	Sample and measurement bias, inclusion of controls	Confounders and method of adjustment	Adverse effects noted
Zones et al 2000	Increased consumption of fruits and vegetables to 7 serves/day will result in beneficial changes in plasma lipid concentrations. Randomised, controlled, unblinded, primary prevention experimental trial	Outcome: plasma lipids (HDL-, LDL-cholesterol). Exposure: Diet measured with 2x4-day diet records (wks 0 and 4) and 1x24 hour recall (wk 6). ***Comments***: Outcome measured with appropriate methods in experienced lab with established QC procedures. Exposure: • needed additional diet measurement at end of study; • did not fully define what was included as fruit and vegetable, e.g. inclusion of processed varieties; • bioavailability not relevant.	n=85, 23 US Caucasian males aged 19-69 years, 62 US Caucasian females aged 18-63 years. Inclusion: • eat ≤ 3 serves fruit and vegetables/day; • total cholesterol <6 mmol/L. Exclusion: • use of lipid-lowering medication; • BMI > 30 Duration: 8 week test, plus 2 week run-in ***Comments***: Sample size adequate, but longer duration would have assisted study weight.	Test and control groups did not differ significantly in key inclusion criteria and baseline lipid parameters. Same measurements applied to all participants; staff blinded to exposure status. No differences in drop-out rates between test and control groups. Blinding not possible due to nature of intervention. Control is individuals maintaining ≤ 3 serves per day. ***Comments***: Further detail required on randomisation techniques.	Changes in antioxidant intake. Decreased total & saturated fat intake and increased carbohydrate intake Body mass increase when energy intake not controlled. ***Comments***: No adjustment for confounders undertaken.	Weight gain in some participants when fruit and vegetables were added to existing food consumption (mean gain – 1.0 kg)

Table 2 Continued

<table>
<tr><th>Study (continued)</th><th>Results</th><th>Strength, statistical significance</th><th>Relationship identified</th><th>Context of the relationship

Overall conclusion</th></tr>
<tr>
<td>Zones et al 1998

Experimental study</td>
<td>
<table>
<tr><th>Intake</th><th>Baseline control</th><th>Baseline test</th><th>Wk 4 control</th><th>Wk 4 test</th><th>Adjusted difference* (95% CI)</th></tr>
<tr><td>Fruit (g)</td><td>37 ± 51</td><td>93 ± 118</td><td>55 ± 84</td><td>256 ± 132</td><td>177 (124-225)</td></tr>
<tr><td>Vegetables (g)</td><td>196 ± 87</td><td>228 ± 127</td><td>218 ± 104</td><td>332 ± 149</td><td>104 (45-160)</td></tr>
<tr><td>Fibre (g)</td><td>17</td><td>19</td><td>19</td><td>25</td><td>6.2 (2.1-9.0)</td></tr>
</table>
* Between treatment and control groups at week 4 adjusted for age, sex, baseline value

Plasma lipid concentration (mmol/L) (mean ± SD)
<table>
<tr><th>Lipid</th><th>B'line cntrol</th><th>B'line test</th><th>Wk 8 cntrol</th><th>Wk 8 test</th><th>Adj diff (95% CI)</th></tr>
<tr><td>LDL</td><td>3.17 ± 0.85</td><td>2.95 ± 0.91</td><td>2.97 ± 0.92</td><td>2.82 ± 0.85</td><td>0.02 (-0.29 - 0.25)</td></tr>
<tr><td>HDL</td><td>1.27 ± 0.38</td><td>1.18 ± 0.38</td><td>1.35 ± 0.40</td><td>1.23 ± 0.41</td><td>-0.08 (-.15-.001)</td></tr>
</table>
</td>
<td>No statistically significant relationship found (P>0.05 for all outcomes).</td>
<td>No relationship identified between consumption of an extra 4 serves of fruit and vegetables per day for 8 weeks, and serum LDL- and HDL-cholesterol levels in healthy, non-obese adult males and females.</td>
<td>Healthy adult individuals, males and females, free living, omnivores, Western diet – study applicable to general adult population in Australia & NZ.

Conclusion:
Does not appear to support proposed health claim. However, the identified weaknesses in study design limit the weight that can be placed on this study.</td>
</tr>
</table>

2.3 Evaluating the totality of the evidence – Step 3

A single study can never be considered definitive in understanding a particular diet–disease relationship. Therefore the totality of evidence across all relevant studies must be assessed by a critical appraisal that involves the use of scientific judgement. This approach recognises the collective strength of different study designs, and allows for weaknesses in certain studies to be complemented by strengths in others. Evaluation of the totality of evidence refers to evaluation of all available data of suitable quality relevant to the relationship, including evidence that supports the relationship as well as equivocal evidence and evidence of no effect and/or opposing effects.

Key matters that will be considered in assessing totality include, but are not limited to:

- The range and type of studies retrieved in step 1 will be assessed to determine whether there is any evidence of appropriate level.

- The quality of these studies, determined in step 2 for individual studies, will be assessed overall and greater weight will generally be placed on higher quality studies.

- The overall relationship (if any) between the type and amount of diet, food or component of food and the health effect will be determined. Causality will be assessed and, where possible, the intake–response relationship or required intake of a food or food component will be determined (see Section 2.3.1 for more detail).

- An assessment will be made of whether the health effect (if any) is of a nature or size that would have population health significance.

- Dietary patterns and/or characteristics of the foods or food components are associated with the outcome, or other lifestyle patterns associated with the outcome, will be determined.

- The relevant characteristics of the populations studied will be determined and compared to the target group to whom the claim is directed. The likely sustainability of the claimed beneficial effect in the target population under experimental and every-day circumstances will be assessed.

- An assessment will be made of whether the required dietary pattern or intake of food or food component could be achieved in practice, as part of an appropriate total diet, and the potential impact of this consumption pattern on the health of New Zealanders and Australians generally.

- Areas where there is lack of evidence across studies will be identified and the impact of these deficiencies will be taken into account.

- Consistency of findings across study types and across and within populations will be evaluated to assess the degree of confidence that new evidence is most unlikely to challenge the claim.

- An assessment of the overall strength of evidence in support of the claim will be made and a rating (convincing, probable, possible, insufficient) assigned (see Section 2.3.3 below for more detail).

- Any undesirable effects will be identified and assessed.

As previously stated, evaluation of totality will be undertaken on a claim-by-claim basis and therefore factors not identified above may be taken into account.

2.3.1 Assessing causality

A causal relationship exists when it is shown, with reasonable certainty, that consumption of a diet, food or component alters the probability of developing a health effect, independent of other factors. Different study designs vary in their ability to show a causal relationship, with experimental studies generally the most effective at establishing causality. Where only observational studies are available, causality has to be inferred through the strength of measured associations.

The assessment of causality will generally involve assessment of each of the following key areas:

- Strength of association and/or size of effect: a relationship is more likely to be causal if there is a large difference (for example, in the relative risk) between test and control groups. However, a smaller observed difference may indicate acceptable strength when it was derived from a study with a large number of participants.

- Independence of association: an association or relationship between a treatment and an outcome is independent of other factors when it cannot be explained by any alternative or confounding explanations.

- Intake–response relationship: in theory the magnitude of an observed response is related to the intake of the food or component. These relationships are not always observed in studies of foods or diets, for example because there is a threshold above or below which no detectable change takes place, or because there is a limit to the amount of food people can consume. However it should be possible to determine from a review of all studies, the minimum intake, or frequency of consumption, of a food or component that is needed to achieve the claimed outcome.

- Relationship in time: if a causal relationship exists, the desired outcome should not occur until after the intervention takes place; in other words, the intervention is required to achieve the outcome. If the outcome occurs before exposure to the intervention, it is not possible to conclude that the intervention was responsible.

- Consistency of findings across related studies will be assessed, as consistency of findings provides further weight for a causal relationship existing.

As many as possible of the following should also be considered:

- Reversal of effect: if a food or component has an effect, this effect should be removed when the food or component is removed from the diet, after an appropriate time period.

- Specificity: if a relationship between an intervention and an outcome is specific, only the intervention should cause the outcome and the intervention should not cause another outcome. Specificity may be very difficult to determine in studies of diets and foods.

- Biological plausibility: evidence for a causal relationship is strengthened if there is a known or postulated biological mechanism to explain the relationship. Supporting evidence is likely to be of particular use in assessing plausibility. Lack of knowledge of a biological mechanism to explain an outcome does not necessarily prevent a diet-disease relationship being substantiated.

2.3.2 Relevant characteristics of the diet, food or component, and of the target group

Assessment of the totality of the evidence will indicate the overall circumstances associated with the food or with the population studied that must be in place for the claimed relationship to be substantiated.

For example, studies supporting specific health benefits of fruit consumption may have involved only whole citrus fruit. In this case, use of the claim would only be substantiated for whole citrus fruit, not for other types of fruit such as apples, or for citrus juices. Studies of the relationship of a food component to a health effect may indicate that the relationship is substantiated only when a specific chemical form of the component is used, or when the component is administered in a particular food matrix. A particular consumption amount may also be necessary before the claim can be substantiated.

Relationships may have been substantiated only for particular population groups, characterised by factors such as age (e.g. studies may have included only those over the age of 45 years), gender (e.g. women only), lifestyle (e.g. in association with an exercise regime), health status (e.g. only those with elevated blood pressure) and ethnicity (e.g. Caucasians only).

2.3.3 Classifying the likelihood that the proposed claim is substantiated

Once the overall relationship has been determined, the strength of this relationship will then be assessed. The following classification scheme (which is based on the classification of the World Health Organization (2003)) will be used:

- **Convincing evidence** – there are consistent associations between the diet, food or component and the health effect, with little or no evidence to the contrary. There should be a substantial number of human studies of acceptable quality, preferably including both observational and experimental studies and preferably conducted in different population groups. Any intake–response relationships should be supportive of a causal relationship and the relationship should be biologically plausible. Supporting evidence sources should be consistent with the findings of human evidence.

- **Probable evidence** – there should be a number of acceptable human studies, preferably including both observational and experimental studies. These studies show associations that are either not so consistent, with a number of studies not supporting the association, or the evidence base is insufficient to make a more definite judgement (for example, there are a limited number of studies or the studies are of limited duration, small sample size or with incomplete follow-up).

Some of the evidence may have only recently emerged and still be subject to ongoing research. Mechanistic and laboratory evidence are usually supportive and the relationship should be biologically plausible.

- **Possible evidence** – studies generally indicate a relationship exists, but the studies may be limited in number, level (for example, only supporting evidence sources may be available) or consistency, or may reflect predominantly emerging evidence. There may or may not be supportive mechanistic or laboratory evidence and the relationship should be biologically plausible. More higher quality studies are required to support the tentative relationship.

- **Insufficient evidence** – there are only a few studies, which while generally consistent, are not of appropriate quality to substantiate a relationship. More well-designed research is needed.

While all high level claims will be assessed on a claim-by-claim basis, approval of such claims is likely to require **convincing** scientific evidence so as to offer reasonable certainty that the claim is unlikely to be contradicted in the future by new evidence.

2.4 Summary of the substantiation process

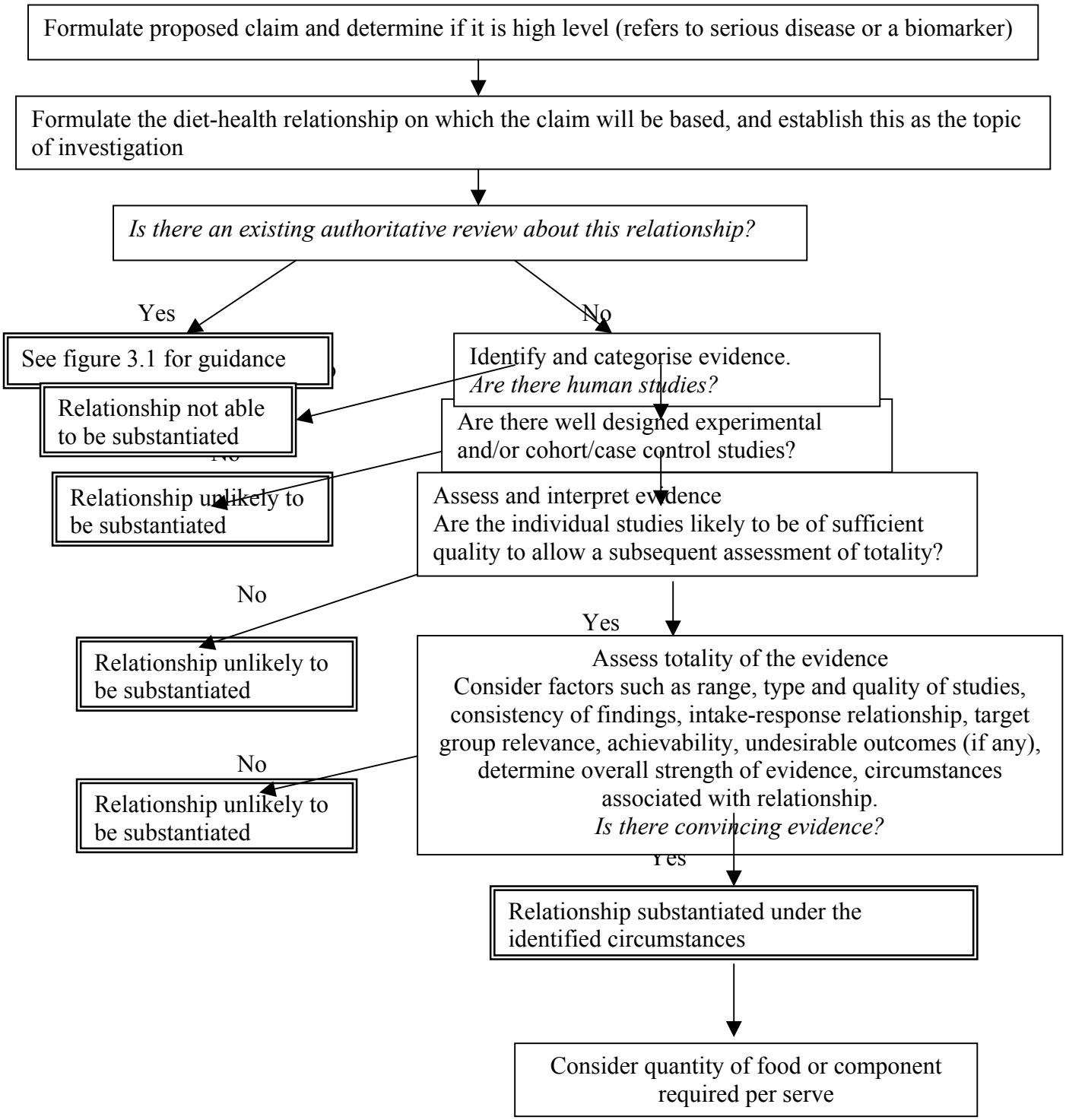
Figure 2.1 presents a schematic representation of the steps involved in substantiating a diet-disease relationship that will be the basis of a proposed high level claim.

2.5 Determining the amount of food or component required per serve

The substantiation process should identify the amount of a food or food component required per day in order for the health effect to be achieved. Consideration then needs to be given to the amount of the food or component that needs to be supplied in a serve of the food before a claim about the relationship is used in the labelling of a specific food.

In determining a reasonable amount of a food or component that should be present in a serve of a food, it is necessary to take into account factors such as the distribution of the food or component in foods, any specific target group needs, the existing requirements of the *Australia New Zealand Food Standards Code* and any safety issues that may be associated with particular levels.

Figure 2.1. Process for substantiating diet-disease relationships that will form the basis of proposed high level nutrition, health and related claims – review based on comprehensive evaluation of evidence



CHAPTER 3: Substantiating a diet-disease relationship proposed to form the basis of a high level claim, based on an authoritative review

In many cases, a proposed high level claim will already have been reviewed by food authorities in countries other than Australia and New Zealand, by Australian and New Zealand government bodies in association with national diet policy statements, or by internationally recognised scientific bodies. Under certain circumstances, these reviews may be able to form the basis of substantiation of a high level claim for use in association with Australian and New Zealand foods.

This chapter sets out the circumstances under which these reviews, referred to as 'authoritative reviews', can be used in the substantiation process.

3.1 Suitable authoritative reviews

Authoritative reviews suitable for use in substantiating a diet-disease relationship that will form the basis of a high level claim (subject to procedures set out in Section 3.2) are:

- Reports of the substantiation of proposed health claims for foods, conducted by overseas governments or international agencies, where these reviews were conducted with a comparable degree of rigour to that proposed by FSANZ for use in Australia and New Zealand (as set out in Chapter 2) and where there have been opportunities for peer review of the reports.

- National diet policy publications such as the current Australian Dietary Guidelines (National Health and Medical Research Council 2003) or the New Zealand Food and Nutrition Guidelines (Ministry of Health 2003) and reports of Australian and New Zealand government reviews into official nutrient reference values.

- Reports of internationally recognised scientific bodies such as the World Health Organization (for example, WHO 2003) and the World Cancer Research Fund, where evaluations have been conducted with a comparable degree of rigour to that proposed by FSANZ for use in Australia and New Zealand (as set out in Chapter 2).

3.2 Use of authoritative reviews

When authoritative reviews are used to streamline the substantiation process, the following steps should also be considered:

- The subject of the authoritative review should be consistent with the diet-disease relationship being assessed for Australia and New Zealand.

- The assessment should have been conducted to standards at least comparable to those established by FSANZ in Chapter 2, i.e. the review should have been based on a systematic and structured analysis of suitable evidence, with an assessment of the totality of evidence and determination of the circumstances under which the diet-disease relationship is substantiated.

- Several pivotal studies cited in the review should be obtained and critically appraised independently to determine the appropriateness of the conclusions reached in the review. Pivotal studies may be those with, for example, the largest sample size, the most relevant subject, the best measurement techniques and the least bias. These 'pivotal' studies are likely to have been given the greatest weight in the review's conclusions.

- A check should be undertaken to ensure no significant sources of evidence were overlooked in the review. If such evidence sources are identified, an assessment should be made of whether or not their omission is likely to have changed the review's conclusions.

- Consideration should be given as to whether the review is of appropriate quality before subsequent steps are undertaken.

- A detailed review of all relevant evidence that has emerged since completion of the report should be undertaken. This evidence should be identified, categorised and analysed according to the standards set out in Chapter 2.

- An assessment should be undertaken to indicate whether the findings of the authoritative review are still valid in the light of any new evidence identified in the previous step.

- The review should be supplemented with consideration of the applicability of the findings to Australian and New Zealand dietary patterns and health status and practices.

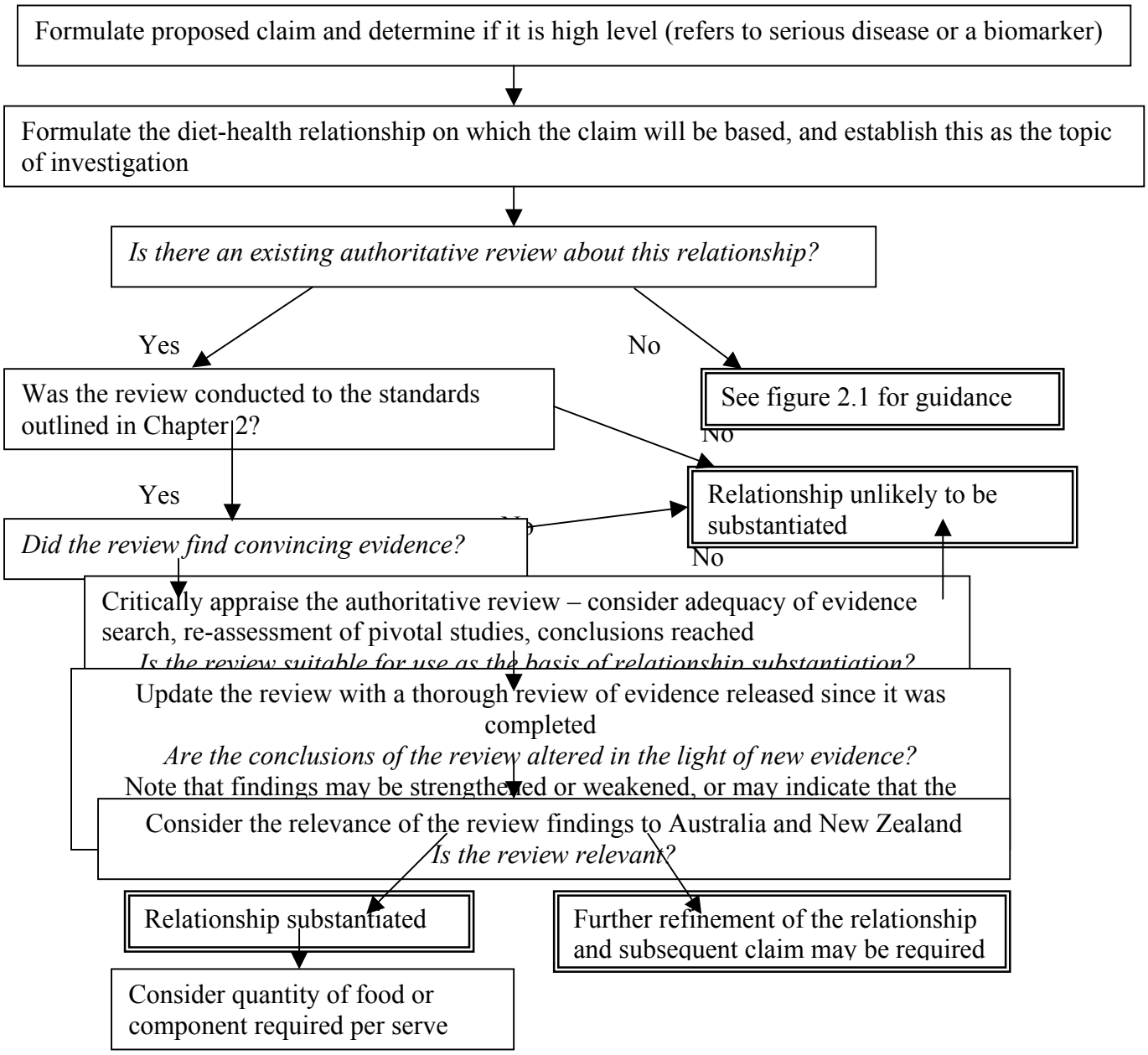
3.3 Summary of the process of substantiation based on authoritative reviews

Figure 3.1 provides a schematic representation of the process outlined in this chapter for substantiating diet-disease relationships intended to form the basis of proposed high level claims.

3.4 Determining the amount of food or component required per serve

While the authoritative review used as the basis for substantiation may have identified a required quantity of food or component per serve, it may be necessary to consider this recommendation in the light of the Australian and New Zealand context, as set out in Section 2.5.

Figure 3.1. Process for substantiating diet-disease relationships that will form the basis of proposed high level nutrition, health and related claims – review based on existing authoritative review



CHAPTER 4: General level claims

General level claims are claims that do not reference a biomarker or a serious disease. General level claims include claims referring to the function of nutrients in the body. Content claims are considered separately in Chapter 5 of this document.

The substantiation principles underpinning general level claims are the same as those for high level claims, but in many instances they may be achieved through simplified processes. There are a number of mechanisms that can be drawn on for substantiating general level claims:

- Selection of a nutrient function statement from the pre-approved list of nutrient function statement prepared by FSANZ. These statements can be used as the basis for appropriate claims without requiring further substantiation of the underlying diet-health relationship. However, wording conditions and criteria for claims must be followed. Further detail is given in Sections 4.1 and 4.2.

- A simplified process, which adheres to general substantiation principles but presents a streamlined process of evidence collection based on use of authoritative, generally-accepted information sources, under some circumstances. This process is described in further detail in Section 4.3.

- Assessment of all available scientific evidence of suitable quality. This option utilises the processes available for substantiation of diet-health relationships for high level claims. Further detail around these approaches is given in Section 4.4.

4.1 General principles for considering evidence to substantiate diet-health relationships for general level claims

There are a number of principles that apply to substantiation of all general level claims:

- all evidence used for substantiation must be relevant to Australians and New Zealanders;

- in cases when appropriate policy documents, reviews and text books are used as the evidence base:

  - attention should be given to any advice relating to the strength of the diet-health relationship or the limitations of the evidence should be considered. For example, where the evidence relates to a particular chemical form or particular matrix, the food bearing the claim should contain that chemical form or be in a comparable matrix;
  - only a totality of evidence that is described in unequivocal terms with a significant degree of confidence with no equally strong opposing, or equivocal evidence should be relied on. Particular attention should be paid to the language describing the strength and quality of the totality of evidence (see below); and

– a search of the literature published since the documents and texts were released should be conducted in order to be satisfied that no major new evidence has emerged that would modify the conclusions reached in these documents. Information on searching scientific literature is provided in Section 2.1.1.

In cases where the above reports do not overtly assess the totality of evidence using FSANZ's evidential classification scheme for high level claims, the language used to describe the authors' confidence in the totality of evidence is likely to be an important indicator of the standard of evidence.

Use of descriptors of evidence or other terms such as: strong, consistent, good quality, overwhelming, confirmed in numerous studies, well conducted or designed studies, provide guidance. On the other hand, reports cannot be taken to provide evidence to substantiate a general level claim when the description of the evidence in support of a diet – health relationship is uncertain, yet to be confirmed, based only on animal or in vitro studies, or is speculative.

Criteria and conditions apply to all general level claims, and must be met in addition to substantiation requirements before claims can be made.

4.2 Substantiating a general level claim based on an accepted diet-health relationship

Many of the nutrient functions described in general level claims are well documented and widely accepted and have, essentially, been previously substantiated in a process analogous to the process FSANZ is using to evaluate high level claims. On this basis, FSANZ has prepared an indicative list of appropriate nutrient function statements that can be used without further substantiation of a diet-health relationship (refer Appendix 2). The list has been prepared by FSANZ taking into account the well understood and generally accepted roles of nutrients in the human body, and is indicative rather than exhaustive.

4.3 Substantiating a diet-health relationship based on authoritative, generally-accepted information sources

Manufacturers may wish to make general level claims based on diet-health relationships that are not included in the pre-approved list (refer Appendix 2). Given that many of these diet-health relationships may also be well documented and widely accepted, and that these claims will not reference serious diseases, it is appropriate to provide a simplified substantiation process for these claims. The simplified process adheres to general substantiation principles but presents a streamlined process of evidence collection based on use of authoritative, generally-accepted information sources.

Authoritative reviews that may be suitable for use in substantiating diet-health relationships that are proposed as the basis of a general level claim are listed below and are further described in the sections referenced.

These five information sources comprise:

- National diet policy publications such as the Australian and New Zealand National Dietary Guidelines and review of Nutrient Reference Values (Section 4.3.1);

- Position papers and scientific reviews conducted by peak[1] medical, nutrition, scientific or public health non-government authoritative organisations from Australia, New Zealand, and, where relevant, overseas countries (Section 4.3.2);
- Reviews conducted by internationally recognised scientific bodies (Section 4.3.3);
- Authoritative, current, science texts presently used in university dietetics courses (Section 4.3.4); and
- Reports of health claims assessed by overseas governments (Section 4.3.5).

4.3.1 Australian and New Zealand diet-related policy documents

In Australia, the National Health and Medical Research Council has published detailed position papers in support of the most recent dietary guidelines. These documents can be accessed at <www.nhmrc.gov.au/publications/nhome.htm>. The New Zealand Ministry of Health publishes comparable documents and other food-related policy statements, including food and nutrition guidelines, which can be accessed at <http://www.moh.govt.nz/moh.nsf/wpg_Index/Publications-Index>. Both countries are currently jointly reviewing Nutrient Reference Values.

When interpreting information contained in dietary guidelines, it is important to bear in mind that the guidelines apply to the total diet and not to a single food within a diet. Where the dietary guidelines documents indicate that evidence for a relationship is weak, this suggests that the relationship is not substantiated to a consistently agreed level.

4.3.2 Information from peak medical, nutrition, scientific or public health authoritative organisations in Australia and New Zealand, and other countries where relevant

Information in position papers and scientific reviews conducted by Australian and New Zealand peak[1] medical, nutrition, scientific or public health non-government authoritative organisations is appropriate as a source of evidence for substantiating general level claims. Similar documents from equivalent overseas organisations may also be drawn upon, providing the content can be demonstrated as being relevant to the Australian and New Zealand population and environments.

Position papers and reviews drawn upon should be free of commercial interests, independently conducted, and preferably peer reviewed. Acceptable scientific reviews should be conducted in accordance with the processes generally drawn on for scientific research, similar to the process outlined in Chapter 2 of this document.

4.3.3 Information in reviews by internationally recognised scientific bodies

Appropriate sources include the reports of the Cochrane Collaboration and the World Health Organization. Acceptable scientific reviews should be conducted in accordance with the processes generally drawn on for scientific research, and be similar to the process outlined in Chapter 2 of this document. The content of reports conducted overseas must be demonstrated as being relevant to the Australian and New Zealand population and environments.

[1] A "peak" organisation is an overarching body that is a lead representative for the interest it represents.
[1]

4.3.4 Information in authoritative, current scientific texts

Authoritative scientific texts suitable for substantiation of general level claims are those of a standard suitable for use in university courses in dietetics.

The Dietitians Association of Australia, in conjunction with the New Zealand Dietetic Association will publish and regularly maintain a list of textbooks that are currently in use in accredited Australian and New Zealand dietetic education programs. These lists will become available at www.daa.asn.au and www.dietitians.org.nz in the near future. Such textbooks are appropriate for use in substantiating general level health claims.

4.3.5 Information from reports of health claims assessed by overseas governments

Reports of the assessment of health claims on foods conducted by overseas governments may be suitable for use as part of the substantiation process for general level claims where:

- the subject of the proposed claim is consistent with that proposed for Australia and New Zealand;
- the assessment was conducted to the standards established by FSANZ for high level claims;
- the evaluation is supplemented with evidence that has become available since the time the overseas assessment was conducted;
- consideration is given to the applicability of the findings to the Australian and New Zealand populations.

4.4 Substantiating a diet-health relationship through assessment of all available scientific evidence of appropriate quality.

In instances where the above resources are not appropriate for substantiating a diet-health relationship for a general level claim, the processes used to substantiate diet-health relationships for high level claims may also be used. This includes the three step review process outlined in Chapter 2 (as described in Section 4.4.1 below), or the streamlined approach based on existing authoritative reviews as outlined in Section 4.4.2 and further described in Chapter 3. In the absence of other data sources, these processes are expected to be appropriate for substantiating general level health claims referring to biologically active substances.

4.4.1 Substantiation based on a comprehensive review of all available evidence

Substantiation of a diet-health relationship underpinning a general level claim may be based on a comprehensive review of all available evidence. The three steps involved in this process are outlined in Chapter 2. This includes determination of the amount of food or food component required per day and per serve of the food in order for the health effect to be achieved.

4.4.2 Substantiating a diet-health relationship based on an existing authoritative reviews

Chapter 3 of this document contains detail on substantiating a diet-health relationship based on an existing authoritative review. A search of the scientific literature published since the texts were released should be carried out to ensure no major new evidence has emerged that would modify the conclusions reached in these documents. Information on searching scientific literature is provided in Section 2.1.1.

CHAPTER 5: Content claims

Content claims are specific types of general level claims for which further streamlining of the substantiation requirements is appropriate. Nutrition content claims include:

- claims about vitamins and minerals, such as 'this food is a source of vitamin C' or 'this food is a good source of iron';
- claims about energy, such as 'this food is a low in kilojoules'
- claims about biologically active substances, such as 'this food contains acidophilus
- claims about components of food, such as 'contains anti-oxidants'
- claims about nutrients, such as 'with fibre'
- claims about ingredients, such as 'source of wholegrains'.

Where applicable, nutrition content claims are referred to as nutrient content claims to indicate the exclusion of biologically active substances.

As content claims do not make reference to any health effect or role of a component, it is not necessary to identify an evidence base to support these relationships. The only substantiation requirements are determination of the level of the component in the food.

5.1 Determining the level of a component present in the food

Foods carrying content claims should contain the component that is the subject of the claim, at the average levels referred to in the claim.

To determine whether a food does indeed contain the stated component content, it is preferable to undertake laboratory analysis to measure the component content in a range of batches manufactured or grown at different times, with the analysis conducted using appropriate and recognised methods of analysis. Samples for analysis should be selected using a structured and validated sampling plan. Laboratories undertaking these analyses should be experienced in that analysis and follow appropriate laboratory quality control procedures.

While food composition tables and tools such as the Nutrition Panel Calculator (available at <www.foodstandards.gov.au>) can be used to determine the level of a nutrient in a food, it is recommended that they are only used with caution when substantiating specific content claims, particularly claims that relate to a multi-ingredient food.

The content should be determined on the form of the food in which it is intended to be consumed. For packaged foods, this will generally be the form suggested in the directions for use included in the label. When determining the nutrient content per serve of a food, nominated serving sizes should be realistic and should not be misleading to consumers.

5.2 Determining whether the food contains component levels required before a claim can be made

Once the level of the nutrient in question has been determined, it is necessary to compare this to any levels stipulated in the Code or related materials. Qualifying and disqualifying criteria that apply to a specific content claim must be met in addition to substantiation requirements before the claim can be made.

APPENDIX 1

Biomarkers in the substantiation of nutrition, health and related claims

What is a biomarker?

For the purposes of draft Standard 1.2.7, a biomarker (or 'biological marker') is:

- a measurable biological parameter which, when present at an abnormal level in the human body, is predictive of the risk of a serious disease.

While outside the scope of this definition, other types of biomarkers (for example, biomarkers of exposure to a food or component) may be encountered when reviewing studies of diet-health relationships.

Why are biomarkers relevant to nutrition, health and related claims?

Biomarkers have two key roles in relation to claims:

- they may be the outcome measures in human studies used to substantiate a diet-disease relationship;
- they may form the subject of a claim (for example, 'Diets low in saturated fats may help maintain healthy cholesterol levels').

Biomarkers as outcome measures may be used in studies for a number of reasons, for example because of a long time period between exposure and clinical manifestations of disease, or for ethical or cost reasons.

What criteria should a biomarker meet?

When biomarkers are used to help substantiate a diet-disease relationship, or as the subject of a claim, the following criteria should be met:

- the biomarker should be a physiological variable, preferably with a known, dynamic response to dietary intervention;
- there should be a biological basis for believing that the biomarker is on the causal pathway between dietary exposure and the health effect;
- the biomarker should be predictive of the health effect; and
- the biomarker should be able to be readily and reliably measured.

Before a biomarker is used to substantiate a health effect or as the subject of a claim, the validity of the biomarker for this purpose should have been rigorously evaluated.

What biomarkers are acceptable for use in claims?

The following biomarkers are acceptable for use in substantiating diet-disease relationships proposed as the basis for high level claims:

Biomarker	Related disease outcome
Serum cholesterol levels (especially total-, and low density lipoprotein cholesterol levels)	Cardiovascular disease
Bone mineral density	Osteoporotic fractures
Blood pressure	Cardiovascular disease

Where can I find more information on biomarkers?

Useful resources on the use of biomarkers in health claims include papers by Health Canada (2000) and Roberts (2002). The PASSCLAIM process (http://europe.ilsi.org/passclaim/) has a series of publications relating to different health effects and these publications include information on biomarkers.

APPENDIX 2

Pre-approved Nutrient Function Statements for Recognised Nutrients

Table 1: Pre-approved statements for recognised vitamins and minerals.

Pre-approved statements for vitamins and minerals are based on the UK Joint Health Claims Initiative (JHCI) list of well-established statements.

Nutrient	Model statement from JHCI
Vitamin D	Vitamin D is necessary for the normal absorption and utilisation of calcium and phosphorus
Vitamin E	Vitamin E is necessary for cell protection from the damage caused by free radicals (such as oxidation of polyunsaturated fatty acids in red blood cell membranes)
Vitamin K	Vitamin K is necessary for normal coagulation (blood clotting)
Thiamin	Thiamine is necessary for the normal metabolism of carbohydrates
Riboflavin	Riboflavin contributes to the normal release of energy from food
Niacin	Niacin is necessary for the normal release of energy from food
Pantothenic acid	Pantothenic acid is necessary for the normal metabolism of fat
Vitamin B_6	Vitamin B_6 is necessary for the normal metabolism of protein
Folate	Folate is necessary for normal blood formation
Vitamin B_{12}	Vitamin B_{12} contributes to normal blood formation
Biotin	Biotin contributes to normal fat metabolism and energy production
Vitamin C	Vitamin C is necessary for normal structure and function of connective tissue (such as that required for normal gums, skin, healing processes, bone and cartilage)
Calcium	Calcium is necessary for normal structure of bones and teeth
Magnesium	Magnesium is necessary for normal energy metabolism
Iron	Iron contributes to normal blood formation
Copper	Copper is necessary for the normal function of the immune system
Iodine	Iodine is necessary for normal production of thyroid hormones
Zinc	Zinc contributes to the normal structure of skin and normal wound healing
Manganese	Manganese contributes to normal bone function
Phosphorus	Phosphorus is necessary for the normal structure of bone and teeth
Selenium	Selenium is necessary for cell protection from some types of damage caused by free radical damage

Table 2: Pre-approved statements for nutrients other than vitamins and minerals

Claims for protein and omega-3 polyunsaturated fatty acids are derived from the Canadian Food Inspection Agency (CFIA) system. The dietary fibre statement is based on background information in the Dietary Guidelines.

Nutrient	CFIA claim	Other claim (derived from the Australian Dietary Guidelines)
Protein	*"helps build and repair body tissues"*	
Docosahexaenoic acid (DHA)	*"DHA, an omega-3 fatty acid, supports the normal development of the brain, eyes and nerves"*	
Dietary fibre		*"contributes to regular laxation"*

GLOSSARY

absolute risk reduction	The difference between the rate of a health effect in the treatment group compared to the control group (National Health and Medical Research Council 1999)
bias	A systematic deviation of a measurement from the 'true' value leading to either an over- or under-estimation of the treatment effect. Bias can originate from many different sources, such as allocation of patients, measurement, interpretation, publication and review of data (National Health and Medical Research Council 2000).
bioavailability	The ability of a food component such as a nutrient to be readily absorbed, distributed and utilised in the body (Elwood 1992).
biological plausibility	The observed association has a known or postulated biological mechanism by which the exposure might reasonably alter the risk of developing the disease (Hennekens 1987).
biomarker	Means a measurable biological parameter which, when present at an abnormal level in the human body, is predictive of the risk of a serious disease.
blinding (or masking)	The process used in epidemiological studies and clinical trials in which the observers and the subjects have no knowledge as to which treatments subjects are assigned. It is undertaken in order to minimise bias occurring in patient response and outcome measurement. In single-blind studies only the subjects are blind to their allocations, whilst in double-blind studies both observers and subjects are ignorant of the treatment allocations (National Health and Medical Research Council 2000).
case-control study	Patients with a certain outcome or disease and an appropriate group of controls without the outcome or disease are selected (usually with careful consideration of appropriate choice of controls, matching etc) and information is obtained on whether the subjects have been exposed to the factor under investigation (National Health and Medical Research Council 2000).
case series	The intervention has been used in a series of patients (may or may not be consecutive series) and the results reported. There is no separate control group for comparison (National Health and Medical Research Council 2000).
clinical significance	The quality of a study's outcome that convinces physicians to modify or maintain their current practice of medicine. The assessment of significance is usually based on the size of the effect observed, the quality of the study on which it is based and the probability that the effect is a true one (Therapeutic Goods Administration 2001).
cohort study	Participants are classified on the basis of the presence or absence of exposure to a particular factor and followed for a specified period of time to determine the development of disease in each exposure group (*American Journal of Clinical Nutrition*: 69 1999)
comparative study	A study including a comparison or control group (National Health and Medical Research Council 2000).
component	A chemical or biological substance contained in, or extracted from, a food. It may include a nutrient or other biologically active substance.

concurrent controls	Controls receive the alternative intervention and undergo assessment concurrently with the group receiving treatment. Allocation to the intervention or control is not random (National Health and Medical Research Council 2000).
confidence interval	An interval within which the true value is expected to lie with a given degree of certainty (usually 95%) (National Health and Medical Research Council 1999).
control	In experimental or observational studies, a person or group that does not receive the intervention under evaluation. Instead, that person or group receives a placebo or no intervention. In a case-control study, the control is the person in the comparison group without the disease or outcome of interest (Therapeutic Goods Administration 2001).
correlational study (or ecological study)	Where the rate of disease is compared across different populations (United States Food and Drug Administration 1999). An example of this would be a study of cancer rates in different states (Last 1995).
crossover trial	A research design where subjects receive a number of treatments in sequence. Generally this means each trial participant receives both the intervention and the control, with or without a 'washout' period between treatments.
cross-sectional study (or prevalence study)	Where both exposure and outcomes are measured at the same time (National Health and Medical Research Council 2000).
dose–response	A gradient of response associated with the degree of exposure (Hennekens 1987).
ecological study (or cross population study)	A study in which those analysed are populations or groups rather than individuals.
epidemiology	Study of the distribution and determinants of health-related states or events in specified populations.
general level claim	means – (p) a nutrition content claim; or (p) a health claim that does not, directly or indirectly, refer to a serious disease or a biomarker.
health effect	means – (a) a measure of the impact of a substance on the healthy functioning of the human body; or (b) a measure of the impact on the health or performance of a specific population, where the impact is associated with a particular dietary intake.
high level claim	means a health claim that directly or indirectly refers to a serious disease or a biomarker.
level of evidence	Study designs are often grouped into a hierarchy according to their validity, or degree to which they are not susceptible to bias. The hierarchy indicates which studies should be given most weight in an evaluation (National Health and Medical Research Council 2000).
meta-analysis	Results from several studies, identified in a systematic review, are combined and summarised quantitatively (National Health and Medical Research Council 2000).
non-randomised cross-over design	Patients are measured before and after introduction or withdrawal of the intervention and order of introduction and withdrawal is not randomised (National Health and Medical Research Council 2000).
number needed to treat	The number of patients who need to be treated to prevent one undesirable outcome (Khan et al. 2001).
odds	The ratio of the number of people in a group with an event to the number without an event.
odds ratio	The ratio of the odds of an event in an intervention group to the odds

	of an event in a control group. An odds ratio less than one indicates that the intervention reduced the odds of that outcome.
observational studies (or epidemiological studies)	Are usually undertaken by investigators who are not involved in the clinical care of the patients being studied and who are not using the treatment under investigation in this group of patients (National Health and Medical Research Council 2000).
p-value	Probability that the observed results of a study could have occurred by chance (Khan et al 2001).
placebo	An inactive substance or treatment that supposedly has no treatment value, that is given to trial participants as a control against which to compare the effects of the test food and/or food component.
pre-test post-test study	A study design where a group is studied before and after an intervention and serves as its own control. Interpretation of the result is problematic as it is difficult to separate the effect of the intervention from the effect of other factors (National Health and Medical Research Council 2000).
randomised controlled trial	An experimental comparison study in which participants are allocated to treatment/intervention or control/placebo groups using a random mechanism. Participants have an equal chance of being allocated to an intervention or control group and therefore allocation bias is eliminated (National Health and Medical Research Council 2000).
randomised cross-over trial	Patients are measured before and after exposure to different treatments (or placebo), which are administered in a random order (and usually blinded) (National Health and Medical Research Council 2000).
relative risk (risk ratio)	The ratio of the proportions in the intervention group and in the control group who experience the health effect (Khan et al. 2001).
risk difference (attributable risk)	The difference in the proportion of a sample with the outcome, between the treatment and control groups. If the risk difference is negative, this suggests the treatment reduces the risk (National Health and Medical Research Council 1999).
serious disease	means a disease, ailment, defect or condition that is not appropriate to diagnose, treat or manage without consultation with or supervision by a health care professional, and includes obesity, but does not include overweight.
statistical significance	The probability that an event or difference occurred by chance alone. It does not indicate whether the difference is small or large, or of clinical significance.
surrogate outcome or endpoint	See biomarker

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