

Supporting document 8

The substantiation process for food-health relationships

P293 – Nutrition, Health & Related Claims

Substantiation at a glance

- (i) The association between a food or property of a food and the health effect must be consistent across studies.
- (ii) The evidence must comprise a number of high quality studies including some experimental studies in humans.
- (iii) The evidence must support a food-health relationship that is biologically plausible.
- (iv) There must be a causal relationship in which it is shown that consumption of a food or property of a food causes the health effect independent of other factors.
- (v) To assess causality and the weight of evidence, most weight is given to well-designed experimental studies in humans.

1 Introduction

This document outlines the principles and approaches for evaluating the evidence that applies to food-health relationships.

A food-health relationship refers to the link between consumption of a food/property of food and a health effect that will form the basis of a general level or high level health claim.

In the context of this document, *substantiation* is defined as the process of evaluating the evidence for a food-health relationship.

2 The substantiation process

The key objective of the substantiation process is to determine whether the evidence for the relationship between a food or property of a food and a health effect is robust. Due to the complexity of the evidence and scientific approaches required in the substantiation process, it will need to be undertaken by a suitably qualified person with expertise in the critical assessment of evidence.

The substantiation process described in Schedule 6 of Standard 1.2.7, based on a systematic review¹, must be used to determine whether a causal relationship between a food or property of a food and the health effect can be established. One of two approaches can be used:

- assessment of all relevant studies in humans through conducting a systematic review that includes all the elements in Schedule 6; or
- updating an existing systematic review.

Both approaches are essentially the same as they involve critical appraisal and quality assessment of the evidence to determine if a food-health relationship is established. Food businesses are able to use an existing systematic review provided:

- elements 1-6 of Schedule 6 are applied to any relevant scientific data that were not included in the existing review
- the conclusions from the new scientific data are incorporated with the conclusions from the existing systematic review.

Irrespective of the approach used, the relevance of the food-health relationship to the Australian and New Zealand populations must be taken into account. For example, it is important to consider whether the findings from studies done in other countries can be extrapolated to Australia and New Zealand.

A systematic review should demonstrate the following features:

- a. **Systematic Approach:** a methodical, consistent approach to examining the relevant studies.
- b. **Transparency:** literature search strategies, selection and evaluation are fully disclosed and can be replicated.
- c. **Comprehensiveness:** all evidence pertaining to the food-health relationship is captured, including evidence in favour and not in favour of the food-health relationship.
- d. **Evidence in humans:** a food-health relationship cannot be established from animal and *in vitro* research alone. Studies in humans are essential.
- e. **Causality:** demonstration of causality is based on the quality and quantity of direct evidence which investigates the food-health relationship. Indirect or mechanistic evidence is not sufficient by itself.
- f. **Temporality:** evidence that the putative cause (food/property of the food) in a food-health relationship precedes, in time, the presumed health effect is essential in establishing causality.

3 Key elements in the substantiation process

Described below are the key elements of a well conducted substantiation process to determine if a food-health relationship has been established. The key elements align with the required elements for a systematic review in Schedule 6 of Standard 1.2.7, but more detail is provided here.

1 Description of the proposed food-health relationship

- It is essential to first describe the proposed relationship between a food or property of a food and the health effect, by clearly stating:

¹ Greater detail about the requirements of a systematic review to substantiate a food-health relationship will be included in the *Application Handbook* and in an accompanying guidance document.

- a. The food or property of the food, of interest.
- b. The specific health effect, including the outcome measure(s)/biomarkers used to assess the health effect in humans (e.g. 'digestive health' is not measurable, frequency of laxation is measurable).

2 Search strategy for scientific evidence

- A comprehensive, transparent, systematic and reproducible review of the available evidence that is of potential relevance to the proposed food-health relationship is an essential component of the substantiation process. To do this, the search terms and inclusion and exclusion criteria must be documented.
- Unpublished material can be included as well as articles published in peer-reviewed scientific journals.
- An existing systematic review may be used as a starting point for a systematic review of the evidence. This approach will reduce the search to be undertaken by limiting the search to encompass only studies not included in the existing review.
- An existing systematic review² would typically include all the elements of the systematic review described in Schedule 6.
- Animal and *in vitro* studies may be useful additional material for describing biological plausibility. However, they alone are not sufficient to substantiate a food-health relationship.

3 Identification of relevant studies

- The final list of studies to be considered in the systematic review should be identified by filtering the retrieved studies using inclusion and exclusion criteria. The dossier of scientific evidence for the food-health relationship must include a list of identified studies and all relevant human studies, and should include any supporting evidence from animal and *in vitro* studies.

4 Tabulation of included studies

- Relevant data from each of the included studies must be presented in tabulated form. Original studies should be organised according to study types in one or more tables.
- Tables must be constructed based upon, but not limited to, the following major headings: study reference; study design, objectives, sample size, participant characteristics, amount consumed, duration, loss to follow-up, compliance, methods used to measure the food or property of food and health effect, statistical analyses, results, confounders and method of adjustment, adverse effects and conclusions.

² An existing systematic review should specify its search strategy, quality appraisal and analytical methods. Many existing systematic reviews also give a grade or score to the evidence summary statements using systems such as the GRADE system or the NHMRC A-D system. These scores indicate the degree of certainty in the relationship being described.

An existing systematic review suitable for substantiation of a food-health relationship includes, but is not limited to, the following examples:

- Scientific reviews e.g. The Cochrane Database of Systematic Reviews;
- Reports of internationally recognised scientific bodies, eg. World Health Organization (WHO), the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR)
- Systematic reviews by the NHMRC

5 Evaluation of study quality

- Evaluation of study quality can discriminate between studies that have a high or low internal validity and risk of bias. A quality appraisal tool can help in the critical appraisal of individual studies and it can help identify studies that are more likely to generate unbiased results (i.e. higher quality studies).
- Summary tables (e.g. total, by high/low quality) can be used to provide an overall synopsis of the relevant information from all the studies included in a standardised and objective manner.

6 Assessment of the evidence

- Consideration should be given to the following key elements when assessing the overall evidence:
 - whether the studies support a consistent association of the proposed food-health relationship
 - whether there is a causal association between the consumption of the food or property of the food and the health effect independent of other factors (with most weight given to well-designed experimental studies in humans)
 - whether the proposed food-health relationship is biologically plausible
 - whether the amount of the food or property of the food to achieve the health effect can be consumed as part of the normal diet of the Australian and New Zealand populations.

7 Determination of whether the food-health relationship is established

- The totality and weight of evidence will determine if a food-health relationship can be established.
- The weight of evidence is a method for combining evidence in support of a hypothesis, such as a food-health relationship. The method will always place greater weight on the results of higher quality studies when drawing conclusions.
- Whether a food-health relationship is sufficiently robust so that it is unlikely to be reversed by an additional well conducted high quality study should also be considered.

8 Conclusion

- A concluding statement is required to articulate the relationship between the food or property of food that has been established along with the amount of the food or property of food required to achieve the health effect and whether this amount is likely to be consumed in the diet of Australia and New Zealand populations or the target population, if relevant.
- If an existing systematic review is used, the conclusions should incorporate any additional relevant scientific data with the existing systematic review.

4 Degree of certainty

To determine whether a food-health relationship is established, consideration needs to be given to the weight of evidence and whether the evidence for the relationship underpinning the health claim is robust and, therefore, unlikely to be overturned by another well conducted study. This degree of certainty applies to food-health relationships underpinning either general level or high level health claims.

The weight of evidence approach has routinely been used by many governments and non-government agencies to support their decision-making framework. To ensure a transparent and consistent application of this approach, various agencies describe not only the relationship of interest but also provide an explicit expression of the degree of certainty in the relationship. Unfortunately, there appears to be very little consistency in terminology for grading scientific evidence but there are typically 4-5 graded tiers of evidence with commensurate degrees of certainty. Table 1 shows a number of examples.

Table 1: Grading of scientific evidence by selected agencies³

NHMRC	TGA	WCRF	WHO	Cochrane
A- Excellent: body of evidence can be trusted to guide practice.	A- body of evidence strongly supports listable indication.	Convincing	HIGH (++++)	No grading scheme
B- Good: body of evidence can be trusted to guide practice in most situations.	B- body of evidence broadly supports listable indication.	Probable	MODERATE (+++)	
C-Satisfactory: body of evidence provides some support for recommendations but care should be taken in its application.	C- body of evidence supports listable indication with qualification.	Limited evidence- suggestive	LOW (++)	
D- Poor: body of evidence is weak and recommendations must be applied with caution.	D- body of evidence that is inconclusive.	Limited evidence- no conclusion	VERY LOW (+)	
	E- body of evidence that does not support listable indication.	Substantial effect on risk unlikely		

From these examples, the terms ‘A’, ‘convincing’ and ‘High’ indicate a high degree of certainty. Accordingly, FSANZ concludes that the following terms from agencies are equivalent to FSANZ’s concept of the required degree of certainty that a food-health relationship underpinning a health claim is robust and unlikely to be overturned by another well conducted study.

- NHMRC–General: Grade A
- NHMRC–Dietary Guidelines: Grade A (also referred to as “convincing”)
- TGA–Grade A, Strongly supports listable indication
- WHO–High (++++)
- WCRF–Convincing

³ NHMRC: National Health and Medical Research Council, Australia

TGA: Therapeutic Goods Administration, Australia

WCRF: World Cancer Research Fund

WHO: World Health Organization

Cochrane Reviews are systematic reviews of primary research in human health care and health policy, and are internationally recognised as the highest standard in evidence-based health care.

Note that these grades apply only to the relationship being graded and not to any other sentence in the surrounding text. Where the degree of certainty is low (e.g. NHMRC – Dietary Guidelines: Grade B), the evidence could not be used to underpin a health claim. However, the existing systematic review could be a useful starting point for updating the evidence to determine whether a higher degree of certainty can be reached.

Food regulatory agencies such as the USA Food and Drug Administration (USFDA) and the European Food Safety Authority (EFSA) use specific terminology to express the degree of certainty. USFDA refers to 'Significant Scientific Agreement' (SSA) to underpin the approval of the food-health relationship/health claims. EFSA states that a food-health relationship is 'established' to underpin their approval.

5 International comparison of approaches used to establish a food-health relationship

In Australia and New Zealand, general and high level health claims will be subject to a substantiation process whether pre-approved (general and high level health claims) or self-substantiated (general level health claims only). In the European Union (EU), all health claims must be pre-approved. In the USA and Canada, only high level health claims require pre-approval.

In the EU, EFSA provides an opinion based on the totality and weight of scientific evidence. This requires consideration of the extent to which:

- the food/constituent is defined and characterised
- the claimed effect is defined and has a beneficial physiological effect in humans
- a cause and effect relationship is established between the consumption of the food/constituent and the claimed effect (for the target population under the proposed conditions of use). This is determined by considering the strength, consistency, specificity, dose-response and biological plausibility of the relationship. Human data are central to this consideration. The relationship is either established or not established.

In the USA, there are two levels of claims (high level health claim and qualified) but only high level health claims are applicable for comparison to Australia and New Zealand. The USFDA evaluates high level health claims based on SSA of the food-health relationship. SSA encompasses consensus, but not necessarily unanimous agreement among qualified experts in the field. The evaluation considers the totality of evidence including: the study type, methodological quality, sample size, consistency of the findings and relevance of the scientific evidence to the USA or target population. An SSA assessment means that the validity of the relationship is not likely to be reversed by new and evolving science, although the exact nature of the relationship may need to be refined. To make an SSA determination, the evidence must be publicly available.

In Canada, the validity of the supporting evidence for a high level health claim is assessed on the basis of guiding principles. The assessment considers the totality of evidence, study quality, causality, relevance, generalisability and feasibility of consumption of an effective dose by the target population, and a systematic and transparent approach. High quality, original research in humans that measures the food and health effect is given the most weight in considering whether there is an association between the food exposure and health effect.

As shown in Table 2 below, there is a similarity in the approach taken to establish a robust food-health relationship among four international jurisdictions (Australia and New Zealand, USA, Canada and EU). Similarly, the degree of certainty which surrounds these food-health relationships is also comparable.

Table 2: Comparison of substantiation process used to establish food-health relationships among four international jurisdictions

	ANZ	EU	Canada	USA
Characterisation of food		yes		
Systematic collation of evidence	yes	yes	yes	Not specifically stated – only publicly available evidence is considered
Documented process for collation of evidence	yes	yes	yes	
Comprehensive collation	yes	yes	yes	
Human studies required	yes	yes	yes	yes
Quality assessment	yes	Study design	yes	yes
Consistency across studies	yes	yes	yes	yes
Causality	yes	yes	yes	yes
Biological relevance	yes	yes	yes	
Feasibility of consuming effective amount	yes	yes	yes	If no, reflected in claim wording
Animal studies only used to establish mode of action	yes	yes	yes	yes