Trends in Food Science & Technology 69 (2017) 315–323

Contents lists available at ScienceDirect

Trends in Food Science & Technology

journal homepage: http://www.journals.elsevier.com/trends-in-food-science-and-technology

Health claims made on food in the EU: The edge between scientific knowledge and regulatory requirements

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ARTICLE INFO

Article history:
Received 17 November 2016
Received in revised form
22 December 2016
Accepted 30 January 2017
Available online 31 January 2017

Keywords:
Food
Health claims
Legal framework
Scientific assessment
Substantiation
Target population

ABSTRACT

Background: The Health Claims Regulation entered into force in January 2007. The European Food Safety Authority (EFSA) has evaluated more than 3000 health claims since then, but EFSA's responsibilities in this area and the extent to which its scientific assessments are in accordance with the current legal framework are still not fully understood.

Scope and approach: The scope of this paper is to provide insight on the use of scientific knowledge in the area of nutrition for the substantiation of health claims made on food. The reasons why a positive evaluation by EFSA may not be sufficient for the authorisation of a health claim are also discussed. Concrete examples are used to illustrate these aspects.

Key findings and conclusions: How health claims are scientifically assessed by EFSA has not been fully understood by stakeholders yet. Thorough knowledge on how EU legislation translates into scientific requirements for substantiation is essential to building successful applications. Other factors which may play a role in the authorisation of a claim and which are not evaluated by EFSA, such as the legal status of the food/constituent, its safety, or the compatibility of the claim with national and international dietary recommendations, should also be considered early in the process. EFSA is committed to providing further guidance to stakeholders on how to prepare applications for authorisation by making use of its 10 years of experience on the scientific evaluation of health claims made on food.

1. Introduction

Regulation (EC) No 1924/2006 on nutrition and health claims made on foods (hereafter, the Health Claims Regulation, HCR) entered into force in January 2007 and applies from 1 July 2007. As of 9 June 2016, the European Food Safety Authority (EFSA) has evaluated about 2849 function claims under Article 13(1), 137 claims under Article 13(5), and 121 claims under Article 14, of which 41 fell under the scope of disease risk reduction claims.

The Article 13(1) procedure, originally meant as an evaluation of well-established functions of nutrients and other substances, proved to be challenging for all parties involved. On the one hand, the scientific requirements for the substantiation of health claims to be applied by EFSA had not been spelt out at the time food business operators (FBOs) had to submit the scientific evidence in support of their claims. On the other hand, several claims used for consumer communication were not framed to allow a scientific evaluation, and the procedure did not allow direct communication between EFSA and FBOs to better define such claims.

Nevertheless, the evaluation of health claims under Article 13(1) was an intense learning experience for EFSA, FBO and risk managers. It helped to clarify the criteria applied by the EFSA expert Panel on Dietetic Products, Nutrition and Allergies (NDA Panel) for the evaluation of claims, the criteria that claims had to comply with to allow a scientific evaluation, and some other aspects which risk managers could consider in the authorisation process. The result was a list of authorised, and a list of rejected, health claims (European Commission, 2016), and a series of guidance documents aiming to help FBOs in preparing applications under Articles 13(5) and 14 (EFSA, 2016a). Still, stakeholder meetings (EFSA, 2014a), public consultations on guidance documents (EFSA, 2016b) and direct communication between EFSA and FBOs during the life cycle of applications revealed some misunderstanding with respect to EFSA's remit, and questioned the extent to which the scientific assessments of the NDA Panel were in accordance with the legal framework set by the HCR.

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http://dx.doi.org/10.1016/j.tifs.2017.01.005
0924-2244/

Acronyms

CHD	Coronary Heart Disease
EFSA	European Food Safety Authority
FBOs	Food Business Operators
HCR	Health Claims Regulation
NDA Panel	Expert Panel on Dietetic Products, Nutrition and Allergies

The most recently published General scientific guidance for stakeholders on health claim applications (EFSA NDA Panel, 2016a) summarises 10 years of experience in this area. It goes some steps beyond the previous guidance issued by the NDA Panel and spells out the scientific reading of a legal text which delineates a clear separation between the scientific assessment of health claims and their authorisation.

This paper aims to provide further insight into when, how, and why sound scientific knowledge in the area of nutrition can (or cannot) be used for the scientific substantiation of health claims made on food within the boundaries of the current legal framework. It also aims to explore why, and in which circumstances, a positive evaluation by EFSA may not be sufficient to allow the authorisation of a claim for use in the Community.

2. Legal context

The legal basis for EFSA's scientific evaluation of health claims is the HCR, which is consistent with the broader legal framework outlined by the general principles and requirements of food law (Regulation (EC) No 178/2002) and the general provisions relating to the labelling, presentation and advertising of foodstuffs (Directive 2000/13/EC; Regulation (EU) No 1169/2011).

Under the HCR, medicinal claims on food (i.e. claims attributing to any food the property of preventing, treating or curing a human disease) are forbidden, whereas reduction of disease risk claims (i.e. any health claim that states, suggests or implies that the consumption of a food category, a food or one of its constituents (hereafter generically denoted as food/constituent) significantly reduces a risk factor in the development of a human disease) are allowed. In addition, food information provided on a voluntary basis shall not be ambiguous or confusing, shall not mislead the consumer, and shall be based on relevant scientific data. Nutrition and health claims are among the voluntary information which FBOs can use in commercial communications to help consumers in making informed food choices. Thus, any health claim made on foods shall be based on relevant scientific data (i.e. on a scientific assessment of the highest possible standard, as specified in the HCR) so as not to mislead the consumer. The HCR does not apply to claims which are made in non-commercial communications, such as dietary guidelines, advice issued by public health authorities and bodies, or scientific publications (Recital (4)).

Health claims, therefore, may be made on commercial communications to inform consumers on the relationship between the consumption of a food/constituent and a specific health benefit if: a) they do not attribute medicinal properties to a food, b) are based on a scientific assessment of the highest possible standard, and c) do not mislead the purchaser.

3. Translation of regulatory requirements into scientific requirements

The scientific assessment of health claims made on food needs an ad-hoc, well-defined and scientifically sound framework, the characteristics of which are not defined in the legal texts regulating the use of such claims. Nevertheless, literal readings of the HCR have been used (i.e. in public consultations on guidance documents, in stakeholder meetings, in the media) to question the scientific reasons given by the NDA Panel for favourable and unfavourable opinions, which indicates that a common understanding of how health claims are scientifically assessed by EFSA has not yet been reached.

This section addresses how the NDA Panel, in consultation with the European Commission, has interpreted the regulatory requirements for health claims made on food, and how this interpretation has been translated into scientific requirements for substantiation (Table 1).

3.1. The purchaser cannot be mislead

European legislation prohibits the use of information that would mislead the consumer in particular as to the characteristics of the food, its effects or its properties (Table 1). In other words, a consumer buying a food product which claims a particular health benefit should have a reasonable chance of obtaining such benefit when consuming the product on a regular basis in the recommended amounts.

From a scientific point of view, causality should be established between the consumption of a food/constituent and the claimed health benefit in the target population (i.e. the consumer buying the food to obtain the benefit) under the proposed conditions of use (i.e. in the recommended amounts and pattern of consumption). Human intervention studies, and in particular randomised controlled trials at low risk of bias, provide the best possible evidence on causality. Questions may remain on whether the effect observed in a (generally small) study group under controlled conditions would also occur on each and every free-living consumer. Indeed, people respond differently to different stimuli, including food, and free-living individuals may be eating the food less frequently or in lower amounts than they should to obtain the effect. Despite these limitations, this type of study design is the best placed to answer the question which matters: would the effect generally occur if the food/constituent is consumed by the target population in the recommended amounts?

Observational prospective cohort studies investigating the relationship between food consumption and the risk of disease have been published in high-quality scientific journals. These studies, often enrolling thousands of individuals and running for several years, have informed dietary guidelines and recommendations for the general population with the aim of maintaining good health in the long term. Some aspects of these guidelines are hardly disputed, such as the frequent consumption of fruits and vegetables. It may seem unreasonable, then, not to consider such prospective cohort studies as evidence to substantiate health claims, for example, on fruit, but there are at least two good reasons why this might be the case. First, people eating high amounts of fruits and vegetables may be at lower risk of disease than individuals consuming less fruits and vegetables for reasons other than their fruit and vegetable consumption, for example because they might also be physically more active, smoke less, or because they differ from their counterparts in other characteristics which affect the risk of disease and are unknown to the investigators. In other words, these studies do not allow causality to be established between the consumption of fruits and vegetables and disease risk.

Table 1
Scientific interpretation of regulatory requirements in the area of health claims made on food, and its translation into scientific requirements for substantiation.

Legislation	Regulatory requirement	Scientific interpretation	Scientific requirement
HCR, Recital (3), Article 3(a)	The use of nutrition and health claims shall not be false, ambiguous or misleading. Generally prohibits the use of information that would mislead the purchaser	The beneficial effect of consuming the food/constituent should be observed in the target population for whom the claim is intended Causality between the consumption of the food/constituent and the claimed effect should be established	Human studies on the relationship between the consumption of the food/constituent and the claimed effect (in the target group under the proposed conditions of use) High-quality RCTs are at the top of the hierarchy of evidence for the scientific substantiation of health claims
HCR, Recital (4)	This Regulation […] should not apply to claims which are made in non-commercial communications, such as dietary guidelines or advice issued by public health authorities and bodies, or non-commercial communications and information in the press and in scientific publications	The purpose and scope of dietary guidelines and other advice issued by public health authorities and bodies, of press articles and scientific publications, is different to that of health claims made on particular food products for commercial communication, and therefore they are not subject to the type of scientific assessment which is required for health claims	The body of evidence on which national food-based dietary guidelines and/or nutrient goals and recommendations for the general population are based may not be sufficient or even appropriate for the substantiation of specific health claims. The same applies to scientific articles published in peer-reviewed journals
HCR, Recital (23)	Health claims should only be authorised for use in the Community after a scientific assessment of the highest possible standard	It is generally accepted by the scientific community that some individual nutrients are essential to maintain one or more body functions, whereas other food/constituents are not. Therefore, different criteria are applied for the evaluation of claims based on the essentiality of nutrients and the evaluation of other claims to achieve, in both cases, a scientific assessment of the highest possible standard	The essentiality of a nutrient is determined by knowledge of its unique ability to reverse clinical signs and symptoms of deficiency and/or by knowledge of its essential mechanistic role in metabolic functions, as well as by the fact that it cannot be synthesised by the body, or cannot be synthesised in amounts which are adequate to maintain normal body function(s). This information cannot be obtained from RCTs
HCR, Article 10.3	Reference to general, non-specific benefits of the nutrient or food for overall good health or health-related well-being may only be made if accompanied by a specific health claim included in the lists provided for in Article 13 or 14	Health claims should refer to a specific function of the body (Art.13) or to a beneficial alteration of a risk factor for disease (Art.14)	Changes in the outcome of interest (body function, risk factor, health/disease outcome) should be well defined and measurable *in vivo* in humans by well accepted methods
HCR, Recital (3), Article 14.1	Food information shall not attribute to any food the property of preventing, treating or curing a human disease, nor refer to such properties (Directive 2000/13/EC, Article 2.1(b); Regulation (EC) No 1169/2011, Article 7.3)	The target population for a health claim cannot be subjects with a disease	Studies in patients can only be used: *As main evidence* if the results can be extrapolated to the target population *As supportive evidence* if studies showing an effect of the food/constituent in the target population are also available
HCR, Article 2	'Reduction of disease risk claim' means any health claim that states, suggests or implies that the consumption of a food category, a food or one of its constituents, significantly reduces a risk factor in the development of a human disease	Health claims cannot refer directly to the reduction of the risk of a disease, and thus a (biologically plausible) risk factor for disease should be identified. However, studies on disease incidence provide the strongest evidence for a causal relationship between the consumption of a food/constituent and disease risk	Studies on disease incidence are required for the substantiation of reduction of disease risk claims, unless there is evidence that the modification of the risk factor directly modifies the risk of disease

Second, fruits and vegetables are a very heterogeneous food category, and thus it would be highly uncertain whether, and the extent to which, fruit alone (or the particular type of fruit bearing the claim) may contribute to the association. Therefore, a body of evidence which is considered sufficient to encourage consumption of fruits and vegetables at a population level may not be sufficient, or even appropriate, to inform the individual consumer about the specific health benefits of a particular type of fruit in commercial communication without being misled.

3.2. Scientific assessment of the highest possible standard

The HCR requires a scientific assessment of the highest possible standard by EFSA for all health claims made on food prior to authorisation and, as correctly pointed out by some stakeholders during the public consultation on the revised guidance document for applicants (EFSA, 2016b), it does not distinguish between essential nutrients and other substances with respect to the scientific standards on which health claims should be based. This does not imply, however, that all claims should be based on the same type of evidence. Under this framework, it is up to the assessor (the EFSA's NDA Panel) to establish, on a case-by-case basis, the scientific evidence required to reach such standard.

Indeed, the type of scientific evidence for the substantiation of health claims related to well-established functions of essential nutrients cannot be the same as the type of scientific evidence for the substantiation of health claims related to non-established functions of essential nutrients or to other substances. As explained in the General scientific guidance for stakeholders on health claim applications (EFSA NDA Panel, 2016a), the essentiality of a nutrient is determined by knowledge of its unique ability to reverse clinical signs and symptoms of deficiency, and/or by knowledge of its essential mechanistic role in metabolic functions. The recognition by the scientific community of the essentiality of individual nutrients for certain body functions is based on a large body of scientific evidence, which includes case reports of clinical signs and symptoms of deficiency (e.g. during long-term total parenteral nutrition), depletion–repletion studies in humans, animal studies and *in vitro* studies. In this context, information about the essentiality of nutrients cannot be obtained from RCTs, which are at the top of the hierarchy of evidence for the scientific substantiation of other health claims (see section 3.1) for two reasons: i) RCTs in most nutrient-deficient subjects are unethical, and ii) RCTs in nutrient-replete subjects are unsuitable because the body functions for which the nutrient is required will not be modified by higher intakes.

3.3. Health claims have to be specific

Reference to general, non-specific benefits of the nutrient or food for overall good health or health-related well-being may only be made if accompanied by a specific health claim. In this context, the scientific translation of "specific" is "measurable *in vivo* in humans by well-accepted methods", and only these types of claims can undergo a scientific evaluation.

For example, claims like "feel better", "gut health", "natural defences" or "anti-aging" may be marketing tools for consumer communication. It may also be argued that consumers have a good understanding of what these claims mean, but scientists don't, unless they are defined by at least one outcome measure and one or more methods of measurement. If the human studies submitted for substantiation measure changes in the frequency and consistency of stools in response to an intervention, the specific claim which the NDA Panel will be in a position to evaluate relates to the maintenance of normal defecation, which is a well-defined bowel function, and thus a claim which could be made together with the non-specific "gut health", which may be preferred by FBOs for consumer communication. Conversely, if the claim is "natural defences" and the human studies provided for substantiation assess changes on a series of biochemical variables with an unclear impact on the immune function of the target population, the claim will not be sufficiently defined for a scientific assessment by the NDA Panel.

3.4. Medicinal claims are forbidden in food

Food information shall not attribute to any food the property of preventing, treating or curing a human disease, nor refer to such properties, and thus individuals with a disease cannot be the target population for a claim made on food. However, whether human studies on diseased subjects can or cannot be used for the substantiation of claims targeted at the general population or subgroups thereof (i.e. individuals not selected on the basis of a disease state) is a matter of scientific judgement made on a case-by-case basis by the NDA Panel. In other words, the legal requirement is about the consumers to which the claim is addressed (cannot be subjects with a particular disease which a food could treat or cure), but it does not preclude the extrapolation of results obtained in patients with a disease to the target population (i.e. individuals without the disease) whenever that is considered scientifically sound.

Table 2 depicts some examples of claims in which studies conducted in subjects with a disease/disorder were considered pertinent for substantiation, either as main evidence or as supportive evidence, and the context in which the case-by-case decision was made by the NDA Panel. Examples of claims in which studies conducted in subjects with a disease/disorder were not considered pertinent for substantiation are given in Table 3, together with the reasons why such studies were excluded from the body of evidence in support of the claim.

If medicinal claims are forbidden on food, health claims can logically not refer to the reduction of the risk of a disease directly (since this would refer to the prevention of a disease), but can only mention the reduction of a risk factor for a disease. The consumer should also be alerted to the fact that the disease to which the claim is referring has multiple risk factors, and that altering one of these risk factors may or may not have a beneficial effect (HCR, Article 14). Again, the legal requirement is that the wording of a claim cannot refer directly to the prevention of a disease, but it does not preclude the use of studies assessing the relationship between the consumption of a food/constituent and the incidence of a disease, as long as a biologically plausible risk factor in the development of the disease can be identified for use in the wording of the claim. Indeed, these types of studies provide the strongest evidence that a particular food could affect one or more risk factors for disease, even if they have not been measured directly.

In this regard, if there is sufficient evidence to conclude that a beneficial modification of a risk factor generally reduces the risk of a disease (e.g. a reduction in blood pressure and/or LDL-cholesterol generally reduces the risk of coronary heart disease (CHD)), evidence for a reduction of the risk factor with the consumption of the food/constituent is sufficient for substantiation of the claim, and evidence for a direct link between the consumption of the food/constituent and a reduction in the risk of the disease itself is not needed. Conversely, if there is evidence for a direct link between the consumption of the food/constituent and a reduction in the risk of the disease, evidence that the food/constituent can also modify a factor that is plausibly involved in the development of the disease is sufficient.

Human studies on well-established risk factors for disease (e.g. blood pressure and LDL-cholesterol concentrations for CHD) and human studies on disease incidence could also be used for the scientific substantiation of function claims. For example, studies on the risk of CHD could substantiate claims on the maintenance of normal cardiac function, and studies on the risk of dental caries could be used for claims on the maintenance of normal tooth mineralisation. When such studies are available, the scope of the claim could either be under Article 13(5) (function claim) or under Article 14 (reduction of disease risk claim), depending on the wording of the claim (Table 4).

4. Translation of the scientific evidence into a decision for authorisation

As the HCR establishes the legal requirements for claims made on foods but not the framework for their scientific assessment, EFSA's scientific opinions conclude on the scientific substantiation of health claims, but not on whether such claims should/should not be authorised for use in the EU. Indeed, EFSA opinions do not constitute an authorisation to place a food/constituent on the market, a positive assessment of its safety, or a decision on whether the food/constituent is, or is not, classified as a foodstuff. These and other legitimate factors are considered by risk managers during the authorisation of health claims.

4.1. Legal status of the food/constituent

Following the submission of an application via a Member State, EFSA conducts the scientific assessment of health claims made on foods regardless of the legal status of the food/constituent for which the claim is intended. For example, EFSA could assess health claims on food/constituents which have not been authorised in the European market (e.g. food/constituents classified as novel foods pending safety clearance), or which are marketed as medicines. Health claims can be authorised under the HCR, however, only if the food/constituent is considered a foodstuff in at least one Member State,[1] and therefore the legal status of a food/constituent could prevent the authorisation of a claim that has been positively evaluated by EFSA.

4.2. Compatibility with national dietary recommendations

A claim on sodium and maintenance of normal muscle function (EFSA NDA Panel, 2011a) and claims on glucose and contribution to normal energy-yielding metabolism (EFSA NDA Panel,

[1] In Europe, the classification of a food/constituent as foodstuff is under the remit of Member States.

Table 2
Examples of claims in which studies conducted in subjects with a disease/disorder were considered pertinent for substantiation, either as main evidence or as supportive evidence.

Food/constituent	Health relationship	Disease	Main evidence	Supportive evidence	Context	Reference
LGG® MAX,	Reduction of gastrointestinal discomfort	IBS	X	–	Disorder diagnosed based on the frequency/severity/ duration of symptoms; absence of a demonstrable anatomical or histological abnormality; symptoms occasionally experienced to a lesser degree by the target population	(EFSA NDA Panel, 2008d)
"Native chicory inulin", lactitol	Maintenance of normal defecation	Functional constipation	X	–	Disorder diagnosed based on the frequency/severity/ duration of symptoms; absence of a demonstrable anatomical or histological abnormality; symptoms occasionally experienced to a lesser degree by the target population	(EFSA NDA Panel, 2015a; 2015c)
Pacran®	Defence against bacterial pathogens in the lower urinary tract	Recurrent UTI	X	–	Study participants free of UTI at recruitment	(EFSA NDA Panel, 2015b)
Cocoa flavanols; IPP and VPP	Maintenance of normal blood pressure	Hypertension	X	–	Study participants not on blood pressure-lowering medications; diagnosis based on arbitrary cut-off of a continuous variable linearly related to disease risk	(EFSA NDA Panel, 2010a, 2012g)
Monacolin K from red yeast rice	Maintenance of normal blood LDL-cholesterol	Primary hypercholesterolaemia	X	–	Study participants not on lipid-lowering medications; diagnosis based on arbitrary cut-off of a continuous variable linearly related to disease risk	(EFSA NDA Panel, 2011f)
Plant sterols/stanols	Reduction of blood LDL-cholesterol concentrations	Primary hypercholesterolaemia	X	X	For main evidence, see above. For supportive evidence = known mechanism of action of the food/constituent + study participants on lipid-lowering medications acting through a different mechanism = no interaction, rather additive effect	(EFSA NDA Panel, 2008b; 2008a)
Meal replacements for weight control	Reduction in body weight; maintenance of body weight after weight loss	Obesity	X	–	Study participants not on pharmacological or surgical treatment for obesity; diagnosis based on arbitrary cut-off of a continuous variable exponentially related to disease risk	(EFSA NDA Panel, 2010c)
Cocoa flavanols	Maintenance of normal EDVD	CHD, T2DM	–	X	Patients under pharmacological treatment affecting endothelial function; evidence for the effect in the target population (healthy individuals) available	(EFSA NDA Panel, 2012d)
Arabinoxilan from wheat endosperm	Reduction of post-prandial glycaemic responses	T2DM	–	X	Some patients under oral hypoglycaemic medications; evidence for the effect in the target population (individuals with normal glucose tolerance) available	(EFSA NDA Panel, 2011c)

CHD = coronary heart disease; EDVD = endothelium-dependent vasodilation; IBS = irritable bowel syndrome; IPP = isoleucine-proline-proline; T2DM = type 2 diabetes mellitus; UTI = urinary tract infections; VPP = valine-proline-proline.

2012a), muscle function (EFSA NDA Panel, 2012b; Commission Regulation (EU) 2015/8) and physical activity (EFSA NDA Panel, 2012c) have been evaluated by EFSA with a positive outcome. These claims, however, have not been authorised for use in the Community (European Commission, 2016). Risk managers considered that the use of such claims would encourage consumption of sodium/sugars, for which national and international authorities inform the consumer that their intake should be reduced, and therefore would convey a conflicting and confusing message to consumers. In other words, such health claims would

Table 3
Examples of claims in which studies conducted in subjects with a disease/disorder were not considered pertinent for substantiation.

Food/constituent	Health relationship	Target population	Disease	Reasons for exclusion	Reference
Calcium and Vitamin D	Reduction of the risk of osteoporotic fractures	Post-menopausal women	Steroid-induced osteoporosis	The main mechanism by which steroids and menopause increase the risk of osteoporotic fractures is different, and so could be the effect of the food/constituent on the risk of osteoporotic fractures	(EFSA NDA Panel, 2009c)
Beta-glucans from oats and barley	Reduction of post-prandial glycaemic responses	General population	T1DM, T2DM	Study patients treated with insulin and/or oral hypoglycaemic medications with an effect on the outcome of interest; no evidence provided that extrapolation to the target population (i.e. subjects NOT on insulin and/or oral hypoglycaemic medications) is biologically plausible.	(EFSA NDA Panel, 2011d)
Glucosamine	Maintenance of normal joint cartilage	General population	Osteoarthritis	Cells and tissues in normal joints are genetically and functionally different from osteoarthritic cells and tissues, and therefore may respond differently to dietary interventions; evidence for the effect in the target population NOT available	(EFSA NDA Panel, 2012e)
Vitis vinifera L. seeds	Maintenance of normal venous blood flow	Adults in the general population	CVI	Normal venous tree is genetically and functionally different from the venous tree of patients with CVI, and therefore may respond differently to dietary interventions; evidence for the effect in healthy individuals NOT available	(EFSA NDA Panel, 2012f)
Spermidine	Prolongation of the growing phase (anagen) of the hair cycle	General population	Chronic telogen effluvium	No evidence that the claimed effect, if observed in the patient population, could also occur in the general population; evidence for the effect in the target population NOT available	(EFSA NDA Panel, 2011e)
Ocean Spray Cranberry Products®	Reduction of the risk of urinary tract infections	Healthy women > 16 years	Neurogenic bladder	Risk of UTI is much higher in patients than in the target population and the mechanisms for infection differ, as may differ the effect of a dietary interventions; evidence for the effect in the target population NOT available	(EFSA NDA Panel, 2009a)
Eye q®	Increasing concentration (attention)	Healthy children 2–18 years	ADHD; DCD	Disorders diagnosed based on the frequency/severity/duration of symptoms/traits; absence of a demonstrable anatomical or histological abnormality; no evidence that the claimed effect, if observed in the patient population, could also occur in the target population; evidence for the effect in the target population NOT available	(EFSA NDA Panel, 2008c)
Acetyl-L carnitine	Contribution to normal cognitive function	General population	Alzheimer's disease	Normal cells and tissues in the CNS are genetically and functionally different from those of patients with Alzheimer's disease, and therefore may respond differently to dietary interventions; evidence for the effect in the target population NOT available	(EFSA NDA Panel, 2011g)
Alpha-lipoic acid	Increase in insulin sensitivity	General population	T2DM	Patients treated with metformin, a drug which is known to affect insulin sensitivity; interaction between the food/constituent and the drug on the claimed effect cannot be excluded = no evidence that the claimed effect, if observed in the patient population, could also occur in the general population; evidence for the effect in the target population NOT available	(EFSA NDA Panel, 2011h)
L-carnitine	Maintenance of normal blood LDL-cholesterol	General population	Chronic renal failure on long-term haemodialysis	Blood lipid profile and lipid metabolism are heavily influenced by the disease; no evidence that the claimed effect, if observed in the patient population, could also occur in the general population	(EFSA NDA Panel, 2011i)

ADHD = attention deficit hyperactivity disorder; CNS = central nervous system; DCD = developmental coordination disorder; CVI = Chronic venous insufficiency; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

not comply with point (a) of the second paragraph of Article 3 of the HCR, which foresees that the use of claims should not be ambiguous or misleading.

4.3. Safety concerns

A safety assessment is not requested in the context of the HCR, and thus EFSA's conclusions on the substantiation of a health claim do not imply that the consumption of the food/constituent is safe, either *per se* or under the proposed conditions of use. Safety aspects are considered by risk managers in the authorisation process and may prevent the authorisation of health claims with a positive assessment by EFSA, or trigger a subsequent request for an ad-hoc safety evaluation of the food/constituent.

Recent examples are health claims related to the consumption of caffeine and improved physical performance and

Table 4
Examples of outcome variables which could be used for the scientific substantiation of both function claims and reduction of disease risk claims.

Outcome variable	Function claim	Reference	Reduction of disease risk claim	Reference
BP	Maintenance of normal BP	(EFSA NDA Panel, 2012g)	Reduction of BP. BP is a risk factor for stroke. Reduction of BP. BP is a risk factor for CHD.	(EFSA NDA Panel, 2011j)
Blood LDL-cholesterol concentrations	Maintenance of normal blood LDL-cholesterol	(EFSA NDA Panel, 2011f)	Reduction of blood cholesterol. Blood cholesterol is a risk factor for CHD	(EFSA NDA Panel, 2008b; 2008a)
Incidence of dental caries	Maintenance of tooth mineralisation	(EFSA NDA Panel, 2009d)	Reduction of [*risk factor*]. [*Risk factor*] is a risk factor for dental caries	(EFSA NDA Panel, 2010b)
Incidence of osteoporotic fractures	Maintenance of normal bone mineralisation	(EFSA NDA Panel, 2009b)	Reduction of [*risk factor*]. [*Risk factor*] is a risk factor for osteoporotic fractures	(EFSA NDA Panel, 2011l)
Incidence of UTI	Defence against pathogens in the upper urinary tract	(EFSA NDA Panel, 2015b; 2016c)	Reduction of [*risk factor*]. [*Risk factor*] is a risk factor for UTI	(EFSA NDA Panel, 2009a)
Incidence of CHD	Maintenance of normal cardiac function	(EFSA NDA Panel, 2011m)	Reduction of [*risk factor*]. [*Risk factor*] is a risk factor for CHD	(EFSA NDA Panel, 2011j)

BP = blood pressure; CHD = coronary heart disease; UTI = urinary tract infections.

psychological functions (i.e. concentration/attention, alertness). The conditions of use for these claims were 3–4 mg of caffeine per kg of body weight taken one hour prior to physical exercise for claims on physical performance and 75 mg of caffeine for claims on psychological functions (EFSA NDA Panel, 2011b, 2011k). During the authorisation of these claims, Member States raised concerns about the safety of caffeine, particularly in adolescents and when consumed in the so called "energy drinks", in combination with alcohol, and prior to intense physical exercise. Overconsumption of caffeine by children was also a concern. Therefore, EFSA was requested to issue a scientific opinion on the safety of caffeine for the general population and specific population subgroups in the afore-mentioned context, and prior to the authorisation of these claims.

4.4. Consumer understanding

For health claims evaluated with a positive outcome, the NDA Panel considers whether the wording of the claim proposed by the applicant reflects the scientific evidence. If not, the NDA Panel proposes a different wording. Although scientifically correct, such wordings do not take into account consumer understanding and may not be appropriate for consumer communication. If so, applicants can negotiate with risk managers during the authorisation process in order to agree alternative wordings which are both scientifically correct and understandable by the average consumer. An example is a claim on water soluble tomato concentrate (WSTC), for which the original wording proposed by the applicant was "helps to maintain a healthy blood flow and benefits circulation". The wording proposed by the NDA Panel (i.e. helps maintain normal platelet aggregation), which was based on the outcome measures used for its scientific assessment, was extended for its authorisation in order to clearly identify the health benefit for consumers (i.e. helps maintain normal platelet aggregation, which contributes to healthy blood flow).

5. Current demands and future perspectives

The lessons learnt in 10 years of experience in the scientific evaluation of health claims made on foods have been key to providing further guidance to stakeholders on how to prepare applications for authorisation. A revised guidance document tackling aspects common to all claims (EFSA NDA Panel, 2016a) and a webinar held on 10 March 2016[2] are a step forward in defining the scientific framework in the context of the HCR. Following several requests from stakeholders, EFSA has updated its guidance on the scientific requirements for health claims related to the immune system, the gastrointestinal tract and defence against pathogenic microorganisms (EFSA NDA Panel, 2016b). EFSA has also compiled a catalogue of support initiatives during the lifecycle of applications for regulated products (EFSA, 2016c), which includes the possibility of organising teleconferences with applicants at different steps of the evaluation process for clarification purposes. Still, the most recurrent request of FBOs to EFSA is the possibility of having pre-submission meetings, i.e. preliminary discussions on specific applications prior to their submission, in order to obtain advice, for example, on the design of human intervention studies, or on the evidence which may be needed for the scientific substantiation of a particular claim. Under the current legal framework, considering EFSA's structure and the allocated resources, EFSA is not in the position to offer such a service.

In 2014, in order to further assist applicants in the preparation of their applications, EFSA launched a grant (GP/EFSA/NUTRI/2014/01) which aims at gathering information in relation to claimed effects, outcome variables and methods of measurement in the context of the scientific substantiation of health claims (EFSA, 2014b). The information collected will be published in a scientific report, which will help to inform the NDA Panel and serve as a basis for further guidance to applicants on health claims in specific areas (EFSA, 2016a).

6. Conclusions

How health claims are scientifically assessed by EFSA has not yet been fully understood by stakeholders. A thorough knowledge on how EU legislation translates into scientific requirements for substantiation is essential to building successful applications. Other factors which may play a role in the authorisation of a claim and which are not evaluated by EFSA, such us the legal status of the food/constituent, its safety, or the compatibility of the claim with national and international dietary recommendations, should also be considered early in the process. EFSA is committed to providing further guidance to stakeholders on how to prepare applications for authorisation by making use of its 10 years of experience in the scientific evaluation of health claims made on foods.

Disclaimer

The author Silvia Valtueña Martínez is employed with the European Food Safety Authority (EFSA) as Senior Scientific Officer in the Nutrition Unit, the Unit that provides scientific and administrative support to the Panel on Dietetic Products, Nutrition and Allergies (NDA Panel) in the area of health claims made on foods.

[2] http://www.efsa.europa.eu/it/events/event/160310.

The author Alfonso Siani is a member of EFSA's NDA Panel and is the Chair of its Working Group on Claims. However, the present article is published under the sole responsibility of the authors and may not be considered as an EFSA scientific output. The positions and opinions presented in this article are those of the authors alone and do not necessarily represent the views/any official position or scientific works of EFSA. To know about the views or scientific outputs of EFSA, please consult its website at http://www.efsa.europa.eu.

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