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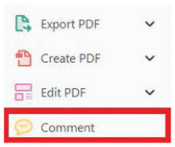

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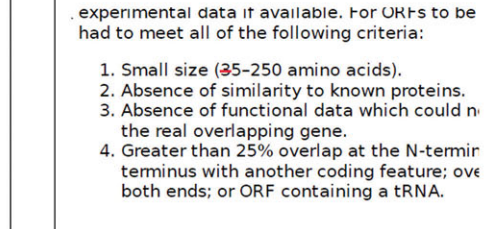

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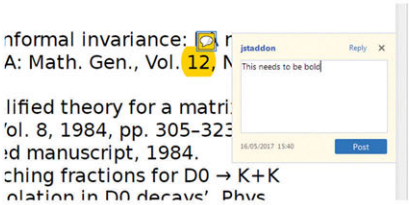

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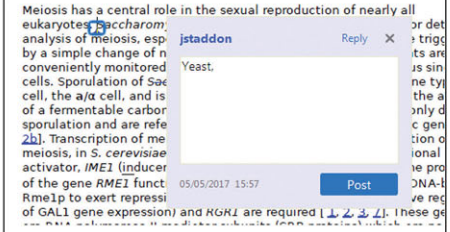

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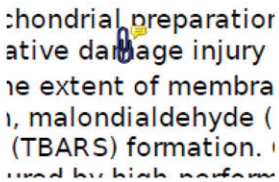

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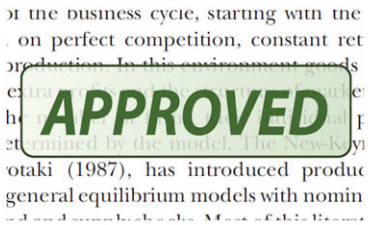

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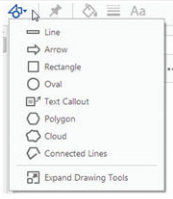

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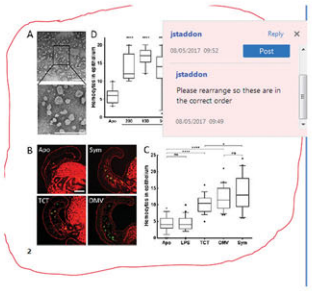

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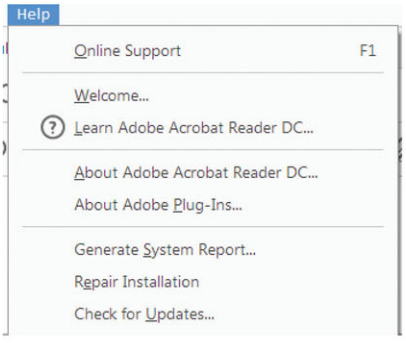

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Scientific Evidence on Functional Food and Its Commercial Communication: A Review of Legislation in Europe and the USA

Cristina González-Díaz, Diana Gil-González, and Carlos Álvarez-Dardet

Abstract: **Purpose:** This study aims at understanding how scientific evidence to substantiate nutrition and health claims in food commercial communication is regulated in Europe and the USA.
Design/methodology/approach: A literature review was performed on the scientific evidence required by the European Food Safety Authority and the US Food and Drug Administration to substantiate food nutrition and health claims. Studies published in Scopus, Medline, Scirus, and Google Scholar from 2007 to 2012 were reviewed as well as documents released by both agencies. A total of 38 documents met our inclusion criteria out of 743 documents initially identified during our search.
Findings: These agencies provide general guidelines on how to conduct food and health studies, intended to demonstrate a cause-and-effect relationship between a given food and a benefit to health. Despite this, they need to broaden the depth and scope of the guidelines provided to companies seeking to substantiate their claims and to provide further and more precise information concerning the evaluation of studies and application processes.
Originality/value: No review has hitherto specifically focused on the subject of scientific evidence required by EU and US food agencies to substantiate health claims. This research thus leads to significant recommendations on how to improve current food industry guides.

Keywords: commercial communication, functional food, health claims, nutritional claims, scientific evidence

Introduction

The US Food and Drug Administration (hereon FDA) has been regulating health claims in the food industry since 1990. This agency currently enforces two different levels of required scientific rigor, defined as: (1) high level of scientific evidence, known as "significant scientific agreement" (SSA); and (2) low level of scientific evidence, known as "qualified health claims" (QHCs; Lalor & Wall, 2011).

In EU member states, there is only one high-level of scientific evidence required, enforced through EU Regulation 1924/2006. Article 13.1 stipulates that health claims must be based on generally accepted scientific evidence and Article 13.5 regulates new claims "based on newly developed scientific evidence and/or which include a request for the protection of proprietary data." Article 14 addresses the reduction of disease risk claims and claims related to children's development and health. The PASSCLAIM process established a set of generally applicable criteria used by the European Food Safety Authority (hereon EFSA) in evaluating submitted scientific evidence (Giselnan, 2011). Although the EFSA issues evaluations, it is the European Commission that decides whether or not any new claim will be approved (Buttris and Benelam, 2010).

JFDS-2018-0335 Submitted 3/12/2018, Accepted 8/29/2018. *Author González-Díaz is with Dept. of Communication and Social Psychology, Univ. of Alicante, Carretera San Vicente del Raspeig s/n, 03690 San Vicente del Raspeig, Alicante, Spain. Authors Gil-González and Álvarez-Dardet are with Dept. of Community Nursing, Preventive Medicine and Public Health and the History of Science, Univ. of Alicante, Carretera San Vicente del Raspeig s/n, 03690 San Vicente del Raspeig, Alicante, Spain. Authors Gil-González and Álvarez-Dardet are also with Public Health Research Group, Univ. of Alicante, Alicante, Spain. Authors Gil-González and Álvarez-Dardet are also with CIBER Epidemiología y Salud Pública (CIBERESP), Spain. Direct inquiries to author González-Díaz (E-mail: cristina.gdiaz@ua.es).*

A number of researchers have analyzed legislation on health claims. The majority have focused on regulations enforced by the EFSA (Aggett, 2012; Asp & Bryngelsson, 2008; Gorny, 2012; Lalor and Wall, 2012; Vero & Gasbarrini, 2012; Walter, 2009) or those governing the work of the FDA (Ellwood, Trumbo, & Kavanaugh, 2010; Hasler, 2008; Lupton, 2009; Schneeman, 2010).

There have also been comparative studies of regulations (Moors, 2008; Jovicic, Novakovic, & Torovic, 2011; Lalor & Wall, 2011; Sanders, Tompkins, Heimbach, & Kolida, 2005). Nevertheless, with the exception of certain studies (Lalor & Wall, 2012; Ellwood et al., 2010; Lupton, 2009), none have focused primarily on the scientific evidence required to substantiate health claims. Nor have there been systematic reviews that have synthesized scientific knowledge required by agencies to make health claims, despite the fact that such regulation has now been in place for seven years in the EU and more than two decades in the United States.

Based on a review of selected literature, this paper reports findings relating to EFSA and FDA requirements concerning the necessary evidence companies have to produce to advertise nutritional values and health benefits of their food products.

We selected these agencies because there are the main agencies about this issue (Lalor & Wall, 2012).

Materials and Methods

Sources and search strategy

We performed a literature review covering the period between 2007, the year in which Regulation (CE) 1924/2006 on nutrition and health claims made on foods came into force, and 2012, the year in which Regulation (CE) 432/2012 authorizing health claims on foods, other than those referring to disease risk reductions and to children's development and health (see Table 1) was enforced.

doi: 10.1111/1750-3841.14359

Table 1–Search strategies.

Scopus search	(a) "scientific evidence" AND "food advertising"; (b) "scientific evidence" AND "health claim"; (c) "scientific evidence" AND "food advertising" AND "health claim"; (d) "systematic review" AND "scientific evidence" AND "food advertising" AND "health claim."
Medline search	-Using the MeSH Thesaurus subject headings "food" and "advertising topic" 1. Exp Health Food/ or exp Food/ or exp Legislation, Food/ or exp Food Quality/ or exp Functional Food/ or exp "United States Food and Drug Administration"/ or exp Food Industry/ or exp Food Labelling. 2. Exp Advertising as Topic/ 3. Limit 3 to year= "2007-2012." 4. Limit 4 to "review articles."
Scirus search	a "scientific evidence" AND "food advertising"; b "scientific evidence" AND "health claim" c "scientific evidence" AND food advertising" AND "health claim" d "systematic review" AND "scientific evidence" AND "food advertising" AND "health claim."
Google scholar search	"scientific evidence" AND "food advertising" AND "health claim" AND "systematic review" AND "FDA AND EFSA."

To do this, we performed searches in Scopus, Medline, Scirus, and Google Scholar. Documents published by both the EFSA and the FDA were also examined.

Inclusion and exclusion criteria

Included studies had to provide an analysis of the scientific evidence required by the FDA and EFSA to substantiate health claims for functional foods. In other words, they had to be related to the standards of scientific evidence required by agencies to approve the commercial communication of health claims.

We excluded studies published in languages other than English or Spanish and studies that did not adequately address the object of our research or meet the above inclusion criteria. We thus excluded literature related to: (1) FDA and EFSA legislation not related to food claims; (2) influence of consumers; (3) biotechnology; (4) professional issues; (5) specific target populations; (6) national and regional policy or organisations; (7) health claims appearing in the media; and (8) legislation from other countries.

Data extraction

During the initial search, 743 documents were identified after discarding duplicates. All initially preselected documents were evaluated by the lead author of this article. Disagreements on whether to include some of the studies were resolved by reaching a consensus between two authors. The final selection consisted of 38 documents (Figure 1).

Variables and data analysis

Documents were classified according to the following categories: (1) Agency analyzed; (2) Author's affiliation; (3) Method used; and (4) Main results, with an emphasis on: (a) the process of evaluating studies submitted to substantiate claims, (b) the type of studies required and their characteristics, (c) the validation of biomarkers, and (e) the concepts defined in the evaluation process. For category 4, main conclusions in the documents were analyzed and suggestions were made on the basis of a review for each text of issues relating to the preparation and evaluation of studies producing scientific evidence.

Results and Discussion

Out of the 38 studies selected for review, 60.5% ($n = 23$) analyzed the EFSA (Aggett, 2007, 2009, 2012; Asp & Bryngelsson, 2008; Biesalski, Aggett, & Anton, 2011; Buttriss, 2010; Buttriss & Benelam, 2010; Coppens, 2009, 2010; Flynn, 2011; Gilsenan, 2011; Gorny, 2012; Kardinaal, Mennen, & Hendriks, 2009; Lalor & Wall, 2012; Mitchell, Aggett, Richardson, Stowell, 2011; O'Connor, 2011; Reuterswärd, 2007; Richardson, 2012; Vero & Gasbarrini, 2012; Walter, 2009; Pravst, 2012; Meisterernst & Haber, 2007; Gallagher, Meijer, & Richardson, 2011); a total of 23.7% ($n = 9$) analyzed the FDA (Aggett, Hathcock, & Jukes, 2012; Ellwood et al., 2010; FDA, 2009; Guzelian & Guzelian, 2008; Hasler, 2008; Kuhn, 2008; Lupton, 2009; Schneeman, 2007, 2010) and 15.8% ($n = 6$) were comparative analyses of both agencies (Binns, 2008; Jovicic et al., 2011; Lalor & Wall, 2011; Martin, 2010; Moors, 2012; Verhagen, Vos, Franch, Heinonen, & van Loveren, 2010). Of the authors whose articles were selected for review, only four were somewhat affiliated with the agencies they analyzed (Ellwood et al., 2010; FDA, 2009; Schneeman, 2007, 2010). All selected studies used nonempirical methods based on a theoretical description of scientific evidence required by each regulatory agency. These studies do not represent systematic reviews or quantitative analyses of the data, such as content analysis. For this reason, this study could not use dedicated tools (Cochrane guidelines for example) to analyses or evaluate their quality. Instead, main conclusions and suggestions were examined for each reviewed study (Table 2).

Evaluating the studies submitted to substantiate claims

Case-by-case evaluation of evidence submitted to substantiate health claims hinders the standardization of regulations (Gilsenan, 2011; Lalor & Wall, 2012). Both agencies' guidelines described the characteristics of required substantiation studies. However, the fact that evaluations focus heavily on the specificities of each case has prompted some authors to suggest that procedures for evaluating scientific support for health claims need to be reviewed and revised (Aggett et al., 2012). Calls have been made to reshape the processes that evaluate scientific substantiation of health claims. For example, some critics have asserted that although PASSCLAIM generated robust tools that provide common criteria for evaluating scientific studies, it did not articulate precisely how the sum of evidence submitted should be evaluated (Gallagher et al., 2011). Studies must therefore be evaluated on a case-by-case basis, a practice that gives rise to a certain level of uncertainty (Biesalski, Aggett, & Anton, 2011; Mitchell et al., 2011).

Types of studies required and their characteristics

Human studies are the most effective means of demonstrating cause and effect relationships between the consumption of particular foods and human health (Aggett, 2009; Binns, 2008; Buttris, 2010; FDA, 2009; Richardson, 2012). Randomized Controlled Trial (RCT) studies are considered to be the most reliable (Asp & Bryngelsson, 2008; Ellwood et al., 2010; Hasler, 2008). Observational studies are not considered to be as conclusive as RCTs but may be useful within the overall context of a research

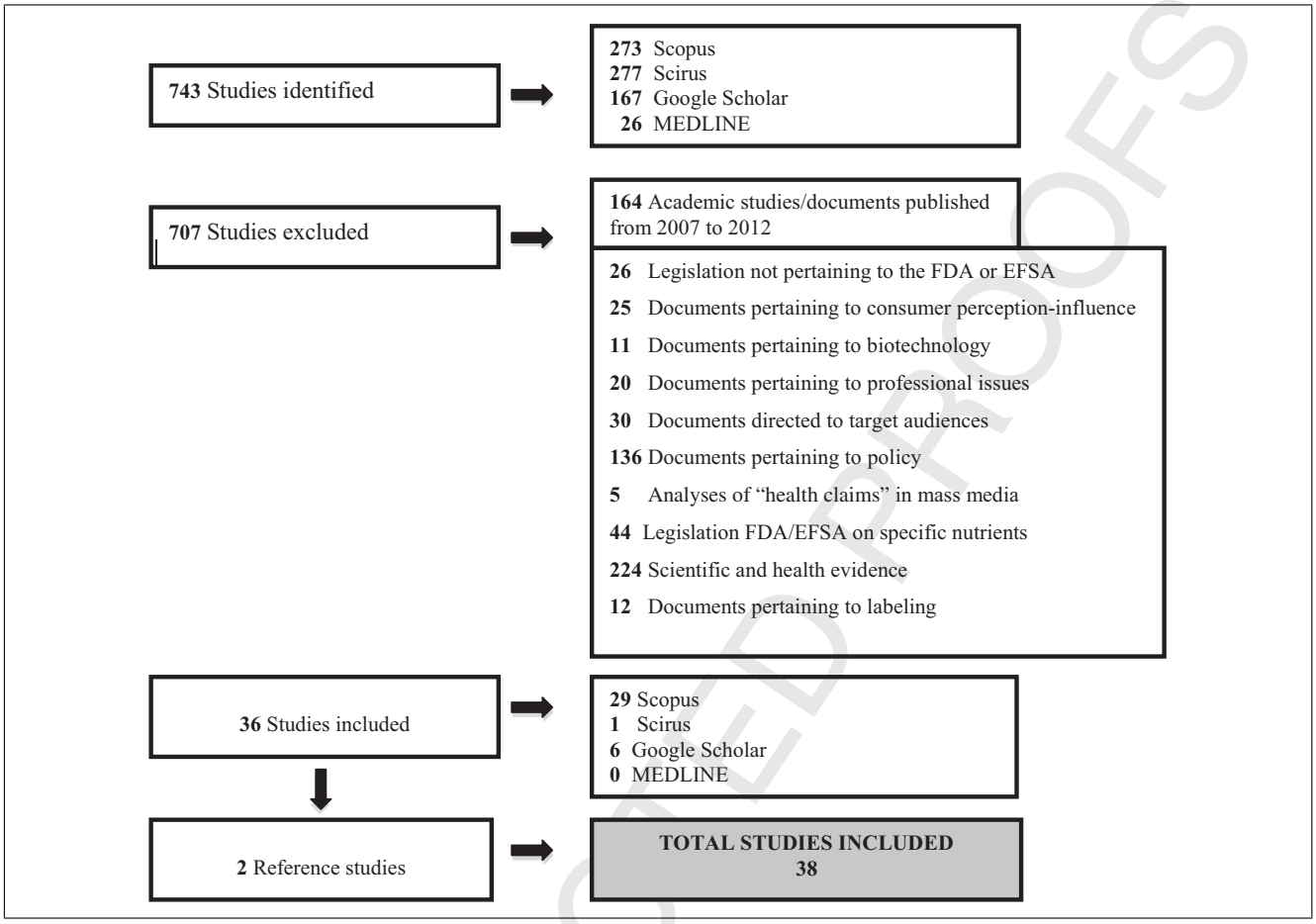

Figure 1–Diagram of systematic review process.

analysis (Aggett, 2009; Ellwood et al., 2010). Although evidence produced by means of an animal or *in vitro* study is insufficient to substantiate a health claim, either of these types of studies may be useful as a basis for further studies involving humans. Reviews of existing literature do not provide sufficient information to definitively establish a cause and effect relationship between specific foods and human health (FDA, 2009).

Criteria relating to the number of studies that a manufacturer must produce and their duration are not sufficiently specified. The justification put forward is that each application has particularities, which, according to agencies, can only be analyzed on a case-by-case basis (Gilsenan, 2011).

Validation of biomarkers

The WHO has stated that a true definition of biomarkers includes "almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical, or biological. The measured response may be functional and physiological, biochemical at the cellular level, or a molecular interaction" (Strimbu & Tavel, 2010).

The identification and validation of biomarkers is crucial for assessing the potential effectiveness and benefits of health-promoting food compounds. This is the basis for new and competitive economic and health developments in the food sector as covered by the recently harmonized legislation on the emerging "health claims made on food" in Europe (Bioclaims Project).

The success of any study designed to provide scientific evidence that a specific food/constituent can have a beneficial effect on health greatly depends on the selection of the relevant biomarkers (Pravst, 2012). However, the range of validated biomarkers (without which it is virtually impossible to scientifically substantiate new health claims) is extremely limited. The immediate impact of this dearth of biomarkers is twofold: many manufacturers produce studies supporting health claims related to diseases for which biomarkers have already been validated whilst others face the challenge of demonstrating a beneficial link between their products and diseases for which biomarkers have yet to be approved (Aggett, Antoine, & Asp, 2005; Kuhn, 2008; Lalor & Wall, 2011).

Kuhn (2008) warns that the range of many studies is limited as many are conducted using biomarkers on the FDA's "short list": cholesterol level, LDL cholesterol, and blood pressure. Because these approved biomarkers are indicators of cardiovascular health, many claims are related to cardiovascular risk reduction.

Definition of concepts applied in the evaluation process

Concepts and terms commonly employed in substantiation studies need to be properly defined and the boundaries of their meanings clearly established. Gallagher et al. (2001) stress the importance of establishing clear definitions of terms and concepts such as "benefit," "beneficial to health," "risk factor," "nutrient function," and "health claim." The EFSA has come under fire for its acceptance of imprecise terms such as "beneficial" and "generally accepted scientific evidence" (Gorny, 2012).

Q6

Table 2–Overview of studies included in the review.

Authors and year	Agency	Main focus
1. Guzelian and Guzelian (2008)	FDA	- Evidence required to meet SSA standards.
2. Aggett et al. (2012)	FDA	- Criticizes lack of transparency in the process of evaluating the scientific substantiation of health claims.
3. Flynn (2011)	EFSA	- Weaknesses in the design, execution and analysis of human studies: inconclusive evidence linking substance to health. - Need to support claims with human trials.
4. Gallagher et al. (2011)	EFSA	- Need to provide clearer guidelines for studies seeking to demonstrate the effectiveness of food products and the evidence required to substantiate claims. - Importance of establishing clear definitions of: "benefit"; "beneficial to health", "risk factor", "nutrient function" and "health claim."
5. Biesalski et al. (2011)	EFSA	- Although PASSCLAIM contemplated the evaluation of individual studies, it did not articulate how the evidence as a whole was to be evaluated.
6. Gilsenan (2011)	EFSA	- No means of determining how many studies should be required has been established. - Current case-by-case policy generates problems.
7. Lalor and Wall (2011)	EFSA FDA	- USA (FDA) two categories: 1. QHC (less rigorous) 2. SSA (highly rigorous). - EUROPE: health claims and nutrition claims (high level)
8.Buttriss and Benelam (2010)	EFSA	- Importance of knowing the composition of a product in the determination of a claim's relevance (currently based on database research).
9. Verhagen et al. (2010)	EFSA	- Functional foods and dietetic supplements do not provide solutions to health problems caused by unhealthy eating habits.
10. O'Connor (2011)	EFSA	- Articles 13.5 and 14: Applications rejected on the basis of an inadequate presentation of evidence. - The evaluation of claims on a case-by-case basis as opposed to the application of a standard formula.
11. Ellwood et al. (2010)	FDA	- The most successful studies involve random clinical testing. Observational studies are useful but not considered to be conclusive. Review studies of existing literature are not considered conclusive.
12. Aggett (2009)	EFSA	- Primary means of substantiation: human studies. Although observational studies are deemed inconclusive, they provide context and support fundamental evidence.
13. Hasler (2008)	FDA	- RCT is the prime vehicle for substantiating claims. How many random trials and/or controlled clinical tests are needed to demonstrate a relationship between a product and health benefits?
14. Asp and Bryngelsson (2008)	EFSA	- Studies involving human subjects, especially RCTs, are essential, although other types of studies can be used to defend generic claims.
15.Reuterswärd (2007)	EFSA	- Article 20 cites restrictions laid out in Art. 4(5) regarding nutrient profiles. - Article 21 refers to a public register of approved claims that can be adapted using equivalent terms.
16. Schneeman (2007)	FDA	- FDA task force report "Consumer Health Information for Better Nutrition Initiative" clarifies QHCs. - "Guidance for Industry": guidelines for the evaluation of health claims for conventional foods and dietary supplements according to SSA standards.
17. Mitchell, Aggett, Richardson, and Stowell (2011)	EFSA	- Author calls for agencies to be more flexible and consider other types of studies. - EFSA has demonstrated a negative outlook on probiotics. According to the agency, future research should focus on the effect of probiotics on healthy rather than at-risk subjects (exclusion of subjects under treatment).
18. FDA (2009)	FDA	- FDA recognizes intervention and observational studies as the most effective vehicles for substantiating health claims, the most reliable being intervention studies and RTCs. - Animal and *in vitro* studies do not provide sufficient information to establish scientific conclusions regarding claims.
19. Richardson (2012)	EFSA	- EFSA has established guidelines for RCTs, observational studies and reviews as well as inclusion and exclusion criteria. - Given that the need to conduct human studies makes the process of substantiating health claims complex and difficult, the PASSCLAIM template needs to be interpreted intelligently.
20. Lupton (2009)	FDA	- How are health claims evaluated? (a) "Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims" (b) Although applications are reviewed on a case-by-case basis, common criteria are applied. (c) Initial question: Does substance x reduce the risk of disease in a given population? The substance, disease and population must all be defined. (d) Serious studies should be conducted on non-diseased populations. However, "nondiseased population" has not been clearly defined.
21. Buttriss (2010)	EFSA	- EFSA places a high priority on: 1. Human studies 2. Identification of constituents 3. Clear identification of relevant variables such as endpoints that link health benefits with the food in question

(continued)

Table 2–Continued.

Authors and year	Agency	Main focus
		4. Populations cited in studies 5. Recommended intakes 6. Auxiliary animal or *in vitro* studies - Information regarding the number of claim applications filed under Articles 13.5 and 14 and that are approved or rejected is made public.
22. Gorny (2012)	EFSA	- The role of science at EFSA Article 6 paragraph 1: Nutrition and health claims shall be based on and substantiated by generally accepted evidence. This author covers various types of studies, but places priority on human studies. Inadequately defined terms such as "beneficial" or "generally accepted scientific evidence" allow the NDA panel a large measure of discretionary leeway and should be clarified.
23.Coppens (2010)	EFSA	Agencies have taken a critical stance on probiotics, stating that health claims have not been sufficiently substantiated.
24. Coppens (2009)	EFSA	- Terminology: The European term "reduction of disease risk claim" has the same meaning as the term "health claim" used in the US.
25.Kardinaal et al. (2009)	EFSA	- Food claims filed under Articles 13.5 and 14 require extensive dossiers whereas claims governed by other articles can be evaluated on the basis of generally accepted scientific evidence. Dossiers must contain 3 types of evidence: (1) data on the bioavailability of the active component; (2) data that demonstrate the product has been effective in human studies; and (3) reviews of evidence. Data must directly concern the relationship between the food or component and the effect. - EFSA does not specify the number of human trials to be undertaken.
26. Aggett (2007)	EFSA	- There are no international regulations regarding criteria for scientific evidence. - Providing human evidence is not easy as it involves long periods of testing, intake measurement, and producing outcomes that identify a mechanism of action and demonstrate a relationship between the benefit cited in the claim with the relevant physiological function or disease-risk reduction.
27. Kuhn (2008)	FDA	- The scope of many studies is limited as many are conducted using biomarkers on the FDA's "short list": cholesterol level, LDL cholesterol and blood pressure. Because these approved biomarkers are indicators of cardiovascular health, many claims are related to cardiovascular risk reduction. - The author warns manufacturers that without an approved biomarker that will allow them to measure the effect of their product within a reasonable amount of time, they might not be able to produce sufficient scientific evidence for their claims.
28. Aggett (2012)	EFSA	- PASSCLAIM developed a template for the evaluative process. Aggett stresses that although RCTs with human subjects carry the most weight, other types of studies should not be ruled out. - The author believes that RCTs provide the best standard of evidence although they require substantial time and large study populations. Aggett criticizes the weight given to this type of study.
29. Vero and Gasbarrini, (2012)	EFSA	- The authors assert that the rigidity of evidence criteria limit the possibilities to make claims for products that deliver real benefits and point out that regulations in force for the pharmaceutical sector are applied to nutritional claim applications.
30. Walter (2009)	EFSA	- The author refers to a graph produced by FUFOSE that illustrates the consensual understanding of the relationship between markers of exposure to functional foods and markers of biological response.
31. Lalor and Wall (2012)	EFSA	- The authors stress the difficulty of demonstrating sufficient evidence in the context of this regulatory system. - Each application is reviewed on a case-by-case basis, a practice that hinders the development of clear rules and guidelines that would help manufacturers to earn a favorable opinion.
32. Schneeman (2010)	FDA	In 1999 the FDA released Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims that laid out criteria for QHC as alternative to SSA. Since 2003 the FDA has published discretionary enforcement letters for QHC. In 2007 it released Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims – Final.
33. Binns (2008)	EFSA, Asia and Japan, USA, Canada, Australia, and New Zealand	- Although every type of study makes a positive contribution, human studies are preferable. - In terms of human studies, randomized placebo-controlled double-blind intervention studies are always considered superior to epidemiological and observational studies.
34. Jovicic et al. (2011)	EFSA, FDA, Japan, and Serbia	- USA The use of health claims in advertising is regulated by the Federal Trade Commission (FTC) - EUROPE Articles 13 and 14 of Regulation No. 1924/2006 Health claims must be approved by the EFSA. Approval criteria were developed during the PASSCLAIM Project. Human studies are advocated.
35. Martin (2010)	BOTH	- The only systemic comparisons of health claim regulations published to date have addressed China and Japan as well as the US, Canada and Europe.

(continued)

Table 2–Continued.

Authors and year	Agency	Main focus
		– Comparison: Only claims submitted to a scientific evaluation by the EFSA, authorized by SCFCAH and entered in the European Register of Claims can be used in the EU. US and Chinese regulation refer to "disease risk reduction" whereas in Europe the term used is "disease risk reduction factor," although the latter term remains vague in the framework of European legislation.
36. Moors (2012)	BOTH	– Based on his own comparison, this author considers European legislation to be more restrictive than US legislation. EU legislation has had an impact on innovation in a number of sectors. Its consequences for the industry include: 1. High development costs. 2. Early mover or product follower strategies. 3. Legal uncertainty. 4. Harmonization and efficiency of procedures. 5. Transparency. 6. Consumer understanding.
37. Pravst (2012)	EFSA	– Whether study results can be extrapolated to the target population is a key issue. Judgments are made on a case-by-case basis, but if patients are not considered to be in an appropriate study group, studies are not considered pertinent. – The claimed effect should be clearly defined and relevant to human health. – Conditions in studies carried out must be similar to conditions of use in the target population to which the product will be sold. Biomarkers are characteristics that can be objectively measured as indicators of normal biological processes.
38. Meisterernst and Haber (2007)	EFSA	– EFSA's lack of authority to establish boundaries between food and medicinal products continues to cause problems. For example, what are sold as medicinal capsules in Germany are marketed as supplements in the UK.

Discussion

Both regulatory agencies reviewed offer consolidated guidelines for designing studies intended to demonstrate cause-and-effect relationships between specific foods or substances and health. Nonetheless, the findings of this review point to the need to provide manufacturers with clearer and more extensive information on certain parameters. These would allow them to base their substantiation studies on standardized criteria. The fact that agency guidelines provide common criteria for manufacturers to substantiate their claims but do not offer clarifications as to how the evidence submitted will be evaluated as a whole also needs to be addressed. Furthermore, current practices consisting in evaluating applications on a case-by-case basis implies that assessments are based on the particularities of each submitted study (Biesalski et al., 2011).

In this regard, we propose a series of recommendations to complement current guidelines that would lead to reinforcing scientific evidence. These recommendations directly derive from the shortcomings and suggestions for improvements identified in the reviewed articles. First, with regard to human studies, establishing the kind of studies that have greater validity (RCT) is not sufficient. It is necessary to go one step further and determine, as commented above, a minimum number of studies substantiating evidence and their minimum duration.

Moreover, it could be relevant to require that test populations comply with certain basic characteristics. They should represent the potential consumers who are likely to ingest the products in the future and thus benefit from the health effects by consuming the food. Criteria such as "(a) substantiation primarily based on human intervention trials (good experimental design, statistically significant); (b) amount needed and frequency of consumption; (c) food matrix and dietary context; and (d) totality of the available data and weighing of evidence" Gilsenan (2011), among others are relevant though these can be considered rather generic and dependent on case by case assessment.

This dearth of validated biomarkers has negative consequences. Not only does it limit the scope of studies being undertaken but it also reduces manufacturers' opportunities for demonstrating the yet unproven health benefits of a wider range of foods and/or constituents. BIOCLAIMS, an interesting project to identify new biomarkers, seeks to remedy this problem and is contributing to the reformulation of EU legislation regarding health claims made for food.

The use of unspecific terminology can also hinder efficient and effective regulation. A concerted effort should be made to reach a consensus regarding the definition and boundaries of concepts relevant to research carried out in this area.

These recommendations are viable because they allow improving policies relating to scientific evidence required for functional foods. In addition, the study shows the limitations of the current system. For this reason, we consider that the suggestions provided are useful and necessary.

The EFSA has in fact recently published a document entitled "General scientific guidance for stakeholders on health claim applications" (EFSA, 2016). They comment that with this document, the Panel on Dietetic Products Nutrition and Allergies (NDA) has completed the evaluation of Article 13.1 claims (except for claims put on hold by the European Commission), and has evaluated additional health claim applications submitted pursuant to Articles 13.5, 14, and also 19. In addition, comments received from stakeholders indicate that general issues that are common to all health claims need to be further clarified and addressed. The document comments that procedures require additional specifications such as those described in this study.

Consumers purchase functional foods because of their health benefits. Therefore, agencies are responsible for ensuring that advertised health benefits have been sufficiently demonstrated and that the level of scientific evidence required is high. They must also regulate the way in which these benefits are publicized in commercial communications and on labels.

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Table 3–Criteria used by agencies to evaluate scientific evidence.

	Criteria for measuring scientific evidence	Relevant issues
EFSA	PASSCLAIM criteria: 1) The food or food component to which the claimed effects is attributed should be characterized; 2) Substantiation of a claim should be based on human data, primarily from intervention studies the design of which should include the following eight considerations; (A). Study groups that are representative of the target group; (B). Appropriate controls; (C). An adequate duration of exposure and follow-up to demonstrate the intended effect; (D). Characterization of the study groups´ background diet and other relevant aspects of lifestyle; (E). An amount of the food or food component consistent with its intended pattern of consumption; (F). The influence of the food matrix and dietary context on the functional effect of the component; (G). Monitoring of subjects´ compliance concerning intake of food or food component under test; (H). The statistical power to test the hypothesis; 3) When the true endpoint of a claimed benefit cannot be measured directly, studies should use markers; 4) Markers should be biologically and methodologically valid; 5) Within a study the target variable should change in a statistically significant way and the change should be biologically meaningful for the target group consistent with the claim to be supported; and 6) A claim should be scientifically substantiated by taking into account the totality of the available data and by weighing the evidence	Key considerations: 1. At least one trial should be a double-blind, placebo-controlled randomized trial (RCT). 2. Product should be satisfactorily characterized. 3. Study population must appropriately reflect the target market for the final product. 4. Methodology used in obtaining statistics must be clear. 5. Study must have sufficient statistical power. 6. Actual claim must be outlined. Note: EFSA has suggested alternative wording to applicants in the past. 7. Where biomarkers are used, they must be appropriate for the claim. A study must provide evidence of the link between the change in biomarker status and the benefit to health. The dose given in the study must reflect that which will be offered on the marketplace. Proper and clear randomization must be clearly outlined.
FDA	Identifying studies: 1. Have the studies specified and measured the substance that is the subject after claim? 2. Have the studies appropriately specified and measured the specific disease or health related condition that is the subject o/the claim? Evaluation of human studies must answer the following questions: 1. Were the study subjects healthy or did they suffer the disease referenced in the health claim? 2. Did the study include an appropriate control group? 3. What type of biomarker of disease risk was measured? 4. Where were the studies conducted? (It is important that the study population be representative of the general US population.	The following requirements must be fulfilled and questions addressed in order to ensure the validity of scientific evidence: a. Studies must identify the substance and define both the disease and a target public. b. To be considered relevant, a study must be conducted on a non-diseased population. Nevertheless, the concept of "nondiseased population" is not clear. For example, if the majority of US citizens qualify as obese or is overweight, can this segment be considered a non-diseased population? c. Have biomarkers been used in the study? d. Statistical methods must be appropriate (e.g., paired T tests are not acceptable).

The fact that the FDA has two levels of scientific support:"high level," significant scientific agreement (SSA) and "low level" qualified health claim (QHC) constitutes in our view a setback. The EFSA only authorizes products with "high level" characteristics. The aim should be to encourage regulations that improve and raise scientific standards rather than create lower levels of required scientific rigor. Our recommendation is that the EFSA should continue to require "high levels" only and that the FDA should allow the highest level only. We believe the FDA should consider abandoning QHCs because the language contained in QHCs is complex, making it difficult for consumers to understand them (Berhaupt-Glickstein, & Hallman, 2017; Berhaupt-Glickstein, Nucci, Hooker & Hallman, 2014). Moreover, authors such as Meisterernst (2013) explain that there is more than just one type of consumer. The latter author suggests there are three types of consumer according to their level of understanding (vulnerable, empowered, and casual consumer) therefore most consumers do not have the ability to assess the veracity of these claims.

Furthermore, this high- and low-level classification also "leads to different levels of scientific support for similar claims which causes consumer confusion and develops an uneven playing pitch for the industry" (Lalor & Wall, 2011).

Only one specific aspect of regulation (evidence required to substantiate a health claim) was reviewed here and this research cannot be considered to be comprehensive. However, according to Martin (2010), there is a lack of comparative studies on regulatory agency requirements on scientific substantiation of health claims. Moreover, future lines of research should consider the purpose of legislation and consider the following issues: What is the objective of the legislation? Does it aim at supporting/informing on products in the market? Is it used to inform consumers? This study can thus be considered as a valid contribution to the literature on this subject. Consumer confidence in functional foods depends on the processes underlying the evaluation of claims. So does the legal certainty of manufacturers who market them. Further research on this subject would therefore be of great utility to both the industry and the general public.

Author's Contributions

The lead author of this article evaluated the pool of 743 documents initially preselected for inclusion in the review sample. Disagreements concerning the inclusion of individual studies were resolved by means of a consensus between two authors.

All the authors contributed intellectually to this research, met authorship requirements and read and approved the final version of the article.

Conflicts of Interest

The authors declare there are no conflicts of interest.

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