Outcome of a public consultation on the draft guidance for the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health

European Food Safety Authority (EFSA)

Abstract

The European Food Safety Authority (EFSA) carried out a public consultation to receive input from the scientific community and all interested parties on the draft guidance for the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health, prepared by the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA Panel) and endorsed by the Panel for public consultation at its Plenary meeting on 28 June 2017. The written public consultation for this document was open from 12 July to 3 September 2017. EFSA received comments from 8 interested parties. EFSA and its NDA Panel wish to thank all stakeholders for their contributions. The current report summarises the outcome of the public consultation, and includes a summary of the comments received and how the comments were addressed. The NDA Panel prepared an updated version of the guidance taking into account the comments received. The guidance was discussed and adopted at the NDA Panel Plenary meeting on 13 December 2017, and is published in the EFSA Journal.

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Key words: health claims, scientific requirements, antioxidants, oxidative damage, cardiovascular health, public consultation

Requestor: EFSA

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1. Introduction

1.1. Background and Terms of Reference as provided by EFSA

Background

Regulation (EC) No 1924/2006\(^1\) harmonises the provisions related to nutrition and health claims and establishes rules governing the Community authorisation of health claims made on foods. According to the Regulation, health claims should only be authorised for use in the Community after a scientific assessment of the highest possible standard to be carried out by EFSA.

Owing to the scientific and technical complexity of health claims, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA Panel) has placed considerable effort into developing scientific criteria for the substantiation of health claims, and has published guidance on the scientific substantiation of health claims since 2007\(^2\).

In the last years, the NDA Panel has gained considerable experience in the evaluation of health claim applications. To further assist applicants seeking approval of health claims, EFSA launched in 2014 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. 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. The format(s) under which such guidance will be provided to applicants (e.g. guidance documents, and/or searchable, interactive databases) will be carefully considered by EFSA.

In this context, note is taken of the need to adapt the existing guidance on the scientific requirements for health claims to the new scientific and technical developments in specific areas taking into account lessons learned from the evaluation of health claim applications and the information collected from the grant.

To this end, the NDA Panel is asked to update the existing guidance on the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health published in 2011\(^3\).

Terms of reference

The NDA Panel is requested by EFSA to update the existing guidance on the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health.

The guidance document shall clarify and address the scientific and technical developments in this area, taking into account the experience gained by the NDA Panel with the evaluation of health claims and the information collected from the grant.

The draft guidance shall be released for public consultation prior to finalisation, and shall be revised taking into account the comments received during the public consultation before adoption by the NDA Panel. A technical report on the outcome of the public consultation shall be published.

1.2. Consideration

Following a request from EFSA to the NDA Panel to update the existing guidance document on the scientific requirements for the substantiation of health claims related to antioxidants, oxidative damage and cardiovascular health published in 2011, the NDA Panel developed a guidance on the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health (hereafter ‘guidance’).

To further assist applicants, EFSA launched in 2014 a grant (GP/EFSA/NUTRI/2014/01) which aimed at gathering information in relation to claimed effects, outcome variables and methods of measurement in the context of the scientific substantiation of health claims. The information collected helped to inform the NDA Panel and served as a basis for updating this guidance to applicants.

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In line with EFSA’s policy on openness and transparency, and in order for EFSA to receive comments on its work from the scientific community and stakeholders, EFSA engages in public consultations on key issues. Accordingly, the draft guidance was discussed and endorsed by the NDA Panel at its plenary meeting on 28 June 2017. The written public consultation for this document was open from 12 July to 3 September 2017 (see Appendix A). The NDA Panel prepared an updated version of the guidance, taking into account the comments received. The updated guidance was discussed and adopted at the NDA Plenary meeting on 13 December 2017, and is published in the EFSA Journal (EFSA NDA Panel, 2018). EFSA is committed to publishing the comments received during the public consultation, as well as a short report on the outcome of the consultation.

2. Assessment

2.1. Comments received

EFSA received 31 comments submitted by means of the electronic form on the EFSA website (Appendix B) and 2 comments submitted by e-mail (Appendix C) from 8 interested parties, including the food industry and food industry associations, and a governmental organisation.

Table 1: List of organisations submitting comments

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Country</th>
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<tbody>
<tr>
<td>Alliance for Natural Health International</td>
<td>UK</td>
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<tr>
<td>Evonik Nutrition &amp; Care GmbH</td>
<td>DE</td>
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<tr>
<td>Health Food Manufacturer’s Association</td>
<td>UK</td>
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<tr>
<td>Individual</td>
<td>UK</td>
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<tr>
<td>Living Life</td>
<td>UK</td>
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<tr>
<td>Nestlé Research Center</td>
<td>CH</td>
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<tr>
<td>New Zealand Ministry for Primary Industries</td>
<td>NZ</td>
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<tr>
<td>Unilever R&amp;D</td>
<td>NL</td>
</tr>
</tbody>
</table>

CH: Switzerland; DE: Germany; NL: Netherlands; NZ: New Zealand; UK: United Kingdom.

A summary of the comments received is given below. All written comments are listed in Appendices B and C. Several parties submitted identical comments.

2.2. General comments

Many comments related to general issues that are rather common to all health claims, but not specific to health claims covered by the guidance for the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health.

Issues related to the scientific substantiation that are common to all claims are addressed in the General scientific guidance on health claim applications (EFSA NDA Panel, 2016a), and will not be reiterated in the present report and in the guidance for the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health.

2.2.1. Comments related to the EFSA assessment approach

Comments were received requesting changes in relation to the approach used by EFSA for the scientific evaluation of health claims. Such comments mentioned:

(a) reliance on the data submitted by an applicant while ignoring existing evidence, that prevents the authorisation of claims being accessible to corporations other than the largest;
(b) an approach closer to the one required for drug licensing;
(c) a series of elements which EFSA should consider for its scientific evaluation of health claims even if not foreseen in Regulation (EC) No 1924/2006, such as provision for evidence of association, grading of the evidence, plausibility of the evidence.
The role of EFSA, the legal framework, the hierarchy of evidence and the approach/criteria used by the Panel for the scientific substantiation of health claims by taking into account the totality of the available scientific data and, where applicable, by weighing the evidence, have been extensively explained in the General scientific guidance on health claim applications (see sections 4, 6, 7.3 and 7.4) and also in the Technical report on the outcome of a public consultation on the draft general scientific guidance for stakeholders on health claim applications.

Comments (a)–(c) are therefore not discussed further in the present report and were not taken into account in updating the guidance.

2.2.2. Comments related to risk management

Several comments referred to risk management aspects, which are outside EFSA’s remit. Such comments mentioned:

(a) absence of rationale for the authorisation of a claim related to “copper and the protection of cells from oxidative stress” for which the conditions of use are 15% of the Nutrient Reference Value (150 mcg/dose), arguing that such an amount is arbitrary and unrelated to the scientific evidence for the mineral in question;

(b) that health claims for a wide range of foods with known beneficial properties (e.g. polyphenol-rich berry fruits), or for foods that meet specific conditions, i.e. amounts of polyphenols (total or specific) per portion or dose (e.g. “[food x] contains polyphenols that are a dietary source of antioxidants”), should be allowed. It was argued that foods or nutrients that increase ‘overall antioxidant capacity of plasma’, as demonstrated from in vivo human studies, are beneficial to humans.

(c) that a nutritional claim for a functional category or classes/groups of “nutrients”, e.g. polyphenols or flavonoids, should be allowed;

(d) a provision to adapt health claim wordings to fit current nutritional scientific knowledge, e.g. the Mediterranean diet (e.g. “contains olive oil, daily consumption of 15-60g/day of which is associated with a reduced risk of heart disease” based on Cochrane and PREDIMED among other scientific studies/publications);

(e) that food business operators should be allowed to communicate to consumers on foods/substances that are rich sources of nutrients able to act as antioxidants;

(f) a proposal to risk managers to relate ‘normal homocysteine metabolism’ directly to cardiovascular disease risk in the claim wording, and to categorise ‘homocysteine normalisation claims’ as Article 14.1(a) disease risk reduction claims.

EFSA wishes to emphasise that the principle applied by EFSA for the scientific substantiation of claims based on the essentiality of nutrients is clearly explained in the General scientific guidance on health claim applications (sections 6.1, 7.8 and 7.9). For these claims (including ”copper contributes to the protection of cell constituents from oxidative damage”), conditions of use are set on the basis that any significant amount of the essential nutrient in the diet will contribute to the claimed effect (e.g. conditions of use can be linked to nutrition claims).

Decisions regarding the authorisation of nutrition and health claims made on foods or category of foods/nutrients, including the final wording and the conditions/restrictions of use, and the interpretation of the scope of Regulation (EC) No 1924/2006 (e.g. whether a claim could be categorised as Article 14.1(a)) are taken by risk managers. In order to make such decisions, risk managers may take into account other legitimate factors, such as consumer understanding (e.g. to modify the wording of the claim), in addition to EFSA’s scientific evaluation.

Based on the evidence provided so far for the scientific substantiation of claims which assessed changes in the overall antioxidant capacity of plasma in vivo in human studies, it has not been established that such changes per se exert a beneficial physiological effect in humans as required by Regulation (EC) No 1924/2006. It is the responsibility of applicants to provide the rationale and pertinent data to establish such relationship in the context of specific applications that will be considered by the Panel.
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Comments (a)–(f) should therefore be addressed to the risk managers (European Commission and Member States), rather than to EFSA. They are not discussed further in the present report and were not taken into account in updating the guidance.

2.2.3. Comments related to the use of observational data

Clarification was requested on the use of observational data for the scientific substantiation of claims, namely:

(a) whether they can be used on their own, in place of randomised controlled trials (RCTs);
(b) what would be the population size/statistical power required;
(c) how they can be considered as supportive evidence, e.g. in view of a risk factor being linked to cardiovascular disease (CVD) risk.

EFSA wishes to highlight that the use of observational data in the substantiation of health claims is addressed in the General scientific guidance on health claim applications in the context of claims based on the essentiality of nutrients (sections 6.1), claims other than those based on the essentiality of nutrients (sections 6.2, 7.4), and for the characterisation of the claimed effect for reduction of disease risk claims (section 7.2.2); examples of type of evidence required for the scientific substantiation of health claims are depicted in section 7.3 of the General scientific guidance.

It is not the role of EFSA to provide instructions on the design of scientific studies (e.g. statistical power/population size), which depends on the specific study objectives/research questions and the hypotheses. Applicants are encouraged to consult epidemiologists/biostatisticians for that purpose.

As outlined in the afore-mentioned General guidance, pertinent human (intervention and observational) studies are central for health claim substantiation. Pertinent human intervention studies are at the top of the hierarchy that informs decisions on substantiation because it is of utmost importance to show that the food/constituent can exert the claimed effect in humans, and that the effect is specific for the food/constituent, information which can only be obtained from human intervention studies. Human intervention (and observational) studies can also provide evidence for a dose–response relationship and for consistency of the effect (or the association) across studies. Each relationship between a food/constituent and a claimed effect is assessed by EFSA separately on a case by case basis for specific claim applications. There is no pre-established rule as to how many or which types of studies are needed for substantiation.

No change was introduced in updating the guidance on the basis of these comments.

2.3. Specific comments

Comments received

1. Several comments related to health claims based on the essentiality of nutrients and to outcome variables/methods of measurement which have not been previously considered by the Panel in the context of specific applications. In particular, there were requests to consider in the guidance:

(a) additional claims based on the essentiality of nutrients;
(b) the use of inflammatory biomarkers as outcome variables in health claim substantiation, since inflammation plays a central role in the pathophysiology of cardiovascular diseases, and the simultaneous measurement of several inflammatory biomarkers for the substantiation of a health claim related to cardiovascular related-inflammation;
(c) biomarkers (e.g. C-reactive protein (CRP), Apolipoprotein A1 (ApoA1), Apolipoprotein B (ApoB), small particle LDL, ox-LDL) around which there is now sufficient scientific evidence regarding oxidative stress;
(d) other acceptable biomarkers for claims on a beneficial change in the blood lipid profile, e.g. plasma ox-LDL and small particle LDL concentrations/fractions; ApoA1 and ApoB, measured alongside CRP, and especially high-sensitivity C-reactive protein (hs-CRP);
(e) other acceptable outcomes than the incidence of coronary heart disease (CHD) for claims on the maintenance of normal cardiac function, such as: cardiac rhythm-related outcomes (e.g. through measurement of parameters related to heart rate), cellular mechanisms (e.g. mitophagy or autophagy);

(f) other appropriate outcomes for claims related to endothelium-dependent vasodilation, e.g. “cerebral blood flow” as measured for example by arterial spin labelling magnetic resonance imaging, laser Doppler flowmetry, or near-infrared spectroscopy, “retinal blood flow” as measured for example by Doppler optical coherence tomography flowmetry, and “skin blood flow” as measured for example by laser Doppler flowmetry.

Panel consideration of comments received

Ad1. As outlined in Section 2 of the guidance, the guidance cannot provide advice on health claims (e.g. additional claims based on the essentiality of nutrients, health claim related to cardiovascular related-inflammation) which have not been evaluated by the Panel, nor set out an exhaustive list of beneficial physiological effects and outcome variables/methods of measurement which could be acceptable for claim substantiation. This is because defining the conditions under which health relationships and outcome variables/methods of measurement for claimed effects may be acceptable is possible only in the context of specific applications, which are often unique and technically complex (e.g. health relationships and outcome variables which may be acceptable in the context of a particular application may not be so in the context of another application with, for example, a different target population). No change was introduced in updating the guidance on the basis of these comments.

Comments received

2. There were requests to specify relevant points identified from the examples of claims evaluated by the Panel cited in the guidance.

Panel consideration of comments received

Ad2. Relevant issues/shortcomings identified from examples of claims evaluated favourably/unfavourably by the Panel have been included throughout the updated guidance.

Comments received

3. There were several questions about the rationale behind the study duration required for different claimed effects. In this context,

(a) It was noted that a metabolic steady-state in blood lipid and lipoprotein concentrations after a dietary intervention is reached within 3-4 weeks, and therefore the eight week duration requested in the guidance does not seem to be justified.

(b) In the absence of a rationale, the minimal duration of human intervention studies required should be harmonised across the different beneficial physiological effects to at least four weeks.

Panel consideration of comments received

Ad3. In principle, the study duration should be adequate not only to allow changes in the primary outcome but also to reflect long-term effects (with continuous consumption of the food/constituent), to investigate whether the changes observed are sustained or disappear, i.e. whether adaptation mechanisms come into place, and to exclude chance findings (e.g. for fluctuating outcome measures) (General scientific guidance on health claim applications, section 7.4).

The guidance document mentioned indicative study duration of eight weeks for intervention studies investigating the effects of a food/constituent on blood lipids, blood pressure and blood concentrations of homocysteine to assess the sustainability of the effect over time during continuous consumption of the food/constituent in order to exclude adaptation through compensatory mechanisms. The Panel acknowledges that blood lipids, blood pressure, and blood concentrations of homocysteine tend to stabilise after 3-4 weeks in response to fixed nutritional interventions. However, the time needed to reach such stabilisation may depend on the study characteristics (e.g. appropriate run-in period) and the nature of the intervention.
In this context, the guidance has been amended as follows: “Regarding the study duration, blood lipids tend to stabilise after about 4 weeks in response to fixed nutritional interventions. However, the time needed to reach such stabilisation may depend on the study characteristics (e.g. appropriate run-in period) and the nature of the intervention. Evidence on the sustainability of the effect with continuous consumption of the food/constituent over longer periods of time (e.g. eight weeks) should be provided”.

This applies to sections 3.3.2 ‘Claims on a beneficial change in the blood lipid profile’, 3.3.4 ‘Claims on the maintenance of normal (arterial) blood pressure’, and 3.3.8. ‘Claims on the maintenance of normal blood homocysteine concentrations by contributing to normal homocysteine metabolism’.

Comments received

4. There were several questions regarding the use of results obtained in study groups under pharmacological treatment for the substantiation of health claims targeting the general population or subgroups thereof, namely:

(a) whether the results obtained in subjects receiving pharmacological treatment for a condition could be used for the substantiation of health claims targeting another physiological variable (e.g. hypercholesterolaemic or hypertriglyceridaemic subjects under blood-pressure lowering medications for claims on a beneficial change in the blood lipid profile or the reduction of post-prandial blood concentration of triglycerides, respectively; hypertensive subjects on cholesterol-lowering medications for claims on the maintenance of normal (arterial) blood pressure;

(b) whether there were examples of suitable study groups on pharmacological treatment for a condition which is the target of the claim because of lack of interaction between the food/constituent and the medications used on the claimed effect;

(c) guidance was requested regarding extrapolation of the results from study groups on pharmacological treatment for a disease/condition and/or under pharmacological treatment for the disease/condition to the general population (or the target population for the claim) if the condition/use of the medication is widespread among the general population (or target population).

Panel consideration of comments received

Ad4. The Panel wishes to clarify that:

In all cases, a rationale for extrapolation of the results from the study group to the target population should be provided where the study group is different from the target population. The rationale for extrapolation of the results from the study group to the target population will be evaluated by the Panel on a case-by-case basis depending on the context of each specific application.

If subjects are under pharmacological treatment (whether or not for the claimed function/effect), the Panel considers whether the effect of the food/constituent is also reasonably expected to occur in subjects without medication (e.g. evidence for a lack of interaction between the food and the medications used on the claimed effect or evidence that the medication does not affect the claimed effect, as appropriate). For instance, cholesterol-lowering medications may also affect blood pressure (Strazzullo P et al., 2007).

A lack of interaction between a food/constituent and a medication on the claimed effect can be demonstrated when the mechanism of action for both the food/constituent and the medication is known and different from each other. Whenever the mechanism by which the food/constituent may exert the claimed effect is unknown, the default assumption is that an interaction between the food/constituent and the medication used on the claimed effect exists, and therefore the results obtained in subjects under medication cannot be extrapolated to the target population for the claim (subjects not under medication).

Examples for a lack of interaction between the food/constituent and the medications used on the claimed effect include plant sterols/stanols and statins on blood LDL-cholesterol concentrations, as well as some dietary fibres (e.g. arabinoxylan, pectins) and some anti-
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Diabetic medications (e.g. metformin, insulin) on post-prandial blood glucose responses. In both cases, the food/constituent (plant sterols/stanols, dietary fibres) reduces or slows down the absorption of dietary fat or glucose in the small intestine, whereas the medications (statins, some anti-diabetic medications) affect either cholesterol or glucose metabolism.

Whenever the food/constituent and the medication act through the same (or similar) mechanisms, an interaction can be expected.

A footnote has been added to clarify the above in section 3.3.2 of the updated guidance.

2.3.1. Function claims related to cardiovascular health [Section 3.3]

Comments received

5. It was suggested to rephrase the paragraph lines 275-279, i.e. “Evidence for a beneficial change in two of these outcome variables (i.e. for a reduction in blood LDL-cholesterol (LDL-c) concentrations; for a reduction in arterial (systolic) blood pressure (SBP)) is sufficient for the scientific substantiation of both function claims [...] and reduction of disease risk claims related, for example, to the risk of coronary heart disease...”. As such, it gives the impression that a beneficial change on both LDL-c and BP should be demonstrated.

Panel consideration of comments received

Ad5. For clarity, the guidance has been amended to read as follows: “Evidence for a reduction in blood LDL-cholesterol (LDL-c) concentrations is sufficient for the scientific substantiation of both function claims (i.e. on the maintenance of normal blood LDL-c concentrations) and reduction of disease risk claims related, for example, to the risk of coronary heart disease (CHD). The same applies to evidence for a reduction in arterial (systolic) blood pressure (SBP) (see section 3.4).

Comments received

6. A stakeholder requested to include a sub-chapter on arterial elasticity/stiffness as markers of cardiovascular health. The proposed rationale includes: arterial elasticity contributes to the maintenance of an adequate blood flow to body cells/tissues; the consequences of reduced arterial elasticity/stiffness include the development of systolic hypertension, systolic heart failure, and small vessel ischaemia; arterial stiffness has been identified as an independent predictor of these cardiovascular morbidities and of cardiovascular mortality; arterial elasticity/stiffness can be assessed in vivo by, for example, carotid-femoral pulse wave velocity (PWV), cardio-ankle vascular index (CAVI).

Panel consideration of comments received

Ad6. The Panel acknowledges that a function claim on the maintenance of the elastic properties of the arteries using measures of arterial stiffness as the outcome variable to assess the claimed effect in vivo in humans has already been evaluated by the Panel (EFSA NDA Panel, 2009), and therefore the Panel considers it appropriate to include such claimed effect in the guidance document.

A new section 3.3.5 has been incorporated to the revised version of the guidance as follows:

"Claims on maintenance of the elastic properties of the arteries"

The elastic properties of conduit arteries vary along the arterial tree. The more elastic (compliant) proximal arteries (e.g. the aorta and its primary branches) mainly attenuate blood flow fluctuations generated by the intermittent pumping of the heart, whereas the more muscular distal arteries mainly contribute to the propagation of the pressure wave. A decrease in the compliance (i.e. in the ability to expand and contract in response to pressure changes through an increase in arterial stiffness) of the big elastic arteries leads to an increase in mean blood pressure, with a disproportionate increase in SBP and little changes in DBP, owing to both increased amplitude of the pressure wave and increased wave velocity. Changes in the stiffness gradient of the arterial tree are observed with ageing, hypertension and diabetes, among
Maintenance of the elastic properties of the arteries is considered a beneficial physiological effect.

The scientific evidence for the substantiation of health claims on the maintenance of the elastic properties of the arteries can be obtained from human intervention studies showing a reduction in indices of arterial stiffness. Evidence on the sustainability of the effect with continuous consumption of the food/constituent over extended periods of time (e.g. 4-8 weeks) should be provided.

Carotid-femoral pulse wave velocity (PWV) is the gold-standard measurement of arterial stiffness. Non-invasive determinations of wave reflections can also be obtained by central pulse-wave analysis through three major parameters: central pulse pressure, central systolic pressure, and the augmentation index (AIX). Central pressure, the AIX, and PWV cannot be used interchangeably as indexes of arterial stiffness because, in contrast to PWV, which is a direct measure of arterial stiffness, central pressure and the AIX are only indirect, surrogate measures of arterial stiffness. There is consensus on the methodological aspects to be considered when measuring arterial stiffness in vivo in humans (Laurent et al., 2006; Van Bortel et al., 2012).

A health claim on the maintenance of the elastic properties of the arteries, by measuring the arterial stiffness, has been evaluated by the Panel with an unfavourable opinion (EFSA NDA Panel, 2009) on the basis that, in addition to the methodological weaknesses of the study submitted for substantiation, the study did not use a generally accepted method for the assessment of arterial stiffness (calculated as ambulatory arterial stiffness index (AASI) from 24-h ABPM measurements)“.

The Panel took note of the publications referred to by the stakeholder proposing other methods and indices for measuring arterial stiffness, which have not been evaluated by the Panel, and considers that their appropriateness for claim substantiation will be assessed by the Panel on a case-by-case basis in the context of specific applications (see also Ad1).

2.3.1.1. Claims on a beneficial change in the blood lipid profile [Section 3.3.2]

Comments received

7. It was considered that measurements of blood lipid markers can be performed under non-fasting conditions, especially for LDL-c and HDL-c, according to a joint consensus statement. It was also proposed that the maintenance of normal blood TG can relate to both fasting and non-fasting blood TG concentrations, because recent observational studies have identified non-fasting TG concentrations to be a superior predictor of CVD risk compared to fasting concentrations.

Panel consideration of comments received

Ad7. The Panel notes that the consensus statement mentioned in the comments (Nordestgaast et al., 2016) refers to measures of the blood lipid profile for routine use in clinical practice (e.g. for the diagnosis of dyslipidaemias, for CVD risk characterisation, for decisions regarding pharmacological treatment), rather than to repeated measures of the blood lipid profile to assess changes in response to an intervention. In the consensus statement, the maximal mean changes at 1–6 h after habitual meals with respect to fasting versus non-fasting values for triglycerides, total cholesterol, LDL-cholesterol and therefore for non-HDL cholesterol are deemed to be not clinically significant (Nordestgaard BG, 2017). However, the Panel notes that, in intervention studies where the effects of the intervention on these variables are expected to be small (e.g. such as for most nutritional interventions), it is important to standardise the blood sampling conditions so that any differences from baseline between groups can be attributed to the intervention rather than to the sampling conditions. In this context, the Panel agrees that non-fasting measurements of the blood lipid profile could be used for the scientific substantiation of these claims, as long as the conditions in which blood sampling is obtained is adequately standardised within each study.

The guidance has been updated accordingly.
2.3.1.2. Claims on the reduction of post-prandial blood concentration of triglycerides [Section 3.3.3]

Comments received

8. Guidance was requested on the criteria to assess the reliability of study findings in the absence of standardised measurements of postprandial triglycerides and lack of specific reference ranges. In this context, it was requested to define the appropriate period of time for the monitoring of a post-prandial challenge (e.g. should be at least 4 hours post-prandially) and the different time points for blood sampling in order to assess triglyceride concentrations.

Panel consideration of comments received

Ad8. The Panel notes that the lack of “specific reference ranges” for post-prandial TG concentrations does not hamper the comparison between test food(s) vs. a reference food in intervention studies with respect to this outcome variable. Generally, measurements should be taken for at least 4 hours, with the first two measurements taken at 30 min and 60 min post-prandial, and every hour thereafter. The guidance has been amended accordingly.

2.3.1.3. Claims on the improvement of endothelial functions [Section 3.3.6]

Comments received

9. Comments were received regarding claims on endothelial functions. In particular,

(a) it was asked to state that the claim “endothelium-dependent vasodilation” is a beneficial physiological effect accepted by EFSA;

(b) it was also asked whether the acute change in ED-FMD occurring shortly after consumption of the food/constituent would be considered an appropriate outcome for a claim related to postprandial ED-FMD;

(c) it was requested to specify other appropriate outcomes for EDV-related claims, e.g. “cerebral blood flow” as measured for example by arterial spin labelling magnetic resonance imaging, laser Doppler flowmetry, or near-infrared spectroscopy, “retinal blood flow” as measured for example by Doppler optical coherence tomography flowmetry, and ”skin blood flow” as measured for example by laser Doppler flowmetry.

Panel consideration of comments received

Ad9. As already outlined in the updated guidance, in section 3.3.6:

“The effect of a food/constituent on endothelium-dependent vasodilation can be expressed as changes in endothelium-dependent FMD (ED-FMD) either in fasting conditions after regular consumption of the food/constituent, or as acute changes in ED-FMD occurring shortly after consumption of the food/constituent”. The Panel considers that “A sustained increase in endothelium-dependent vasodilation in fasting conditions in response to an intervention (regular consumption of a food/constituent for at least four weeks) is a beneficial physiological effect”.

No evidence has been provided that post-prandial changes in ED-FMD can be considered, per se, beneficial physiological effects in humans. Measurements of acute changes in ED-FMD occurring shortly after consumption of the food/constituent can provide, under certain conditions and depending on the context of a specific application, supportive evidence for substantiation of claims on the improvement of endothelial functions (EFSA NDA Panel, 2012).

No applications have been evaluated by the Panel in which changes in cerebral, retinal or skin blood flow have been proposed as outcome variables for the scientific substantiation of a health claim, either in relation to claims on endothelial functions or otherwise. The appropriateness of these outcome variables for claims substantiation will be considered by the Panel on a case-by-case basis in the context of specific applications (see also Ad1).
2.3.1.4. Venous blood flow [Section 3.3.9]

Comments received

10. It was suggested to state that maintenance of normal venous-capillary permeability is a valid outcome, to specify the appropriate method(s) of measurement, and to consider a separate section for normal venous-capillary permeability.

Panel consideration of comments received

Ad10. The Panel has received a limited number of applications on claims related to venous-capillary permeability, in which no appropriate outcome variable(s)/method(s) of measurement have been proposed, and none has been evaluated with a favourable outcome that can be used to provide guidance to applicants on the scientific requirements for the substantiation of these claims.

Claims related to venous function are already covered in the section on venous blood flow. No change has been introduced in the updated guidance on the basis of this comment.

2.3.2. Reduction of disease risk claims related to cardiovascular diseases [Section 3.4]

Comments received

11. There were several comments, questions and suggestions regarding acceptable risk factors for reduction of disease risk claims related to cardiovascular diseases. In particular, it was requested to explain why only LDL-cholesterol and systolic blood pressure (and not triglycerides, or other markers) have been considered on their own as relevant to substantiate disease risk reduction claims. Several other outcome variables were proposed as risk factors for disease risk claims related to cardiovascular diseases, including ApoA1, ApoB, small particle LDL, ox-LDL, C-reactive protein (CRP), and especially high-sensitivity (hs)-CRP, the carotid intima-media thickness (cIMT), TG, and measures of arterial stiffness.

Panel consideration of comments received

Ad11. The general principles applied by the Panel for disease risk reduction claims are explained in the General scientific guidance on health claim applications (i.e. Section 7.2.2. Characterisation of the claimed effect for reduction of disease risk claims).

The rationale for the use of LDL-cholesterol and systolic blood pressure as the only outcome variables needed for the substantiation of reduction of disease risk claims related to CVDs (namely CHD and stroke) is outlined in the updated Guidance, section 3.4 “Reduction of disease risk claims related to cardiovascular diseases”. The use of proposed risk factors other than LDL-c and SBP is acceptable if evidence is provided for a reduction in the incidence of the disease, and that possibility is also outlined in the updated guidance, section 3.4 “Reduction of disease risk claims related to cardiovascular diseases”.

For proposed risk factors other than LDL-c and SBP (e.g. HLD-c, homocysteine, TG concentrations, arterial stiffness), there is some evidence for an independent association between the proposed risk factor and the incidence of some cardiovascular diseases from observational studies, and the involvement of the risk factor in the development of the disease is biologically plausible. However, changes in any of these factors (by dietary modification and/or drugs) have not generally been shown to reduce the risk of any cardiovascular disease. A reduction of the proposed risk factor may be considered a beneficial physiological effect in the context of a reduction of disease risk claim. However, evidence that the dietary intervention with the specific food/constituent induces a reduction (or beneficial alteration) of the risk factor and also a reduction of the risk of disease needs to be provided.

The Panel will consider on a case-by-case basis in the context of specific applications other risk factors (e.g. ApoA1, ApoB, small particle LDL, ox-LDL, C-reactive protein (CRP), hs-CRP, the carotid intima-media thickness (cIMT)) that have been proposed in the comments received but have not been evaluated by the Panel in the context of a reduction of disease risk claim application.
No change has been introduced in the updated guidance on the basis of this comment.

Comments received

12. It was requested to clarify that the requirement to provide evidence for a reduction in the incidence of the disease is in relation to these other risk factors, noting that Lines 546 and 547 are currently not specific as to which risk factors they are referring.

Panel consideration of comments received

Ad12. The guidance has been amended as follows: “Evidence for a reduction in the incidence of the disease (e.g. CHD, stroke) is necessary, but not sufficient, for the scientific substantiation of reduction of disease risk claims related to risk factors other than LDL-c and arterial SBP. Evidence for a beneficial alteration of one or more risk factors (e.g. reduction in blood concentration of (fasting) TG, reduction in blood homocysteine concentration, or an increase in blood HDL-c concentration) with the consumption of the food/constituent is also required”.

EFSA and its NDA Panel wish to thank all stakeholders for their comments and contributions.

References


EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2009. Scientific Opinion on the substantiation of health claims related to isoleucine-proline-proline (IPP) and valine-proline-proline (VPP) and maintenance of normal blood pressure (ID 615, 661, 1831, 1832, 2891), and maintenance of the elastic properties of the arteries (ID 1832) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 on request from the European Commission. EFSA Journal 2009;7(9):1259, 18 pp. doi:10.2903/j.efsa.2009.1259


## Glossary and Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>AIX</td>
<td>Augmentation index</td>
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<tr>
<td>ApoA1</td>
<td>Apolipoprotein A1</td>
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<tr>
<td>ApoB</td>
<td>Apolipoprotein B</td>
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<tr>
<td>cIMT</td>
<td>Carotid intima-media thickness</td>
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<td>CAVI</td>
<td>Cardio-ankle vascular index</td>
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<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<td>CV</td>
<td>Cardiovascular</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<td>CVI</td>
<td>Chronic venous insufficiency</td>
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<td>DBP</td>
<td>Diastolic blood pressure</td>
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<td>ED-FMD</td>
<td>Endothelium-dependent flow-mediated dilation</td>
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<td>EDV</td>
<td>Endothelium-dependent vasodilation</td>
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<td>EIVD</td>
<td>Endothelium-independent vasodilation</td>
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<tr>
<td>FMD</td>
<td>Flow-mediated dilation</td>
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<td>HDL-c</td>
<td>High-density lipoprotein cholesterol</td>
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<td>Hs-CRP</td>
<td>High-sensitivity C-reactive protein</td>
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<td>LDL-c</td>
<td>Low-density lipoprotein cholesterol</td>
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<td>Ox-LDL</td>
<td>Oxidised LDL</td>
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<td>PWV</td>
<td>Pulse wave velocity</td>
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<td>SBP</td>
<td>Systolic blood pressure</td>
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<td>TG</td>
<td>Triglyceride</td>
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Appendix A — Explanatory text for the Public consultation on the draft guidance for the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health (revision 1)

EFSA has launched an open consultation on its draft guidance for the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health (revision 1).

This document is intended to assist applicants in preparing applications for the authorisation of health claims related to the antioxidants, oxidative damage and cardiovascular health. It focuses on key issues, particularly:

- claimed effects which are considered to be beneficial physiological effects, and
- characteristics of the human intervention studies which can provide evidence for the scientific substantiation of specific claims addressed in this guidance.

In line with EFSA’s policy on openness and transparency and in order for EFSA to receive comments from the scientific community and stakeholders, EFSA has launched a public consultation on the draft document developed by the NDA Panel of EFSA.

Interested parties are invited to submit written comments by 3 September 2017. Please use the electronic template provided to submit comments and refer to the line and page numbers. Please note that after 2 hours your working session will expire and comments submitted after that time will not be recorded and transmitted. If you would like to submit additional data to support your comments or files send an email to: NDA.PublicConsult.99@efs.europa.eu. Please note that comments will not be considered if they:

- are submitted after the closing date of the public consultation;
- are not related to the contents of the document;
- contain complaints against institutions, personal accusations, irrelevant or offensive statements or material;
- are related to policy or risk management aspects, which are out of the scope of EFSA’s activity.

EFSA will assess all comments from interested parties which are submitted in line with the criteria above. The comments will be further considered by the relevant EFSA Panel and taken into consideration if found to be relevant.

Persons or entities participating in the EFSA Public Consultation are responsible for ensuring that they hold all the rights necessary for their submissions and consequent publication by EFSA. Comments should inter alia be copyright cleared taking into account EFSA’s transparency policy and practise to publish all submissions. In case your submission reproduces third party content in the form of charts, graphs or images, please ensure that the required prior permissions of the right holder have been obtained.

All comments submitted will be published. Comments submitted by individuals in a personal capacity will be presented anonymously. Comments submitted formally on behalf of an organisation will appear with the name of the organisation.

Submit comments (deadline: 3 September 2017).
### Appendix B – Full list of comments submitted by means of the electronic form on the EFSA website

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<tr>
<th>Organisation</th>
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<th>Comment</th>
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<tr>
<td>Alliance for Natural Health</td>
<td>0. Generic comments</td>
<td>The guidance is useful but in places does not provide sufficient detail of requirements and excludes certain key biomarkers (e.g. CRP, ApoA1, ApoB, small particle LDL, ox-LDL) around which there is now sufficient scientific evidence regarding oxidative stress or CVD risk reduction.</td>
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| Living Life                         | 0. Generic comments | Requirement for a global change to EFSA assessment approach Article 6(1) of the Nutrition and Health Claims Regulation (1924/2006/EC requires that “...health claims shall be based on and substantiated by generally accepted scientific 2 evidence”, while Article 13(1)(c)(ii) also requires that such claims are “well understood by the average consumer.” EFSA has evolved a highly reductionist approach, that relies almost entirely on the data that have been submitted by an applicant while ignoring the peripheral, existing evidence. This approach fails to meet the legal requirements and results in discretion, disproportionality and inequality in considering the overall evidence in relation to beneficial foods and nutrients. For example, it is not scientifically rational that there is an authorised claim for 15% of the Nutrient Reference Value (150 mcg/dose) of copper (this amount being arbitrary and unrelated to the scientific evidence for the mineral in question) relating to “the protection of cells from oxidative stress”, while there is no claim for any botanical substance for this same function. This is despite generally accepted evidence that plant-based diets are strongly associated with protection against oxidative stress and chronic disease risk, viz (including references therein): Hever J, Cronise RJ. Plant-based nutrition for healthcare professionals: implementing diet as a primary modality in the prevention and treatment of chronic disease. J Geriatr Cardiol. 2017; 14(5): 355–368. EFSA should review the entirety of its approach, not simply tweak guidelines, a process that prevents the claims authorisation pathway being accessible to corporations other than the largest. The latter represent the only stakeholder group with the financial capacity to pay for the EFSA-specific trials that are effectively creating a new paradigm in nutritional science that is becoming ever-closer to the approach required for drug licensing. From causal evidence to evidence of association
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|                                     |          | One of the major stumbling blocks for EFSA is its decision to require causal evidence of a highly conclusive or unequivocal nature. Such a view requires that the totality of scientific evidence on which a claim is based is entirely free of any contradictions. This is very rarely the case with nutritional science, where the evidence continues to emerge and for which there are differences in individual response as result of differences in nutritional requirement, physiological stress, gene expression, epigenetic background, polymorphisms, xenobiotic exposure, etc. The nature of nutritional research and public health policy that has evolved alongside it is that evidence of association has been sufficient to justify the vast majority of public health advice, such as salt reduction, increased fruit and vegetable intake or decrease in certain categories of food (e.g. foods high in sugars, processed... |
meats).

For the purpose of the Regulation and to ensure the public is both informed and not misled, EFSA should adapt its scientific approach so as to include evidence of association between the consumption of particular foods or nutrients and beneficial effects. Such an approach would then allow health claims to be made for a wide range of foods with known beneficial properties such as polyphenol-rich berry fruits which have yet to receive authorised health claims.

Another indication of the failure of EFSA’s assessment methodology is the rejection of health claims for any of the essential amino acids, without which humans cannot survive.

From conclusive to plausible evidence

Linked to the need by EFSA, in order to fulfil its role as a scientific assessor, is the degree of conclusivity of the evidence. It is well established that nutritional science is rarely black and white, and given it is an emerging science that relates to a highly complex and variable interaction between multiple population groups, is not appropriate that only highly conclusive evidence is accepted.

The notion of graded evidence has already been widely used in many branches of medical and nutritional science. It continues to be used effectively by the Therapeutic Research Center’s Natural Medicines™ Professional Database (https://naturalmedicines.therapeuticresearch.com/), formerly Natural Standard™, where the available proposed evidence is broken into one of 6 categories depending on the strength or conclusivity of that evidence: https://naturalmedicines.therapeuticresearch.com/grading.aspx.

Given that establishing highly conclusive evidence, either for licensed pharmaceutical products and even more from foods and related substances, that are consumed alongside varying diets by highly variable population groups, provision of plausible evidence should be sufficient.

The dismissal of health claims based on all but highly conclusive evidence has resulted in hundreds of plausible or credible claims, such as the benefits associated with consumption of essential amino acids, being rejected and now being ‘non-authorised’ throughout the EU.

Of relevance here is the US case, Alliance for Natural Health USA vs Sebelius (786 F.Supp.2d 1 (D.D.C. 2011), in which the Alliance for Natural Health USA successfully challenged the imposition of a ban on qualified health claims for the antioxidant status of vitamins C and E by the US Food & Drug Administration (FDA). The threshold required for making qualified health claims in the US is “significant scientific agreement” which is similar to the EU’s “generally accepted scientific data” requirement established in the Regulation (1924/2006) on nutrition and health claims. In summary, the District Court of Columbia found that evidence is rarely conclusive or significantly agreed. A ban on the health claims was regarded as an infringement of a manufacturer or seller’s
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<tr>
<td>Nestlé Research Center</td>
<td>0. Generic comments</td>
<td>First Amendment right to freedom of expression and the only legal requirement was that the evidence be credible scientifically. We raise this case because we suggest that plausible or credible evidence should be a sufficient threshold of evidence to allow a health claim to be made on the basis that conditions relating to it, these being based on the scientific assessment of the food or substance in question, are met. Adaptation of health claim wording to fit with current nutritional scientific knowledge Another approach that should be taken by EFSA and the European Commission in the determination of authorised health claims is to allow food business operators to communicate the presence of a specific food or nutrient that is associated with a dietary regime for which there is generally accepted evidence of benefit, e.g. the Mediterranean diet. By way of example, olive oil with the claim to promote heart health was issued with a negative opinion by EFSA in 2011 (<a href="http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2044/abstract">http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2044/abstract</a>). However, the Cochrane Collaboration has found that there is “limited evidence to date [that] suggests some favourable effects on cardiovascular risk factors” from the Mediterranean diet (Rees et al. 'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2013; 8 (CD009825). DOI: 10.1002/14651858.CD009825.pub2; <a href="http://www.cochrane.org/CD009825/VASC_mediterranean-diet-for-the-prevention-ofcardiovascular-disease">http://www.cochrane.org/CD009825/VASC_mediterranean-diet-for-the-prevention-ofcardiovascular-disease</a>). More recently, the PREDIMED study has found that additional olive oil consumption as part of a Mediterranean diet improves HDL which is associated with reduced cardiovascular disease risk (Hernández et al, Mediterranean Diet Improves High Density Lipoprotein Function in High-Cardiovascular-Risk Individuals Clinical Perspective. Circulation, 2017; 135 (7): 633 DOI: 10.1161/CIRCULATIONAHA.116.023712). Based on these kinds of evidence, EFSA should be able to flex any originally proposed wording to meet the current state of knowledge of the nutritional science. In the case of olive oil, the following proposed wording entirely meets the legal requirements of Article 13(1) of the Regulation, being substantiated by both Cochrane and PREDIMED (among other scientific studies/publications): &quot;contains olive oil, daily consumption of 15-60g/day of which is associated with a reduced risk of heart disease&quot;.</td>
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Although Nestlé acknowledges the fact that inflammation is not specific to any disease, and that the inflammatory biomarkers have been addressed by EFSA in their separate guidance on gut-related health claims, Nestlé suggests consideration for adding a specific statement on inflammatory biomarkers (1), as inflammation plays a central role in the pathophysiology of cardiovascular diseases. More specifically, even though a single biomarker would not be relevant, Nestlé suggests EFSA to specify whether the simultaneous measurement of several biomarkers could be considered as relevant to substantiate a health claim related to cardiovascular related-inflammation. For example, some authors have proposed a composite score of low-grade inflammation as a mean to overcome weaknesses |
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<tr>
<td>Unilever R&amp;D</td>
<td>0. Generic comments</td>
<td>From the draft guidance document, it is not clear whether and how epidemiological (observational) study evidence is considered as supporting evidence, e.g. in view of a risk factor being linked to cardiovascular disease (CVD) risk. This should be clarified.</td>
</tr>
<tr>
<td>Individual</td>
<td>3.1. Function claims related to antioxidants and the protection of body cells and molecules (i.e. proteins, lipids, DNA) from oxidative damage, including photo-oxidative (UV-induced) damage</td>
<td>0. EFSA should review the entirety of its approach, not simply tweak guidelines, a process that prevents the claims authorisation pathway being accessible to corporations other than the largest. The latter represent the only stakeholder group with the financial capacity to pay for the EFSA-specific trials that are effectively creating a new paradigm in nutritional science that is becoming ever-closer to the approach required for drug licensing. 3.1 It is important that food business operators can communicate to consumers about those foods or substances that are rich sources of nutrients that are able to act as antioxidants.</td>
</tr>
<tr>
<td>Living Life</td>
<td>3.1. Function claims related to antioxidants and the protection of body cells and molecules (i.e. proteins, lipids, DNA) from oxidative damage, including photo-oxidative (UV-induced) damage</td>
<td>Antioxidant is a property of a nutrient  It is accepted that the process by which homeostatic redox status is maintained in humans is highly complex, and one that varies in space and time, both between and within individuals. This homeostatic mechanism is ultimately down to a balance between exogenous and endogenous antioxidants and pro-oxidant load, this in turn being the result of metabolic/physiological function and pro-oxidant exposure. However, in an effort to help consumers make informed decisions about their diet, it is important that food business operators can communicate to consumers about those foods or substances that are rich sources of nutrients that are able to act as antioxidants. 5</td>
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Dietary antioxidants: hybrid nutrition and functional health claims

EFSA’s reductionist approach separates out functional antioxidant effects from reduction of disease risk, yet the two are interconnected. This is well illustrated by the research on polyphenols, and is discussed by Roche et al. (Representative literature on the phytoneutrients category: Phenolic acids. Crit Rev Food Sci Nutr. 2017; 57(6): 1089-1096; http://www.tandfonline.com/doi/abs/10.1080/10408398.2013.865589?journalCode=bfsn20) who state “research has emerged in strong support of the antioxidant capacity of polyphenols and their role in the prevention and/or treatment of certain cancers, diabetes, cardiovascular diseases, and inflammation.”

Therefore, the significant presence of antioxidants such as catechins, ellagic acid, gallic acid, tannic acid and capsaicin should allow a nutritional claim for a functional category of nutrient, such as flavonoids. Such nutritional claims for functional substances, that could be referred to as ‘hybrid nutritional and functional claims’ should be authorised subject to conditions (notably concentration/daily intake of beneficial compounds in the functional group) without any need for further scientific substantiation.

Such an approach not only better fits the intent of the Nutrition and Health Claims Regulation, it also reduces the assessment burden on EFSA and the requirement for stakeholders to undertake new scientific research that aims simply to meet EFSA’s guidelines for scientific substantiation.

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<tr>
<td>Health Food Manufacturer's Association</td>
<td>3.1.1. Claims based on the essentiality of nutrients</td>
<td>Lines 172-181: Section 3.1.1 - It would be helpful if the Guidance could clarify whether additional claims based on the essentiality of nutrients are possible.</td>
</tr>
<tr>
<td>Living Life</td>
<td>3.1.1. Claims based on the essentiality of nutrients</td>
<td>Validate the new approach using model nutrient groups</td>
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<td>The starting point for any such approach is ensuring that the methodology used by EFSA delivers a positive opinion for nutrients for which there is generally accepted scientific evidence of beneficial properties. Given the complexity of nutritional science, the evidence is generally more robust for classes or groups of nutrients consumed as part of a food matrix than it is for individual, isolated compounds in foods.</td>
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<td>Good examples that would be useful candidates allowing evaluation of the suitability of EFSA’s assessment methodology would be polyphenols or flavonoids, as found in fruits and vegetables.</td>
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<tr>
<td>Health Food Manufacturer's Association</td>
<td>3.2. Function claims related to the protection of DNA from strand breaks</td>
<td>Line 263: Where EFSA opinions for previous claim applications are referred to, some with positive and some with negative opinions, it would be helpful if the relevant points could be distilled from these opinions into the guidance. This will help applicants to identify general principles that the Panel wishes to underline, as it is not necessarily possible to tell if relevant points in the opinion that the panel wishes to draw attention to have been made on a...</td>
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<tr>
<td>Evonik Nutrition &amp; Care GmbH</td>
<td>3.3.</td>
<td>Chapter 3.3. of the guidance discusses function claims related to cardiovascular health, which can be measured by several physiological markers such as blood lipid profile or endothelial function. We apply to include a sub-chapter on arterial elasticity, or arterial stiffness, to the markers of cardiovascular health. We reason that the cumulative evidence from clinical studies [1] shows that arterial elasticity contributes to the maintenance of an adequate blood flow to body cells and tissues. The consequences of reduced arterial elasticity, also termed as arterial stiffness, include the development of systolic hypertension, systolic heart failure, and small vessel ischaemia; arterial stiffness has been identified as an independent predictor of these cardiovascular morbidities and of cardiovascular mortality [2]. Additionally, arterial elasticity or stiffness can be easily assessed in vivo by well-established methods [3]. Carotid-femoral pulse wave velocity (PWV) was considered as the ‘gold standard’ measurement of arterial stiffness. However, several limitations and sources of inaccuracy have been described for PWV. Recently, the cardio-ankle vascular index CAVI, which assesses the heart-to-ankle arterial pathway using oscillometric cuffs, has gained much popularity due to its ease of use, its relative independency from blood pressure levels, and other advantages. The number of published papers on CAVI is increasing year by year and reached more than 400 to date. We therefore propose to add to the draft guidance as follows: Line 271: Arterial blood pressure, arterial stiffness... Line 441: Claims on the reduction of arterial stiffness Arterial elasticity contributes to the maintenance of an adequate blood flow to body cells and tissues. The consequences of reduced arterial elasticity, also termed as arterial stiffness, include the development of systolic hypertension, systolic heart failure, and small vessel ischaemia. Arterial stiffness has been identified as an independent predictor of these cardiovascular morbidities and of cardiovascular mortality. Thus, maintenance of arterial elasticity or reduction of arterial stiffness is a beneficial physiological effect. The scientific evidence for substantiation of health claims can be obtained from human intervention studies showing a reduction of arterial stiffness. This can be assessed in vivo at different regions of the arterial tree by the measurement of pulse wave velocity (PWV) using well-established methods (e.g. carotid-femoral PWV [4], or the cardio-ankle vascular index (CAVI) for blood pressure-independent assessment of PWV [2,5]).</td>
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| Nestlé Research Center           | 3.3. Function claims related to cardiovascular health                   | 1: References listed in file: CAVI articles 240717  
2: Asmar 2017 (https://doi.org/10.1093/eurheartj/suw058)  
3: Williams 2017 (https://doi.org/10.1093/eurheartj/suw057)  
4: Laurent et al. 2006 (PMID: 17000623)  
5: Shirai et al. 2006 (PMID: 16733298)  
Lines 275-279  
Nestlé suggests to rephrase the paragraph. As such, it gives the impression that a beneficial change on both LDL-c and BP should be demonstrated. |
| Alliance for Natural Health      | 3.3.1. Claims on maintenance of normal cardiac function                | It is not useful to stakeholders to use the EPA/DHA opinion re maintenance of normal cardiac function as a template given the sheer extent of basic research carried out over many decades that has resulted in a “wealth of human observational studies showing a consistent association”. What would be relevant to know is the extent of observational data required – could this be used on its own, what might be the population sizes, significance, statistical power, etc? For such dietary ingredients it would also be important to clarify that observational data may be used in place of randomised controlled clinical studies. |
| International                    |                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Health Food Manufacturer's       | 3.3.1. Claims on maintenance of normal cardiac function                | Line 291: Where EFSA opinions for previous claim applications are referred to, some with positive and some with negative opinions, it would be helpful if the relevant points could be distilled from these opinions into the guidance. This will help applicants to identify general principles that the Panel wishes to underline, as it is not necessarily possible to tell if relevant points in the opinion that the panel wishes to draw attention to have been made on a case-by-case basis or are general principles that will apply to all applications for similar claims. For example, in section 3.4 lines 551 to 558 more explanation of the relevant points in the opinion are provided and this would be helpful for all other such references to claim opinions. |
| Association                      |                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Nestlé Research Center           | 3.3.1. Claims on maintenance of normal cardiac function                | Line 288  
Nestlé suggests to specify whether other outcomes than the incidence of CHD outcomes would be accepted for this specific claim. For example, cardiac rhythm-related outcomes (e.g. through measurement of parameters related to heart rate). Would cellular mechanisms, such as mitophagy or autophagy (1) be considered as reliable outcomes to be measured?  
(1) Lee et al. (2017). Potential signaling pathways of acute endurance exercise-induced cardiac autophagy and |
mitophagy and its possible role in cardioprotection. J Physiol Sci. [Epub ahead of print]

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<tr>
<td>Nestlé Research Center</td>
<td>3.3.2. Claims on a beneficial change in the blood lipid profile</td>
<td>Lines 343-348 Nestlé suggests to add a comment on studies conducted in hypercholesteraemic subjects, but receiving drugs for conditions other than hypercholesterolemia (e.g. anti-hypertensive drugs). How should such study be dealt with?</td>
</tr>
<tr>
<td>Unilever R&amp;D</td>
<td>3.3.2. Claims on a beneficial change in the blood lipid profile</td>
<td>We welcome that in the revised draft version - different to the 2011 guidance document - next to a reduction in fasting blood LDL-cholesterol (LDL-c) concentrations (for claims on maintenance of normal blood concentrations of LDL-c) now also a reduction in fasting triglycerides (TG) and an increase in fasting blood HDL-cholesterol (HDL-c) concentrations are considered beneficial physiological effects. This reflects the current scientific evidence regarding the importance of all blood lipids for cardiovascular health. Concerning the statement that all measurements should be performed in fasting conditions using well-accepted methods and following standardized conditions and</td>
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protocols, it should be noted that fasting, especially for measuring LDL-c and HDL-c may not be needed.

Blood lipids can also be measured in a fed stage, as was recently discussed in a joint consensus statement by leasing experts (Nordestgaast et al. Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points- a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine; Eur Heart J, 2016; 37: 1944-1958.)

Therefore, we recommend the NDA panel to consider that the maintenance of normal blood TG can relate to both fasting and non-fasting blood TG concentrations.

In support of this, we refer to observational studies, which have identified non-fasting TG concentrations to be a superior predictor of CVD risk compared to fasting concentrations (e.g. Nordestgaard et al. Non-fasting hyperlipidemia and cardiovascular disease; Curr Drug Targets 2009;10(4):328-35; Nordestgaard et al. Non-fasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. JAMA. 2007;298 (3):299-308; Miller M et al. Triglycerides and Cardiovascular Disease: A scientific statement from the American Heart Association. Circulation. 2011;123(20): 2292-333).

In view of the period of time needed to demonstrate a beneficial effect, the draft guidance state the following: “Even if a significant effect on one or more of these outcome variables is observed within short periods of time (e.g. three to four weeks), evidence on the sustainability of the effect with continuous consumption of the food/constituent over longer periods of time (i.e. at least eight weeks) should be provided”.

Concerning the sustainability of an effect, typically four weeks intervention studies should be sufficient. To consider only evidence of at least eight weeks seems rather strict. A clear rationale why a duration of eight weeks is required is not given.

There is ample and strong evidence that a new stable metabolic steady-state condition in blood lipid and lipoprotein concentrations after a dietary intervention is reached within 3-4 weeks (Kris-Etherton PM, Dietschy J. Design criteria for studies examining individual fatty acid effects on cardiovascular disease risk factors: human and animal studies. Am J Clin Nutr. 1997; 65 (5 Suppl): 1590S-1596S; AbuMweis SS, Jew S, Jones PJH. Optimizing clinical trial design for assessing the efficacy of functional foods. Nutr Reviews 2010; 68(8):485-499). Hence, an eight weeks intervention seems not justified and therefore we suggest the NDA panel to replace “eight weeks” with “at least 4 weeks” as guidance for a sustained effect on blood lipids and lipoproteins.

Health Food Manufacturer’s Association

3.3.3. Claims on the reduction of post-prandial blood concentration of line 374/5: Where EFSA opinions for previous claim applications are referred to, some with positive and some with negative opinions, it would be helpful if the relevant points could be distilled from these opinions into the guidance. This will help applicants to identify general principles that the Panel wishes to underline, as it is not necessarily possible to tell if relevant points in the opinion that the panel wishes to draw attention to have been made on a
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<td>Nestlé Research Center</td>
<td>triglycerides</td>
<td>case-by-case basis or are general principles that will apply to all applications for similar claims. For example, in section 3.4 lines 551 to 558 more explanation of the relevant points in the opinion are provided and this would be helpful for all other such references to claim opinions.</td>
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| Nestlé Research Center               | 3.3.3. Claims on the reduction of post-prandial blood concentration of triglycerides | Lines 363-365  
In the absence of standardized measure of postprandial triglycerides, and lack of specific reference ranges, what are the criteria that EFSA would apply to assess the reliability of study findings? Nestlé suggests further guidance on these aspects.  
Lines 368-373  
Nestlé suggests to add a comment on studies conducted in hypertriglyceridaemic subjects, but receiving drugs for conditions other than hypertriglyceridemia (e.g. anti-hypertensive drugs). How should such study be dealt with? |
| Unilever R&D                         | 3.3.3. Claims on the reduction of post-prandial blood concentration of triglycerides | We welcome that in the revised draft guidance, a reduction in post-prandial blood concentrations of TG is considered a beneficial physiological effect for an adult population. This reflects the current scientific evidence regarding the importance of all blood lipids, either in a fasted or fed stage.  
As stated, the scientific evidence for the substantiation of a reduction of post-prandial blood TG concentrations claim can be obtained from human intervention studies showing a reduction of post-prandial blood concentrations of TG at different time points during an appropriate period of time after consumption of the test food in comparison to the reference food. There are no details provided regarding the different time points during an appropriate period of time neither on the period of time as such after the post-prandial challenge. Therefore, we suggest that the NDA panel defines this is a more detailed way. For instance, an appropriate period of time should be at least 4 hours post-prandially. |
| Nestlé Research Center               | 3.3.4. Claims on the maintenance of normal (arterial) blood pressure    | Lines 400-404  
Nestlé suggests to add comment on studies conducted in hypertensive subjects, but receiving drugs for conditions other than hypertension (e.g. cholesterol-lowering drugs). How should such study be dealt with? |
| New Zealand Ministry for Primary Industries | 3.3.4. Claims on the maintenance of normal (arterial) blood pressure | Sometimes there is a short summary of the main reason why the Panel gave a favourable/unfavourable opinion on a health claim (eg, line 292, line 468, line 497, line 528) but this is not consistent throughout the guidance document. In the following places no short summary is provided (Line 263, line 374, line 439, line 451, line 495). Is there a reason for this?  
Line 400: It may be quite difficult to provide evidence for lack of an interaction between the food and the }
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<td>Health Food Manufacturer's Association</td>
<td>3.3.5. Claims on the improvement of endothelial functions</td>
<td>medications used on the claimed effect especially where studies only include either users or non-users of the medication. Does the EFSA Panel have an example where lack of an interaction between the food and the medications used on the claimed effect has been demonstrated? On the consideration of health claims for healthy populations, would the NDA Panel consider adding something to the effect that results from a study group can be extrapolated to the general population (or target population) if the condition/use of the medication is widespread in the general population (or target population)? Section 3.3.5 Lines 423/4: It should clearly state that this is a beneficial physiological effect accepted by EFSA rather than just outline the claim.</td>
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<td>Nestlé Research Center</td>
<td>3.3.5. Claims on the improvement of endothelial functions</td>
<td>Lines 425-426</td>
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<td>Besides forearm blood flow, Nestlé suggests to specify whether respectively “cerebral blood flow” as measured for example by arterial spin labelling magnetic resonance imaging, laser Doppler flowmetry, or near-infrared spectroscopy (1), “retinal blood flow” as measured for example by Doppler optical coherence tomography flowmetry (2), and “skin blood flow” as measured for example by laser Doppler flowmetry (3) would be considered as similarly reliable outcomes for EDV-related health claims.</td>
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<td>Line 426</td>
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<td>Nestlé suggests to specify what other well-established non-invasive methods could be used to measure endothelial function. For example, would techniques such as finger plethysmography (RH-PAT) and digital thermal monitoring (DTM) be considered as reliable?</td>
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<td>Lines 430-433</td>
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<td>Nestlé suggests to specify whether the acute change in ED-FMD occurring shortly after consumption of the food/constituent would be considered a valid outcome for a health claim related to postprandial ED-FMD.</td>
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In respect to effects of a food/constituent on endothelium-dependent vasodilation, it is stated that a sustained increase in endothelium-dependent vasodilation in fasting conditions in response to an intervention can be substantiated after regular consumption of a food/constituent for at least four weeks. There is no clear rationale why here four weeks intervention is being considered sufficient, while in contrast for blood lipids effects at least eight weeks intervention are required. The reasoning for this should either be explained, or the minimal required duration of human intervention studies should be harmonized across the different beneficial physiological effects to at least four weeks.

Although more relevant to the risk manager (EC) than the risk/benefit assessor (EFSA), it is important for successful claim applications relating to ‘normal homocysteine metabolism’ to be related in the claim wording directly to cardiovascular disease risk. While the draft currently indicates there is no consistent relationship, this is down to the weakness of methodologies in evaluating the relationship between homocysteine and CVD risk. The Framingham study researchers are of the view that such a relationship exists, viz: http://www.framingham.com/heart/4stor_02.htm. Accordingly, homocysteine normalisation claims would therefore need to be categorised as Article 14.1(a) health claims. This is justified because the average consumer is highly unlikely to understand the relationship between homocysteine and heart disease risk. The absence of such a relationship would mean the claim (‘contributes to normal homocysteine metabolism’) would not meet the legal requirement of the Regulation (Article 3, NHCR).

lines 495 and 497: Where EFSA opinions for previous claim applications are referred to, some with positive and some with negative opinions, it would be helpful if the relevant points could be distilled from these opinions into the guidance. This will help applicants to identify general principles that the Panel wishes to underline, as it is not necessarily possible to tell if relevant points in the opinion that the panel wishes to draw attention to have been made on a case-by-case basis or are general principles that will apply to all applications for similar claims. For example, in section 3.4 lines 551 to 558 more explanation of the relevant points in the opinion are provided and this would be helpful for all other such references to claim opinions.

Line 497-503

Nestlé suggests to state more clearly that maintenance of normal venous-capillary permeability is considered a valid outcome for a health claim (1), and specify which method(s) of measure would be considered as reliable to measure such outcome. It would seem to fit best as a section separated from “venous blood flow”.

(1) Scientific Opinion on the substantiation of a health claim related to Vitis vinifera L. seeds extract and maintenance of normal venous blood flow pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Journal
Outcome of public consultation: Guidance for health claims on antioxidants, oxidative damages and cardiovascular health

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<td>Health Food Manufacturer's Association</td>
<td>3.4. Reduction of disease risk claims related to cardiovascular diseases</td>
<td>Lines 546-7: Clarify that the requirement to provide evidence for a reduction in the incidence of the disease is in relation to these other risk factors, as it is stated in the paragraph above (lines 516-27) that such evidence is not required for reduction of LDL-cholesterol or reduction of arterial SBP. Lines 546 and 547 are currently not specific as to which risk factors they are referring and this needs clarification.</td>
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| Nestlé Research Center | 3.4. Reduction of disease risk claims related to cardiovascular diseases | Line 504
Carotid intima-media thickness (cIMT) is considered a robust marker for atherosclerosis, which itself correlates well with CVD. Nestlé suggests to indicate whether measurement of cIMT with well-established methods would be considered a valid outcome for a health claim related to CVD risk?

Lines 516-523
Nestlé suggests to clarify why only LDL-cholesterol and systolic blood pressure (and not triglycerides, or other markers) have been considered as relevant to substantiate a disease risk reduction claim.

Lines 551-558
Taking into account recommendations from both European expert group (1) and American Heart Association (2), Nestlé suggests to add a dedicated section on “arterial stiffness” (3). Indeed, brachial-ankle pulse wave velocity (4-5), or carotid-femoral pulse wave velocity (6-7) have both been associated with incident cerebrovascular or cardiovascular diseases in recent meta-analyses. Other techniques have also been described such as pulse wave analysis, pulse contour analysis and carotid wall distensibility coefficient (8). Nestlé suggests to add comment on these methods as well.


Organisation  | Chapter | Comment
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Unilever R&D  | 3.4. Reduction of disease risk claims related to cardiovascular diseases  | While elevated blood LDL-c concentrations (as well as elevated blood pressure) are considered independently associated with an increased risk of CVD, for the other blood-l lipid related risk factors, i.e. elevated blood concentrations of (fatty) TG and low blood HDL-c concentrations the evidence on a relationship with CVD development is judged as not strong.

Furthermore, while reducing blood LDL-c concentrations (by dietary modification and/or drugs) would generally reduce the risk of development of CVD, it is said that lowering elevated fasting TG and increasing low HDL-c has not generally been shown to reduce the risk of CVD.

Hence, providing human study evidence for lowering elevated TG is not considered sufficient for a disease risk claim. Therefore, human studies on how the consumption of the food/constituent prospectively modifies the risk of CVD are required for the substantiation of disease risk reduction claims “in order to validate the association between these variables and the risk of disease in the context of a particular nutritional intervention.” No further details on e.g. the design or execution of such disease endpoint studies are provided.


As further support, there is convincing evidence that blood TG and especially that TG-rich lipoproteins are independent predictors of cardiovascular disease risk. This has been acknowledged and endorsed by several leading expert groups (e.g. Chapman et al. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. Eur Heart J 2011; 32:1345-1361; Miller et al. Triglycerides and Cardiovascular Disease: A scientific statement from the American Heart Association. Circulation. 2011;123(20):2292-333; Nordestgaard and Varbo. Triglycerides and cardiovascular...
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Appendix C – Full list of comments submitted by email

Comment 1

Dear Sir or Madam,

please find the attached files as supplementary information to the comment I made today.

I am very happy to assist further if needed.

Please do not hesitate to contact me.

Kind Regards

{signed}

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Registered Office Essen
Register Court
City Local Court Essen
Commercial Registry B 25784

Comment 2

From: {signed}

To: NDA.PublicConsult.99

COMMENTARY ON SECTION 0. GENERIC COMMENTS: Requirement for a global change to EFSA assessment approach Article 6(1) of the Nutrition and Health Claims Regulation (1924/2006/EC requires that “...health claims shall be based on and substantiated by generally accepted scientific evidence”, while Article 13(1)(c)(ii) also requires that such claims are “well understood by the average consumer.” EFSA has evolved a highly reductionist approach, that relies almost entirely on the data that have been submitted by an applicant while ignoring the peripheral, existing evidence. This approach fails to meet the legal requirements and results in discretton, disproportionality and inequality in considering the overall evidence in relation to beneficial foods and nutrients. For example, it is not scientifically rational that there is an authorised claim for 15% of the Nutrient Reference Value (150 mcg/dose) of copper (this amount being arbitrary and unrelated to the scientific evidence for the mineral in question) relating to “the protection of cells from oxidative stress”, while
there is no claim for any botanical substance for this same function. This is despite generally accepted evidence that plant-based diets are strongly associated with protection against oxidative stress and chronic disease risk, viz (including references therein): Hever J, Cronise RJ. Plant-based nutrition for healthcare professionals: implementing diet as a primary modality in the prevention and treatment of chronic disease. J Geriatr Cardiol. 2017; 14(5): 355–368. EFSA should review the entirety of its approach, not simply tweak guidelines, a process that prevents the claims authorisation pathway being accessible to corporations other than the largest. The latter represent the only stakeholder group with the financial capacity to pay for the EFSA-specific trials that are effectively creating a new paradigm in nutritional science that is becoming ever-closer to the approach required for drug licensing. Validate the new approach using model nutrient groups. The starting point for any such approach is ensuring that the methodology used by EFSA delivers a positive opinion for nutrients for which there is generally accepted scientific evidence of beneficial properties. Given the complexity of nutritional science, the evidence is generally more robust for classes or groups of nutrients consumed as part of a food matrix than it is for individual, isolated compounds in foods. Good examples that would be useful candidates allowing evaluation of the suitability of EFSA’s assessment methodology would be polyphenols or flavonoids, as found in fruits and vegetables. From causal evidence to evidence of association One of the major stumbling blocks for EFSA is its decision to require causal evidence of a highly conclusive or unequivocal nature. Such a view requires that the totality of scientific evidence on which a claim is based is entirely free of any contradictions. This is very rarely the case with nutritional science, where the evidence continues to emerge and for which there are differences in individual response as result of differences in nutritional requirement, physiological stress, gene expression, epigenetic background, polymorphisms, xenobiotic exposure, etc. The nature of nutritional research and public health policy that has evolved alongside it is that evidence of association has been sufficient to justify the vast majority of public health 3 advice, such as salt reduction, increased fruit and vegetable intake or decrease in certain categories of food (e.g. foods high in sugars, processed meats). For the purpose of the Regulation and to ensure the public is both informed and not misled, EFSA should adapt its scientific approach so as to include evidence of association between the consumption of particular foods or nutrients and beneficial effects. Such an approach would then allow health claims to be made for a wide range of foods with known beneficial properties such as polyphenol-rich berry fruits which have yet to receive authorised health claims. Another indication of the failure of EFSA’s assessment methodology is the rejection of health claims for any of the essential amino acids, without which humans cannot survive. From conclusive to plausible evidence Linked to the need by EFSA, in order to fulfil its role as a scientific assessor, is the degree of conclusivity of the evidence. It is well established that nutritional science is rarely black and white, and given it is an emerging science that relates to a highly complex and variable interaction between multiple population groups, is not appropriate that only highly conclusive evidence is accepted. The notion of graded evidence has already been widely used in many branches of medical and nutritional science. It continues to be used effectively by the Therapeutic Research Center’s Natural Medicines™ Professional Database (https://naturalmedicines.therapeuticresearch.com/), formerly Natural Standard™, where the available proposed evidence is broken into one of 6 categories depending on the strength or conclusivity of that evidence: https://naturalmedicines.therapeuticresearch.com/grading.aspx. Given that establishing highly conclusive evidence, either for licensed pharmaceutical products and even more from foods and related substances, that are consumed alongside varying diets by highly variable population groups, provision of plausible evidence should be sufficient. The dismissal of health claims based on all but highly conclusive evidence has resulted in hundreds of plausible or credible claims, such as the benefits associated with consumption of essential amino acids, being rejected and now being ‘non-authorised’ throughout the EU. Of relevance here is the US case, Alliance for Natural Health USA vs Sebelius (786 F.Supp.2d 1 (D.D.C. 2011), in which the Alliance for Natural Health USA successfully challenged the imposition of a ban on qualified health claims for the antioxidant status of vitamins C
and E by the US Food & Drug Administration (FDA). The threshold required for making qualified health claims in the US is “significant scientific agreement” which is similar to the EU’s “generally accepted scientific data” requirement established in the Regulation (1924/2006) on nutrition and health claims. In summary, the District Court of Columbia found that evidence is rarely conclusive or significantly agreed. A ban on the health claims was regarded as an infringement of a manufacturer or seller’s First Amendment right to freedom of expression and the only legal requirement was that the evidence be credible scientifically. We raise this case because we suggest that plausible or credible evidence should be a sufficient threshold of evidence to allow a health claim to be made on the basis 4 that conditions relating to it, these being based on the scientific assessment of the food or substance in question, are met. Adaptation of health claim wording to fit with current nutritional scientific knowledge Another approach that should be taken by EFSA and the European Commission in the determination of authorised health claims is to allow food business operators to communicate the presence of a specific food or nutrient that is associated with a dietary regime for which there is generally accepted evidence of benefit, e.g. the Mediterranean diet. By way of example, olive oil with the claim to promote heart health was issued with a negative opinion by EFSA in 2011 (http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2011.2044/abstract). However, the Cochrane Collaboration has found that there is "limited evidence to date [that] suggests some favourable effects on cardiovascular risk factors" from the Mediterranean diet (Rees et al. 'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2013; 8 (CD009825). DOI: 10.1002/14651858.CD009825.pub2; http://www.cochrane.org/CD009825/VASC_mediterranean-diet-for-the-prevention-ofcardiovascular-disease). More recently, the PREDIMED study has found that additional olive oil consumption as part of a Mediterranean diet improves HDL which is associated with reduced cardiovascular disease risk (Hernández et al, Mediterranean Diet Improves HighDensity Lipoprotein Function in High-Cardiovascular-Risk Individuals Clinical Perspective. Circulation, 2017; 135 (7): 633 DOI: 10.1161/CIRCULATIONAHA.116.023712). Based on these kinds of evidence, EFSA should be able to flex any originally proposed wording to meet the current state of knowledge of the nutritional science. In the case of olive oil, the following proposed wording entirely meets the legal requirements of Article 13(1) of the Regulation, being substantiated by both Cochrane and PREDIMED (among other scientific studies/publications): "contains olive oil, daily consumption of 15-60g/day of which is associated with a reduced risk of heart disease” COMMENTARY ON SECTION 3.1: FUNCTION CLAIMS RELATED TO ANTIOXIDANTS Antioxidant is a property of a nutrient It is accepted that the process by which homeostatic redox status is maintained in humans is highly complex, and one that varies in space and time, both between and within individuals. This homeostatic mechanism is ultimately down to a balance between exogenous and endogenous antioxidants and pro-oxidant load, this in turn being the result of metabolic/physiological function and pro-oxidant exposure. However, in an effort to help consumers make informed decisions about their diet, it is important that food business operators can communicate to consumers about those foods or substances that are rich sources of nutrients that are able to act as antioxidants. 5 Contrary to the opinion of EFSAS, it is generally accepted scientifically that foods or nutrients that increase “overall antioxidant capacity of plasma”, as demonstrated from in vivo human studies, are beneficial to humans. That is because they have the potential to combat prooxidant load. If the food contains significant amounts (e.g. >250mg) of polyphenols per portion, there are ample data to show these foods are beneficial. This should allow general function claims for foods that meet specific conditions i.e. amounts of polyphenols (total or specific) per portion or dose, e.g. “[food x] contains polyphenols that are a dietary source of antioxidants.” Dietary antioxidants: hybrid nutrition and functional health claims EFSA’s reductionist approach separates out functional antioxidant effects from reduction of disease risk, yet the two are interconnected. This is well illustrated by the research on polyphenols, and is discussed by Roche et al. (Representative literature on the phytonutrients category: Phenolic acids. Crit Rev Food Sci Nutr. 2017; 57(6): 1089-1096; http://www.tandfonline.com/doi/abs/10.1080/10408398.2013.865589?journalCode=bfsn2 0) who
state “research has emerged in strong support of the antioxidant capacity of polyphenols and their role in the prevention and/or treatment of certain cancers, diabetes, cardiovascular diseases, and inflammation.” Therefore, the significant presence of antioxidants such as catechins, ellagic acid, gallic acid, tannic acid and capsaicin should allow a nutritional claim for a functional category of nutrient, such as flavonoids. Such nutritional claims for functional substances, that could be referred to as ‘hybrid nutritional and functional claims’ should be authorised subject to conditions (notably concentration/daily intake of beneficial compounds in the functional group) without any need for further scientific substantiation. Such an approach not only better fits the intent of the Nutrition and Health Claims Regulation, it also reduces the assessment burden on EFSA and the requirement for stakeholders to undertake new scientific research that aims simply to meet EFSA’s guidelines for scientific substantiation.