1 **DRAFT SCIENTIFIC OPINION**

2 Guidance on the scientific requirements for health claims related to 3 antioxidants, oxidative damage and cardiovascular health[1]

4 **EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)**[2, 3]

5 European Food Safety Authority (EFSA), Parma, Italy

6 **SUMMARY**

7 The European Food Safety Authority (EFSA) asked the Panel on Dietetic Products, Nutrition and
8 Allergies (NDA) to draft guidance on scientific requirements for health claims related to antioxidants,
9 oxidative damage and cardiovascular health. This draft guidance has been drawn from scientific
10 opinions of the NDA Panel on such health claims. Thus, this guidance document represents the views
11 of the NDA Panel based on the experience gained to date with the evaluation of health claims in these
12 areas. It is not intended that the document will include an exhaustive list of beneficial effects and
13 studies/outcome measures which are acceptable. Rather, it presents examples drawn from evaluations
14 already carried out to illustrate the approach of the Panel, as well as some examples which are
15 currently under consideration within ongoing evaluations. This draft guidance document was
16 endorsed by the NDA Panel on 25 March 2011, and is released for public consultation from
17 26 April 2011 to 31 August 2011.

18 **KEY WORDS**

19 Health claims, scientific requirements, antioxidants, oxidative damage, cardiovascular health.

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[1] On request from EFSA, Question No EFSA-Q-2010-01182, endorsed for public consultation on 25 March 2011.

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BACKGROUND AS PROVIDED BY EFSA

Regulation (EC) No 1924/2006[4] harmonises the provisions that relate 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 has been carried out by EFSA.

EFSA and its NDA Panel have been engaging in consultation with stakeholders, and have published guidance on scientific substantiation of health claims, since 2007[5]. Most recently, a briefing document on scientific evaluation of health claims was published for consultation in April 2010, followed by a technical meeting with experts from the food industry, Member States and the European Commission in Parma, in June 2010[6].

Based on experiences gained with the evaluation of health claims and to further assist applicants in preparing and submitting their applications for the authorisation of health claims, the NDA Panel is asked to develop guidance documents on the scientific requirements for the substantiation of health claims in selected areas, in addition to the guidance for the scientific substantiation of health claims related to gut and immune function (EFSA-Q-2010-01139).

TERMS OF REFERENCE AS PROVIDED BY EFSA

The NDA Panel is requested by EFSA to develop guidance documents on the scientific requirements for health claims in the following areas:

- Post-prandial blood glucose responses/blood glucose control
- Weight management, energy intake and satiety
- Protection against oxidative damage
- Cardiovascular health
- Bone, joints, and oral health
- Neurological and psychological functions
- Physical performance

Specific issues to be addressed in these guidance documents include:

- which claimed effects are considered to be beneficial physiological effects?
- which studies/outcome measures are appropriate for the substantiation of function claims and disease risk reduction claims?

Each guidance document should be subject to public consultation, and may be followed up as appropriate by scientific meetings with experts in the field.

Before the adoption of each guidance document by the NDA Panel the draft guidance shall be revised, taking into account the comments received during the public consultation. A report on the outcome of the public consultation for each guidance document shall be published. All guidance documents should be finalised by July 2012.

[4] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.
[5] http://www.efsa.europa.eu/en/nda/ndaclaims.htm
[6] http://www.efsa.europa.eu/en/ndameetings/docs/nda100601-ax01.pdf

92 **ASSESSMENT**

93 **1. Introduction**

94 To assist applicants in preparing and submitting their applications for the authorisation of health
95 claims, EFSA and in particular its Scientific Panel on Dietetic Products, Nutrition and Allergies
96 (NDA) has ongoing consultations with stakeholders, and has published guidance on the scientific
97 substantiation of health claims since 2007[7]. In April 2010, a draft briefing document on the scientific
98 evaluation of health claims was published for consultation and was followed by a technical meeting
99 with experts from the food industry, Member States and the European Commission in Parma in June
100 2010. The draft briefing document has been transformed into a Panel output, taking into account the
101 questions/comments received. This document constitutes the general guidance for stakeholders on the
102 evaluation of Article 13.1, 13.5 and 14 health claims, and outlines the approach of the NDA Panel to
103 the evaluation of health claims in general. In response to requests from industry, EFSA is engaged in
104 further consultation with stakeholders, and is developing additional guidance on specific types of
105 claims.

106 The objective of the present public consultation is to discuss with scientific experts in the field the
107 scientific requirements for the substantiation of health claims related to antioxidants, oxidative
108 damage and cardiovascular health. This consultation document will be revised to take into account the
109 comments received in order to provide additional guidance to applicants for the substantiation of
110 health claims in these areas.

111 The consultation document focuses on two key issues regarding the substantiation of health claims
112 related to antioxidants, oxidative damage and cardiovascular health:

113 - claimed effects which are considered to be beneficial physiological effects.

114 - studies/outcome measures which are considered to be appropriate for the substantiation of
115 health claims.

116 Issues which are related to substantiation and are common to health claims in general (e.g.
117 characterisation of the food/constituent) are addressed in the general guidance for stakeholders on the
118 evaluation of Article 13.1, 13.5 and 14 health claims[8].

119 This document has been drawn from scientific opinions of the NDA Panel on health claims related to
120 antioxidants, oxidative damage and cardiovascular health. Thus, it represents the views of the NDA
121 Panel based on the experience gained to date with the evaluation of health claims in these areas. The
122 document should be read in conjunction with the general guidance for stakeholders on the evaluation
123 of Article 13.1, 13.5 and 14 health claims.

124 It is not intended that the document should include an exhaustive list of beneficial effects and
125 studies/outcome measures which are acceptable. Rather, it presents examples drawn from evaluations
126 already carried out to illustrate the approach of the Panel, as well as some examples which are
127 currently under consideration within ongoing evaluations.

[7] http://www.efsa.europa.eu/en/ndaclaims/ndaguidelines.htm
[8] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2011. General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims. EFSA Journal, 9(4):2135, 24 pp.

2. General considerations

2.1. Beneficial physiological effects

According to Regulation (EC) No 1924/2006, the use of health claims shall only be permitted if the food/constituent, for which the claim is made, has been shown to have a beneficial physiological effect. In assessing each claim, the NDA Panel makes a scientific judgement on whether the claimed effect is considered to be a beneficial physiological effect in the context of the specific claim, as described in the information provided and taking into account the population group for whom the claim is intended. For function claims, a beneficial effect may relate to maintenance or improvement of a function.

For reduction of disease risk claims, 'beneficial' refers to whether the claimed effect relates to the reduction (or beneficial alteration) of a risk factor for the development of a human disease (not reduction of the risk of disease). A risk factor is a factor associated with the risk of a disease that may serve as a predictor of development of that disease. Whether or not the alteration of a factor is considered to be beneficial in the context of a reduction of disease risk claim depends on the extent to which it is established that:

- The factor is an independent predictor of disease risk (such a predictor may be established from intervention and/or observational studies);
- The relationship of the factor to the development of the disease is biologically plausible.

Except for well established risk factors (e.g. LDL-cholesterol concentrations, blood pressure), the extent to which the reduction of a factor is beneficial in the context of a reduction of disease risk claim needs to be considered on a case-by-case basis.

The NDA Panel considers that the population group for which health claims are intended is the general (healthy) population or specific subgroups thereof, for example, elderly people, physically active subjects, or pregnant women. In its evaluation, the NDA Panel considers that where a health claim relates to a function/effect which may be associated with a disease, subjects with the disease are not the target population for the claim, for example, patients with myocardial infarction. Applications for claims which specify target groups other than the general (healthy) population are the subject of ongoing discussions with the Commission and Member States with regard to their admissibility.

The NDA Panel also considers whether the claimed effect is sufficiently defined to establish that the studies identified for substantiation of the claim were performed with (an) appropriate outcome measure(s) of that claimed effect. Reference to general, non-specific benefits of the nutrient or food for overall good health or health-related well-being may only be made if accompanied by a specific health claim.

2.2. Studies/outcome measures appropriate for substantiation of claims

As human studies are central for substantiation of health claims, this document focuses in particular on such studies. In considering whether the studies provided are pertinent (i.e. studies from which conclusions can be drawn for the scientific substantiation of the claim), the NDA Panel addresses a number of questions, including:

- Whether the studies have been carried out with the food/constituent for which the claim is made. This requirement means that there should be sufficient definition of the food/constituent for which the claim is made, and of the food/constituent which has been investigated in the studies which have been provided for substantiation of the claim. The

evaluation also considers how the conditions under which the human studies were performed relate to the conditions of use (e.g. quantity and pattern of consumption of the food/constituent) proposed for the claim.

- Whether the design and quality of the studies allow conclusions to be drawn for the scientific substantiation of the claim. The evaluation takes into account the hierarchy of evidence as described in the scientific and technical guidance of the NDA Panel[9], for example, intervention studies generally provide stronger evidence than observational studies. Intervention studies should be appropriately conducted so as to minimise bias. In observational studies adequate control for factors other than the food/constituent known to have an impact on the claimed effect is important. Each health claim is assessed separately and there is no pre-established formula as to how many or what type of studies are needed to substantiate a claim. In this regard, the reproducibility of the effect of the food/constituent as indicated by consistency between studies is an important consideration.

- Whether the studies have been carried out in a study group representative of the population group for which the claim is intended. Can the results obtained in the studied population be extrapolated to the target population? For studies in groups (e.g. subjects with a disease) other than the target group for a claim (e.g. the general population), the NDA Panel considers on a case-by-case basis, the extent to which it is established that extrapolation from the study group to the target group is biologically plausible.

- Whether the studies used (an) appropriate outcome measure(s) of the claimed effect. For this, the NDA Panel considers what is generally accepted in the relevant research fields, and consults experts from various disciplines, as appropriate.

3. Antioxidant properties, antioxidant status, antioxidant defence

3.1. Claims on antioxidant properties of foods

Claims on the antioxidant content/properties/activity of foods have been proposed. The references provided for the scientific substantiation of these claims include *in vitro* studies on the capacity of foods/constituents to scavenge free radicals. Claims made on the antioxidant capacity/content or properties of foods/constituents based on their capability of scavenging free radicals *in vitro* refer to a property of the foods/constituents measured in model systems, and it is not established that this capability exerts a beneficial physiological effect in humans as required by Regulation (EC) No 1924/2006.

3.2. Claims on antioxidant status and antioxidant defence

Claims referring to antioxidant status and antioxidant defence have been proposed. The references provided for the scientific substantiation of these claims include *in vivo* human studies which assess changes in the overall antioxidant capacity of plasma using methods such as the total reactive antioxidant potential (TRAP), the trolox-equivalent antioxidant capacity (TEAC), the ferric reducing antioxidant potential (FRAP), the oxygen radical absorbance capacity (ORAC) or the ferrous oxidation-xylenol orange (FOX) assays. It is not established that changes in the overall antioxidant capacity of plasma exert a beneficial physiological effect in humans as required by Regulation (EC) No 1924/2006.

[9] EFSA (European Food Safety Authority), 2007. Opinion of the Panel on Dietetic Products, Nutrition and Allergies (NDA) on a request from the Commission related to scientific and technical guidance for the preparation and presentation of the application for authorisation of a health claim. The EFSA Journal, 530, 1-44.

For claims related to the "antioxidant defence system", references assessing the effects of foods/constituents on enzymes and endogenous compounds (e.g. glutathione) belonging to the body's antioxidative network have been provided. Induction of antioxidant enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GSH-Px) and haemoxigenase or limiting the decrease in glutathione, indicates a biological response to oxidative stress of any origin, including diet, and as such is not specific, and can also reflect a pro-oxidant effect of a dietary component. Therefore, induction of antioxidant enzymes cannot be used as evidence for claims related to the "antioxidant defence system", with the exception of essential vitamins and minerals with an established role in the human antioxidative network.

3.3. Claims on the protection of cells from premature ageing

Claims referring to the "protection of cells from premature ageing" or to "healthy aging" have been proposed in relation to antioxidant properties of foods/constituents. The references provided for the scientific substantiation of these claims include a variety of *in vitro* and *in vivo* animal and human studies assessing the effects of foods/constituents on a variety of outcomes, including the antioxidant capacity of foods, changes in antioxidant status, oxidative damage to proteins, lipids and DNA, non-oxidative DNA damage, neoplastic degeneration of cells, etc. For these claims, no definition has been provided of "premature aging" or of "healthy aging" in relation to the antioxidant properties of foods, and therefore the claimed effect is general and non-specific, and does not comply with the criteria laid down in Regulation (EC) No 1924/2006.

4. Oxidative damage, including photo-oxidative (UV-induced) damage

4.1. Claims on the protection of body cells and molecules (i.e. DNA, proteins and lipids) from oxidative damage, including photo-oxidative (UV-induced) damage

The protection of body cells and molecules such as DNA, proteins and lipids from oxidative damage, including photo-oxidative (UV-induced) damage, may be a beneficial physiological effect, assuming that any significant oxidative modification of the target molecule is potentially harmful. In this specific context, an appropriate method of assessment should be able to determine accurately and specifically the oxidative modification of the target molecule *in vivo*. The scientific substantiation of health claims on the protection of molecules from oxidative damage requires at least one appropriate marker of oxidative modification of the target molecule assessed in human studies, preferably in combination with other marker(s) as defined in sections 4.1.1 to 4.1.3. However, other markers of oxidative damage to molecules cannot be used alone for substantiation as they have some limitations, either because they represent a result of two processes (oxidative damage and repair), because they suffer from technological limitations (interferences with other unrelated processes or substances), or both. A marker cannot be accepted for substantiation when these limitations are considered to be severe. Different markers of oxidative stress to molecules should preferably be determined in the same study, but their determination in similar studies could be acceptable on a case-by-case basis.

The antioxidant properties of foods (measured *in vitro*), and changes in the overall antioxidant capacity of plasma (measured *in vivo* as, for example, TRAP, TEAC, FRAP, ORAC or FOX), do not predict an effect of the food/constituent in the protection of body cells and molecules such as DNA, proteins and lipids from oxidative damage *in vivo*, and therefore are not suitable outcome measures for the scientific substantiation of the claimed effect.

4.1.1. Oxidative damage to proteins

Direct measurements of oxidative damage to proteins *in vivo* (e.g. measurement of specific products of amino acid oxidation in proteins after hydrolysis) could be obtained by means of HPLC-MS and

other methods, as long as separation of such molecules in plasma from other substances is successfully achieved. Measures of protein oxidation by-products (e.g. protein carbonyls) by using conventional assays (e.g. colorimetric procedure which involves dinitrophenylhydrazine (DNPH) derivatisation of carbonyl groups) or ELISA methods (either directly or after DNPH derivatisation) are usually susceptible to interferences by molecules other than proteins, and could only be used in combination with at least one direct marker of oxidative damage to proteins *in vivo* if assessed directly in blood or tissue (e.g. skin).

4.1.2. Oxidative damage to lipids

Direct measurements of oxidative damage to lipids (i.e. lipid peroxidation) could be obtained *in vivo* by measuring changes in $F_{2\alpha}$-isoprostanes in 24-h urine samples (i.e. better matrix than plasma for this measurement) using gas-chromathography (GC) techniques with various detection modes. The preferred method is analysis in combination with mass spectrometry (MS). $F_{2\alpha}$-isoprostanes can also be measured using immunoassays. However, lack of specificity owing to possible cross reactions with other prostanoids needs to be taken into account.

Measurements of oxidative damage to lipids (i.e. lipid peroxidation) could also be obtained *in vivo* by measuring oxidised LDL particles in blood using immunological methods (i.e. antibodies) with appropriate specificity. Phosphatidylcholine hydroperoxides (PCOOH) measured in blood or tissue by high-performance liquid chromatography (HPLC) is also an acceptable marker of lipid peroxidation.

Other methods proposed are not reliable *in vivo* markers of lipid peroxidation (e.g. thiobarbituric acid reactive substances (TBARS), malondialdehyde (MDA), HDL-associated paraoxonases, conjugated dienes, breath hydrocarbons, auto-antibodies against LDL particles and *ex vivo* LDL resistance to oxidation). However, some of these could be used as evidence (i.e. in addition to measurements of $F_{2\alpha}$-isoprostanes and *in vivo* LDL oxidation) if appropriate techniques are used for analysis (e.g. concentrations of MDA in blood or tissue assessed by HPLC).

4.1.3. Oxidative damage to DNA

Direct measurements of oxidative damage to DNA could be obtained *in vivo* by using modifications of the comet assay, which allow the detection of oxidised DNA bases. Quantitative comparison is possible but provides no absolute values, and the result depends on the validity of the control. This assay directly reflects DNA oxidative damage within cells when assessed, for example, in circulating lymphocytes.

Measures of DNA damage using the traditional comet assay (single-cell microgel electrophoresis, SCGE) detect DNA strand breaks by the appearance of tailing, and are not specific for oxidative damage. Other variants of the comet assay determine resistance against oxidative modification using *ex vivo* pro-oxidant challenges. Neither of these measurements is appropriate to assess *in vivo* oxidative damage to DNA.

Analyses of 8-hydroxy-2-deoxy-guanosin (8-OHdG) in blood (e.g. lymphocytes), tissue (e.g. skin) and urine have been used to assess oxidative damage to DNA. Free 8-OHdG results from oxidative damage and excision-repair; it may also result from oxidation of free bases or nucleotides, from oxidation of other nucleic acids, and from artefacts during sample work up. Urinary 8-OHdG does not directly reflect DNA oxidation within cells, but could be used in combination with direct measurements of oxidative damage to DNA if appropriate techniques are used for analysis (e.g. HPLC).

5. Cardiovascular health

5.1. Claims related to changes in the blood lipid profile

The scientific substantiation of health claims related to changes in the blood lipid profile requires identification of the particular markers which should be considered for the evaluation (e.g. LDL-cholesterol, HDL-cholesterol and triglycerides).

5.1.1. Claims related to blood LDL-cholesterol concentrations

Maintenance of normal LDL-cholesterol concentrations is a beneficial physiological effect. The scientific evidence for the substantiation of health claims on the maintenance of normal blood cholesterol concentrations can be obtained from human intervention studies showing a sustained (e.g. two months) reduction of fasting LDL-cholesterol concentrations in humans following the consumption of the food/constituent as compared to an appropriate food/constituent which is neutral with respect to the claimed effect, or to no treatment.

Claims for a beneficial effect of the absence (or reduced content) of a food constituent in a food or category of food on LDL-cholesterol concentrations have been proposed. Substantiation may be based on evidence for an independent role of the food constituent in increasing LDL-cholesterol concentrations. For example, for claims on a reduced content of saturated fatty acids (SFAs) in relation to blood LDL-cholesterol concentrations, SFAs have been shown to increase blood LDL-cholesterol concentrations when compared to carbohydrates which have a neutral effect on LDL-cholesterol concentrations, and therefore SFAs have an independent role in increasing LDL-cholesterol concentrations.

Claims for a beneficial effect of a food constituent when used in replacement of a food constituent with an independent role in increasing LDL-cholesterol concentrations have also been proposed. Substantiation may be based on evidence for an independent role of the replaced food constituent in increasing LDL-cholesterol concentrations, together with evidence for the lack of an effect or a reduced effect of the food constituent which is used for replacement (e.g. claims for unsaturated fats and reduced LDL-cholesterol concentrations when replacing saturated fats).

With respect to the study population, results from studies conducted in hypercholesterolaemic subjects treated with lifestyle measures only (e.g. diet) could be used for the scientific substantiation of these claims. However, the rationale for extrapolation of results obtained in hypercholesterolaemic subjects under pharmacological treatment with cholesterol-lowering medications (e.g. statins) to the target population for the claim should be provided and considered on a case-by-case basis (e.g. evidence for a lack of interaction between the food and the medications used on the claimed effect).

5.1.2. Claims related to blood HDL-cholesterol concentrations

Maintenance of normal HDL-cholesterol concentrations may be a beneficial physiological effect as long as LDL-cholesterol concentrations are not increased.

The scientific evidence for the substantiation of health claims on the maintenance of normal HDL-cholesterol concentrations can be obtained from human intervention studies showing a sustained (e.g. two months) increase of fasting HDL-cholesterol concentrations (without a concomitant increase in LDL-cholesterol concentrations) in humans following the consumption of the food/constituent as compared to an appropriate control food/constituent with respect to the claimed effect or to no treatment.

5.1.3. Claims related to blood concentrations of triglycerides

Maintenance of normal blood concentrations of triglycerides may be a beneficial physiological effect.

The scientific evidence for the substantiation of health claims on the maintenance of normal blood concentrations of triglycerides can be obtained from human intervention studies showing a sustained (e.g. two months) decrease in fasting triglyceride concentrations following the consumption of the food/constituent as compared to a control food/constituent which is neutral with respect to the claimed effect, or to no treatment.

With respect to the study population, results from studies conducted in hypertriglyceridaemic subjects treated with lifestyle measures only (e.g. diet) could be used for the scientific substantiation of these claims. However, the rationale for extrapolation of results obtained in hypertriglyceridaemic subjects under treatment with "triglyceride-lowering" medications (e.g. fibrates) to the target population for the claim should be provided and will be considered on a case-by-case basis (e.g. evidence for a lack of interaction between the food and the medications used on the claimed effect).

5.2. Claims on the reduction of blood pressure

Maintenance of normal blood pressure is a beneficial physiological effect. The scientific evidence for the substantiation of health claims on the maintenance of normal blood pressure can be obtained from human intervention studies showing a sustained (e.g. two months) reduction of systolic (with no increase in diastolic) blood pressure following the consumption of the food/constituent as compared to a control food/constituent which is neutral with respect to the claimed effect, or to no treatment. Blood pressure should be measured using well-accepted protocols and devices.

With respect to the study population, results from studies conducted in hypertensive subjects treated with lifestyle measures only (e.g. diet) could be used for the scientific substantiation of these claims. However, the rationale for extrapolation of results obtained in hypertensive subjects under treatment with blood pressure-lowering medications (e.g. ACE-inhibitors, beta-blockers, calcium channel blockers and diuretics) to the target population for the claim should be provided and will be considered on a case-by-case basis (e.g. evidence for a lack of interaction between the food and the medications used on the claimed effect).

5.3. Claims on endothelial function

Endothelial function *per se* is not sufficiently defined for a scientific evaluation, because endothelium-derived active factors play a role in the maintenance of several functions of the vascular system. These include vasomotion, smooth muscle proliferation, thrombosis, inflammation, coagulation, fibrinolysis and oxidation, which can be assessed by indirect methods. Some of the claims referred to the improvement of specific endothelial functions (e.g. endothelium-dependent vasodilation) which can be assessed *in vivo* using well established methods. An improvement of specific endothelial functions (e.g. endothelium-dependent vasodilation) after sustained exposure to the food/constituent (e.g. one month) may be considered as a beneficial physiological effect.

5.4. Claims on reduced platelet aggregation

Platelet hyperactivity and hypercoagulability states are more commonly observed in subjects with cardiovascular (CV) risk factors. Healthy subjects at very low risk of CV disease normally have non-activated circulating platelets, and thus, decreasing platelet aggregation in subjects with constitutive platelet activation after sustained exposure to the food/constituent (e.g. one month) would be a beneficial physiological effect.

5.5. Claims on homocysteine

Contribution to normal homocysteine metabolism is a beneficial physiological effect. Evidence for the scientific substantiation of this claim may come from the well established role of a food in contributing to the remethylation of homocysteine to methionine (e.g. some vitamins) or from human studies showing an effect of the food/constituent on blood homocysteine concentrations after sustained exposure to the food/constituent (e.g. two months).

5.6. Claims on cardiovascular health

Claims referring to cardiovascular health are too general for a scientific evaluation, and therefore need to be accompanied by a specific claim. Evidence from human studies on specific cardiovascular outcomes (e.g. coronary events) could be used for substantiation of a health claim on the normal function of the heart.

5.7. Disease risk reduction claims

It is well established that elevated blood LDL-cholesterol concentrations are independently associated with an increased risk for coronary heart disease (CHD), and that reducing blood LDL-cholesterol concentrations (by dietary modification and drugs) would generally reduce the risk of development of CHD. It is also well established that elevated (systolic) blood pressure is independently associated with an increased risk for CHD and stroke, and that reducing (systolic) blood pressure (by dietary modification and drugs) would generally reduce the risk of development of CHD and stroke. Reduction in blood LDL-cholesterol concentrations, therefore, may be considered beneficial in the context of a reduction of disease risk claim for CHD, and reduction in (systolic) blood pressure may be considered beneficial in the context of a reduction of disease risk claim for CHD and stroke.

For other proposed risk factors, the evidence may not be as strong. There is some evidence, for example, that low blood HDL-cholesterol concentrations, elevated blood concentrations of triglycerides, or elevated blood homocysteine concentrations are associated with an increased risk of CHD. Reduction of blood concentrations of triglycerides, blood homocysteine concentrations, or an increase in blood HDL-cholesterol concentrations, have been associated with a decreased incidence of CHD following certain dietary interventions in some human intervention studies. However, changes in any of these factors (by dietary modification or drugs) have not generally been shown to reduce the risk of CHD. Therefore, human studies on the risk of CHD are required for the substantiation of these claims to validate the association between these variables and the risk of disease in the context of a particular nutritional intervention.

CONCLUSIONS

The draft guidance document focused on two key issues regarding the substantiation of health claims related to antioxidants, oxidative damage and cardiovascular health:

- claimed effects which are considered to be beneficial physiological effects.
- studies/outcome measures which are considered to be appropriate for the substantiation of health claims.

The document has been drawn from scientific opinions of the NDA Panel on health claims related to antioxidants, oxidative damage and cardiovascular health. Thus, it represents the views of the NDA Panel based on the experience gained to date with the evaluation of health claims in these areas.

GLOSSARY AND ABBREVIATIONS

8-OHdG	8-hydroxy-2-deoxy-Guanosin
ACE	Angiotensin converting enzyme
CHD	Coronary heart disease
CV	Cardiovascular
DNA	Deoxyribonucleic acid
DNPH	Dinitrophenylhydrazine
ELISA	Enzyme-linked immunosorbent assay
FOX	Ferrous oxidation-xylenol orange
FRAP	Ferric reducing antioxidant potential
GC	Gas-chromathography
GSH-Px	Glutathione peroxidase
HDL	High-density lipoprotein
HPLC	High-performance liquid chromatography
LDL	Low-density lipoprotein
MDA	Malondialdehyde
MS	Mass spectrometry
ORAC	Oxygen radical absorbance capacity
PCOOH	Phosphatidylcholine hydroperoxides
SCGE	Single-cell microgel electrophoresis
SFA	Saturated fatty acid
SOD	Superoxide dismutase
TBARS	Thiobarbituric acid reactive substances
TEAC	Trolox-equivalent antioxidant capacity
TRAP	Total reactive antioxidant potential
UV	Ultraviolet