1 **DRAFT SCIENTIFIC OPINION**

2 Guidance on the scientific requirements for health claims related to bone, 3 joints, and oral 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8 Allergies (NDA) to draft guidance on scientific requirements for health claims related to bone, joints,
9 and oral health. This draft guidance has been drawn from scientific opinions of the NDA Panel on
10 such health claims. Thus, this guidance document represents the views of the NDA Panel based on the
11 experience gained to date with the evaluation of health claims in these areas. It is not intended that the
12 document will include an exhaustive list of beneficial effects and studies/outcome measures which are
13 acceptable. Rather, it presents examples drawn from evaluations already carried out to illustrate the
14 approach of the Panel, as well as some examples which are currently under consideration within
15 ongoing evaluations. This draft guidance document was endorsed by the NDA Panel on
16 25 March 2011, and is released for public consultation from 26 April 2011 to 31 August 2011.

17 **KEY WORDS**

18 Health claims, scientific requirements, bone, joints, oral health.

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[1] On request from EFSA, Question No EFSA-Q-2010-01184, 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

ASSESSMENT

1. Introduction

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

The objective of the present public consultation is to discuss with scientific experts in the field the scientific requirements for the substantiation of health claims related to bone, joints, and oral health. This consultation document will be revised to take into account the comments received, in order to provide additional guidance to applicants for the substantiation of health claims in these areas.

The consultation document focuses on two key issues regarding the substantiation of health claims related to bone, joints, and oral 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.

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

This document has been drawn from scientific opinions of the NDA Panel on health claims related to bone, joints, and oral 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. The document should be read in conjunction with the general guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims.

It is not intended that the document should include an exhaustive list of beneficial effects and studies/outcome measures which are acceptable. Rather, it presents examples drawn from evaluations already carried out to illustrate the approach of the Panel, as well as some examples which are 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, 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, joint health and osteoarthritis patients. 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 that 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. Bone and joints

3.1. Claims related to maintenance of bone and to the reduction in the risk of osteoporotic fractures

Contribution to the maintenance of normal bone throughout the lifespan is considered to be a beneficial physiological effect. Evidence for the scientific substantiation of these claims can be obtained from human studies by assessing the relationship between the food/constituent and measures of bone mass and bone mineral density (BMD) using appropriate methods of measurement (e.g. dual-emission X-ray absorptiometry (DXA)) and study duration (e.g. at least one year). Biochemical markers of bone turnover (e.g. of bone formation and bone resorption) can be used as evidence for a mechanism by which the food/constituent could exert the claimed effect. An increase in bone formation and/or a decrease in bone resorption are considered beneficial physiological effects when they lead to an increase (or reduced loss) in bone mass/density.

A decrease in BMD is associated with an increased risk of osteoporotic fractures. However, modification of BMD is only beneficial when the change has a positive impact on fracture incidence. Increasing BMD, or limiting the reduction of BMD in older adults including post-menopausal women has been shown to reduce the risk of osteoporotic fractures following certain dietary interventions (e.g. calcium supplementation) but not others (e.g. fluoride supplementation), probably because BMD (g/cm^2) does not provide any information on the micro-architecture of bone. Therefore, for reduction of disease risk claims in older adults, measures of both BMD and fracture incidence should be

[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.

provided. Biochemical markers of bone turnover (e.g. of bone formation and bone resorption) can be used as evidence for a mechanism by which the food/constituent could exert the claimed effect.

3.2. Claims related to maintenance of joints and to the reduction in the risk of osteoarthrosis

Contribution to the maintenance of normal joints is considered to be a beneficial physiological effect.

Possible outcomes related to joint structure and function include, for example, joint space width, mobility, stiffness and (dis)comfort (e.g. pain).

Studies performed in non-diseased (including high risk) population subgroups in which the incidence of disease (e.g. osteoarthrosis or (osteo)arthritis) is the outcome measure could be used for substantiation of health claims on maintenance of normal joints.

Patients with osteoarthrosis or (osteo)arthritis of different origin (rheumatoid arthritis, psoriatic arthritis, arthritis of infectious origin) are not representative of the general population with regard to the status of joint tissues, and therefore studies on subjects with osteoarthrosis or (osteo)arthritis of different origin relating to the treatment of symptoms of these diseases (e.g. erosion of articular cartilage, and reduced mobility of joints) cannot be used for the scientific substantiation of health claims on the maintenance of normal joints in the general population.

Osteoarthritis is a disease characterised by the erosion of articular cartilage. Cartilage degeneration may proceed to clinical osteoarthritis. Slowing cartilage degeneration in individuals without osteoarthritis may reduce the risk of development of the disease, and thus studies measuring the rate of cartilage degeneration (e.g. changes in joint space width) in individuals without osteoarthritis could be used for the scientific substantiation of disease risk reduction claims.

4. Teeth and gums

4.1. Function claims on plaque acid neutralisation and on reduction of acid production in dental plaque

Plaque formation is a stepwise building of a bacterial biofilm on teeth and soft tissues, i.e. a highly specific initial attachment of bacteria to host receptors (e.g. cells), followed by secondary attachment of bacteria, binding to already colonising bacteria. Acid is produced in plaque through the fermentation of carbohydrates by acid-producing bacteria, and low plaque pH contributes to demineralisation of tooth tissues. Plaque acid neutralisation or the reduction of acid production in dental plaque may prevent demineralisation, and promote remineralisation of hydroxyapatite crystals, and are therefore considered beneficial physiological effects. Plaque acid/pH should be measured *in vivo* or *in situ* using appropriate methods.

4.2. Function claims on the reduction of dental plaque and calculus

Dental plaque and calculus formation can contribute to adverse effects on dental health (e.g. in relation to approximal caries, gingivitis and periodontitis) when they occur at sites such as the cervical third, and interdentally below the approximal contact point between teeth, along the gingival margin, and in the fissures and pits of the teeth. A reduction in the amount of dental plaque and/or calculus at relevant sites may be a beneficial physiological effect. The amount of plaque or calculus can be measured *in vivo* and *in situ* using appropriate methods.

4.3. Function claims on reduction of oral dryness

A dry mouth (i.e. symptoms because of a lowered saliva secretion or inadequate moistening/lubrication of oral tissues) may lead to oral discomfort, and to difficulties in swallowing and speaking. Therefore, reducing oral dryness is a beneficial physiological effect. Changes in oral dryness can be assessed *in vivo* by measuring saliva flow or by measuring self-perceived oral dryness using validated questionnaires.

4.4. Function claims on maintenance of tooth mineralisation

Claimed effects referring to the promotion of tooth (re)mineralisation and/or the prevention of tooth demineralisation are interpreted as referring to a beneficial balance between de- and remineralisation of tooth enamel and dentin. Maintaining tooth mineralisation is a beneficial physiological effect.

Studies on tooth mineralisation including *in vivo* studies with dental caries and/or dental erosion as outcomes and *in situ* models can be used for the substantiation of these claims.

Claims for a beneficial effect of a food constituent (e.g. non/low-fermentable carbohydrates, intense sweeteners, and sugar alcohols) when used in replacement of a food constituent (e.g. sugars) with an independent role in increasing tooth demineralisation (e.g. by decreasing plaque pH) have been submitted. Substantiation may be based on evidence for an independent role of the replaced food constituent in increasing tooth demineralisation, together with evidence for the lack of an effect, or a reduced effect of the food constituent which is used as a replacement.

4.5. Claims on dental health, oral health, tooth protection, "teeth friendly"

Claims referring to dental health, oral health, tooth protection and "teeth friendly" are too general for a scientific evaluation, and therefore need to be accompanied by a specific claim (e.g. maintenance of tooth mineralisation, or plaque acid neutralisation).

4.6. Disease risk reduction claims

There is evidence, for example, that colonisation with *Streptococcus mutans*, dental plaque in particular locations, and a decrease in plaque pH are associated with an increased risk of dental caries. A reduction of colonisation with *Streptococcus mutans*, a reduction of dental plaque in particular locations, and an increase in plaque pH have been associated with reduction in the incidence of dental caries following certain dietary interventions (e.g. frequent consumption of xylitol-sweetened and other sugar-free chewing gums). However, isolated changes in any of these factors have not generally been shown to reduce the risk of dental caries. Therefore, human studies on the incidence of dental caries 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.

5. Connective tissue

5.1. Claims on collagen formation

Collagen is a structural component of many tissues in the body including bones, cartilage, gums, skin, tendons and blood vessels. Contribution to normal collagen formation is therefore considered a beneficial physiological effect. Claims on the contribution to normal collagen formation have been submitted for essential micronutrients (e.g. vitamin C). The scientific substantiation of these claims was based on the biochemical role of such nutrients in collagen synthesis. However, whether

increasing net collagen formation, or reducing net collagen breakdown, is a beneficial physiological effect needs to be considered on a case-by-case basis.

5.2. Claims on maintenance of skin function

Changes in skin structure leading to an improvement (or reduced loss) in skin function(s) can be considered beneficial physiological effects. Evidence on whether (and the extent to which) changes in skin function could be measured by specific changes in skin structure should be provided and considered on a case-by-case basis.

Studies reporting on clinical outcomes with respect to skin damage leading to a loss of function can be used for the scientific substantiation of claims related to the maintenance of skin function.

5.3. Claims on the protection of the skin from UV-induced damage

Protection of the skin against UV-induced changes, including photo-oxidative changes of molecules, which may lead to impaired skin function is a beneficial physiological effect.

The protection of the skin (cells and molecules such as DNA, proteins and lipids) from photo-oxidative (UV-induced) damage may be a beneficial physiological effect because any significant oxidative modification of the target molecule may lead to a change in function. In this specific context, direct measurement of oxidative damage to skin with appropriate methods is required for substantiation. Guidance for the scientific substantiation of health claims related to the protection of body cells and molecules from oxidative (including photo-oxidative) damage has already been provided[10].

Overexposure to UV (sun) light may lead to direct DNA damage (e.g. strand breaks, thymidine dimers, and type I cell death (apoptosis)). Usually the majority of DNA damage is repaired. However, incomplete or deficient repair may lead to skin lesions in the longer term (e.g. neoplasms). Therefore, decreasing DNA damage after UV light exposure is considered a beneficial physiological effect, which can be measured directly in skin biopsies.

Overexposure to UV (sun) light may also lead to depletion of Langerhans cells, which reflects direct damage to the immunological function of the skin. Therefore, decreasing depletion of Langerhans cells after UV light exposure is considered a beneficial physiological effect, which can be measured directly in skin biopsies.

Erythema (sunburn or skin reddening) is an inflammatory response of the skin to UV-induced molecular and cellular damage. If severe, sunburn may lead to blisters and loss of the barrier function of the skin. A reduction in UV-induced erythema (e.g. measured as change in minimal erythemal dose (MED) or erythema grade (reddening)) may indicate less UV-induced damage to the skin, but it can also reflect a reduction in the capacity of the skin to react to molecular and cellular damage. Therefore, UV-induced erythema cannot be used alone as an outcome measure for the substantiation of health claims on the protection of the skin from UV-induced damage.

Delayed-type hypersensitivity (DTH) immune responses to recall antigens in the skin reflect a systemic effect of UV-radiation on the immune system, and cannot be considered in isolation as a marker of UV-induced damage to the skin. Therefore, DTH immune responses to recall antigens in the skin cannot be used alone as an outcome measure for the substantiation of health claims on the protection of the skin from UV-induced damage.

[10] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2011. Draft guidance on the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health released for public consultation.

CONCLUSIONS

The draft guidance document focused on two key issues regarding the substantiation of health claims related to bone, joints, and oral 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 bone, joints, and oral 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

BMD	Bone mineral density
DNA	Deoxyribonucleic acid
DTH	Delayed-type hypersensitivity
DXA	Dual-emission X-ray absorptiometry
MED	Minimal erythemal dose
UV	Ultraviolet