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EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of a health claim related to vitamin K2 and contribution to the normal function of the heart and blood vessels (ID 125, further assessment) pursuant to Article 13(1) of Regulation (EC) No 1924/2006

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to vitamin K2 and contribution to the normal function of the heart and blood vessels (ID 125, further assessment) pursuant to Article 13(1) of Regulation (EC) No 1924/2006[1]

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

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following a request from the European Commission, pursuant to Article 13 of Regulation (EC) No 1924/2006, the Panel on Dietetic Products, Nutrition and Allergies was asked to provide a scientific opinion on a health claim related to vitamin K2 and contribution to the normal function of the heart and blood vessels. The food constituent that is the subject of the claim, vitamin K2, is sufficiently characterised. The claimed effect, contribution to the normal function of the heart and blood vessels, is a beneficial physiological effect. The proposed target population is the general population. In weighing the evidence, the Panel took into account the absence of human intervention studies from which conclusions could be drawn for the scientific substantiation of the claim, the inconsistency of the results reported in two cross-sectional studies regarding arterial calcification in women, that the results of two prospective cohort studies are in conflict regarding the risk of coronary heart disease associated with vitamin K2 intakes, that high intakes of vitamin K2 were associated with a significantly lower degree of aortic calcification in one prospective cohort study after adjustment for confounders, and that the evidence provided for a proposed mechanism is weak. On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the dietary intake of vitamin K2 and contribution to the normal function of the heart and blood vessels.

KEY WORDS

Vitamin K, menaquinones, heart, blood vessels, calcification, health claims.

[1] On request from the European Commission, Question No EFSA-Q-2012-00125, adopted on 26 April 2012.

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[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Claims for the preparatory work on this scientific opinion: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Marina Heinonen, Hannu Korhonen, Martinus Løvik, Ambroise Martin, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Inge Tetens, Hendrik van Loveren and Hans Verhagen.

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SUMMARY

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to provide a scientific opinion on a list of health claims pursuant to Article 13 of regulation (EC) No 1924/2006. The Commission has agreed with EU Member States that a certain number of Article 13 health claims would be eligible for further assessment by EFSA in order to be able to take a final decision on whether or not to include these claims in the list of permitted health claims. This opinion addresses the scientific substantiation of a health claim in relation to vitamin K2 and contribution to the normal function of the heart and blood vessels. The scientific substantiation is based on the information provided by the Member States in the consolidated list of Article 13 health claims, references that EFSA has received from Member States or directly from stakeholders and the additional information provided by the competent Authority of the United Kingdom for further assessment of this claim.

The food constituent that is the subject of the health claim is vitamin K2. The Panel considers that vitamin K2 is sufficiently characterised.

The claimed effect, which is eligible for further assessment, is normal function of the heart and blood vessels. The proposed target population is the general population. The Panel considers that contribution to the normal function of the heart and blood vessels is a beneficial physiological effect.

In its earlier opinion the Panel considered three cross-sectional studies and one prospective cohort study which investigated the relationship between vitamin K intake and arterial calcification or the elastic properties of the arteries, which may interfere with normal vascular structure and function. In the framework of further assessment one prospective cohort study on the association between vitamin K2 intakes and the risk of coronary heart disease and three unpublished human intervention studies which investigated the effect of vitamin K2 on blood concentrations of a matrix Gla-protein (MGP) and two animal studies on the mechanisms by which vitamin K2 could exert the claimed effect were provided.

This evaluation is based on the scientific references provided in the present and the previous submissions which addressed the relationship between vitamin K2 intake and changes in vascular/heart function (e.g. coronary heart disease) or changes in vascular/heart structure leading to changes in vascular/heart function (e.g. arterial calcification). Scientific references on the mechanisms by which vitamin K2 could exert the claimed effect in the target population were also considered.

Two prospective cohort studies investigated the association between vitamin K2 intakes and incidence of coronary heart disease and the degree of aortic calcification. The Panel notes that the results of the two prospective cohort studies are in conflict regarding the risk of coronary heart disease associated to vitamin K2 intakes, and that high intakes of vitamin K2 were associated with a significantly lower degree of aortic calcification after adjustment for confounders in one prospective cohort study.

Two cross-sectional studies investigated the relationship between vitamin K intake and arterial calcification. The Panel notes that one cross-sectional study reported that vitamin K2 intake was inversely related to the presence of coronary calcification while the other showed no association between vitamin K2 intake and breast arterial calcification, after adjustment for confounders.

The proposed mechanism by which vitamin K2 could exert the claimed effect is by contributing to the vitamin K-dependent activation (carboxylation) of MGP, a matrix Gla-protein which has been identified in vascular tissue. Increased levels of carboxylated MGP would reduce vascular calcification and decrease the risk of vascular (including coronary) events.

There is some evidence for a role of MGP in preventing calcification of soft tissues. In an MGP knock-out mouse model, spontaneous calcification of soft tissues (mostly arteries) occurred. Also in

the Keutel syndrome, which results from a mutation of the gene encoding the human MGP, patients display several of the same features as the knockout mice, including abnormal calcification of ear and nose cartilage, and of the respiratory tract. However, whether changes in vitamin K2 intakes may induce changes in MGP carboxylation, which in turn could affect vascular function (e.g. calcification) or the risk of vascular events, has not been established.

In weighing the evidence, the Panel took into account the absence of human intervention studies from which conclusions could be drawn for the scientific substantiation of the claim, the inconsistency of the results reported in two cross-sectional studies regarding arterial calcification in women, that the results of two prospective cohort studies are in conflict regarding the risk of coronary heart disease associated with vitamin K2 intakes, that high intakes of vitamin K2 were associated with a significantly lower degree of aortic calcification in one prospective cohort study after adjustment for confounders, and that the evidence provided for a proposed mechanism is weak.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the dietary intake of vitamin K2 and contribution to the normal function of the heart and blood vessels.

TABLE OF CONTENTS

BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

See Appendix A

TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

See Appendix A

EFSA DISCLAIMER

See Appendix B

INTRODUCTION

The Commission has agreed with EU Member States that a certain number of Article 13 health claims would be eligible for further assessment by EFSA in order to be able to take a final decision on whether or not to include these claims in the list of permitted health claims. These claims include already assessed claims related to micro-organisms which the Panel considered to be not sufficiently characterised and claims for which the NDA Panel concluded that there was insufficient evidence to establish a cause and effect relationship between the consumption of the food and the claimed effect.

Following an opinion of the NDA Panel on a health claim pursuant to Article 13 of Regulation (EC) No 1924/2006[4] in which the Panel concluded that the evidence provided was insufficient to establish a cause and effect relationship between the dietary intake of vitamin K and the normal function of the heart and blood vessels (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2009), EFSA received additional information from the competent Authority of the United Kingdom for further assessment of this claim.

ASSESSMENT

1. Characterisation of the food/constituent (ID 125)

The food constituent that was the subject of the health claim in the initial assessment was vitamin K (i.e. phylloquinone and menaquinones) (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2009). Upon request, in the framework of further assessment the present evaluation refers to vitamin K2 (i.e. menaquinones) only, which is a well recognised nutrient and is measurable in foods by established methods.

Vitamin K is a family of structurally similar, fat soluble, 2-methyl-1,4-naphthoquinones, including phylloquinone (2-methyl-3-phytyl-1,4-naphthoquinone, vitamin K1) and menaquinones (collectively known as vitamin K2). Menaquinones are a series of compounds containing an unsaturated side chain with differing numbers of isoprenyl units at the 3 position in the methyl-1,4-naphthoquinone nucleus. Depending on the number of isoprenyl units, the individual compounds are designated as menaquinone-n (MK-n). Menaquinones (vitamin K2) occur naturally in foods such as meat, liver, fish, butter, egg yolk, natto (which consists of fermented soy beans), and dairy products including cheese and curd cheese, and can also be produced by many bacteria (MK-7 to MK-10) (Schurgers and Vermeer, 2000).

Menaquinones (vitamin K2) are naturally present in foods and have been authorised for addition to foods and for use in food supplements (Annex II of Regulation (EC) No 1925/2006[5] and Annex II of Directive 2002/46/EC[6]). This evaluation applies to vitamin K2 naturally present in foods and added to foods, including food supplements (Annex II of Regulation (EC) No 1925/2006 and Annex II of Directive 2002/46/EC).

The Panel considers that the food constituent, vitamin K2, which is the subject of the health claim, is sufficiently characterised.

[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] Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods. OJ L 404, 30.12.2006, p. 26–38.

[6] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. OJ L 183, 12.7.2002, p. 51–57.

2. Relevance of the claimed effect to human health (ID 125)

The claimed effect, which is eligible for further assessment, is normal function of the heart and blood vessels (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2009). The proposed target population is the general population.

A request was made, in the framework of further assessment, to interpret the claimed effect as "vascular health". The Panel notes that this claimed effect is not sufficiently defined for a scientific evaluation, that ID 125 has been previously assessed as a claim on the normal function of the heart and blood vessels, and that this is the claim which is eligible for further assessment.

The Panel considers that contribution to the normal function of the heart and blood vessels is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect (ID 125)

In its earlier opinion (for ID 124, 125 and 2880) (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2009), the Panel considered three cross-sectional studies (Beulens et al., 2009; Jie et al., 1995; Maas et al., 2007) and one prospective cohort study (Geleijnse et al., 2004) which investigated the relationship between vitamin K intake and arterial calcification or the elastic properties of the arteries, which may interfere with normal vascular structure and function. One of the studies did not report on vitamin K2 intakes specifically and will not be considered further in this evaluation, as requested in the application for further assessment (Jie et al., 1995). In addition, one animal study (Luo et al., 1997), which reported on a Matrix Gla Protein (MGP) knockout mouse model, and one human study (Munroe et al., 1999) reporting on a mutation of the gene encoding human MGP, were considered for the scientific substantiation of the claim.

In the framework of the further assessment, one prospective cohort study on the association between vitamin K2 intakes and the risk of coronary heart disease (CHD) (Gast et al., 2009), as well as three unpublished human intervention studies which investigated the effect of vitamin K2 on blood concentrations of MGP (Braam and Vermeer, 2011, unpublished; Moschonis et al., 2011, unpublished; Vermeer, 2008, unpublished) and two animal studies on the mechanisms by which vitamin K2 could exert the claimed effect (Schurgers et al., 2007; Spronk et al., 2003), were provided.

This evaluation is based on the scientific references provided in the present and the previous submissions which addressed the relationship between vitamin K2 intake and changes in vascular/heart function (e.g. CHD) or changes in vascular/heart structure leading to changes in vascular/heart function (e.g. arterial calcification). Scientific references on the mechanisms by which vitamin K2 could exert the claimed effect in the target population were also considered.

Two prospective cohort studies investigated the association between vitamin K2 intakes and incidence of CHD (Gast et al., 2009; Geleijnse et al., 2004) and the degree of aortic calcification (Geleijnse et al., 2004).

A Dutch prospective cohort study (Geleijnse et al., 2004) was conducted in 7,983 men and women aged 55 years and over, who completed at baseline a semi-quantitative food-frequency questionnaire to assess foods and beverages consumed more than once a month during the preceding year. At baseline, calcified deposits were detected in the abdominal aorta parallel and anterior to the lumbar spine on a lateral radiographic film, and the severity of this calcification was graded as "absent or mild" ($\leq$1 cm calcification), "moderate" (>1 and <5 cm) or "severe" ($\geq$5 cm). Risk of non fatal myocardial infarction, of incident CHD and of CHD mortality during follow-up was examined. After exclusion of institutionalised subjects, subjects with no or unreliable dietary data, and subjects with a history of myocardial infarction, 4,807 individuals, with a mean follow-up of 7.2 years, were included in the analysis for coronary events. After exclusion of subjects with no or unreliable baseline radiographic films, 4,473 subjects were included in the analysis on abdominal aortic calcification. The risk ratios (RR) of coronary events in energy-adjusted tertiles of intake of vitamin K2 were studied in a Cox regression model and the association (odd ratios, OR) between the tertiles of intake and moderate or severe aortic calcification was assessed in a multivariate logistic regression model. Analyses were performed with adjustment for age, sex and total energy intake (model 1), and with additional adjustment for Body Mass Index (BMI), diabetes mellitus, smoking status, pack/year of cigarette smoking, category of education, and intakes of alcohol, calcium, flavonols, and saturated and polyunsaturated fatty acids (model 2). In this population, 64.3 % (n=2,874), 30.4 % (n=1,359) and 5.4 % (n=240) of subjects had “absent or mild”, “moderate” or “severe” calcification, respectively. Compared with the first tertile of vitamin K2 intake, high intakes of vitamin K2 (third tertile only) were associated with a lower incidence of CHD only in model 2 (RR: 0.59, 95 % CI: 0.40-0.86), and with a lower CHD mortality (models 1 and 2), but not with a lower risk of non fatal myocardial infarction (models 1 and 2). Compared with the first tertile of vitamin K2 intake, high intakes of vitamin K2 (third tertile only) were associated with a lower risk of severe aortic calcification (models 1 and 2; OR: 0.48, 95 % CI: 0.32-0.71 for model 2). No significant association was observed with moderate calcification. Results did not change with further adjustment for intakes of vitamin E, vitamin C, beta-carotene and fibre. The Panel notes that higher intakes of vitamin K2 were associated with a significantly lower degree of aortic calcification and lower incidence of CHD in this study, after adjustment for confounders.

Another Dutch prospective cohort study (Gast et al., 2009) was conducted in 17,357 women aged 49-70 years, with a mean follow-up of 8.1 years, and investigated the relationship between vitamin K2 intake and risk of CHD. After exclusion of women with dietary energy intake below 500 kcal/day or above 6,000 kcal/day, with no baseline general questionnaires or no retrievable data on vital status, or with either a reported history of CHD or cerebrovascular events or a reported use of vitamin K antagonists, 16,057 post-menopausal women completed a food frequency questionnaire at baseline to estimate intakes of vitamin K2 during the year preceding enrolment in the study. Cox proportional hazards regression models were used to estimate the hazard ratio (HR) for coronary events, in a univariate analysis (model 1), after adjustment for age at baseline (model 2), after additional adjustment for BMI, smoking status, presence of diabetes, hypertension and hypercholesterolaemia, and energy-adjusted alcohol intake (model 3), after further adjustment for dietary factors, i.e. energy and energy-adjusted intakes of saturated and polyunsaturated fatty acids (model 4), or after further adjustment for calcium intakes, which were found to be strongly correlated with vitamin K2 intakes (model 5). The HR for risk of CHD per 10 µg increase in vitamin K2 intake was significantly reduced in models 1 and 2, but not in model 3. The HR was 0.92 (95 % CI: 0.83 to 1.01) in model 5, and was 0.91 (95 % CI: 0.85 to 1.00) when calcium was excluded from the model (model 4). The Panel notes that higher intakes of vitamin K2 were not significantly associated with a reduced risk of CHD in this study, after adjustment for confounders.

The Panel notes that the results of two prospective cohort studies (Gast et al., 2009; Geleijnse et al., 2004) are in conflict regarding the risk of CHD associated to vitamin K2 intakes, and that high intakes of vitamin K2 were associated with a significantly lower degree of aortic calcification after adjustment for confounders in one prospective cohort study (Geleijnse et al., 2004).

Two cross-sectional studies (Beulens et al., 2009; Maas et al., 2007) investigated the relationship between vitamin K intake and arterial calcification in women in random samples of the Dutch cohort described by Gast et al. (2009).

The study by Beulens et al. (2009) was undertaken on post-menopausal women (n=564, after exclusion of eight subjects with missing information on coronary calcification and one subject with missing information on vitamin K intakes) who did not use contraceptives or were not on hormone replacement therapy and who underwent (seven to eleven years after enrolment) a multislice multi-detector computed tomography, from which coronary arterial calcium was quantified using the

Agatston calcium score. Presence of calcium in the coronary arteries was defined as a score >0. Energy-adjusted menaquinone intakes (estimated during the year preceding enrolment in the study) were categorised in quartiles. Prevalence ratios of coronary calcification for these quartiles were estimated using Poisson regression, and were adjusted for age (model 1), as well as smoking status, presence of diabetes and hypertension, categories of education, HDL- and LDL-cholesterol (model 2), and, in addition, alcohol consumption and energy-adjusted intakes of protein, calcium and fibre (model 3). Sixty-two percent of the women had coronary calcification. The prevalence ratio of coronary calcification was significantly lower only for the highest quartile of menaquinone intake, compared to the lowest, in models 1 and 3 (respectively 0.82, 95 % CI: 0.68-0.99; and 0.80, 95 % CI: 0.65-0.98). The Panel notes that vitamin K2 intake was inversely related to the presence of coronary calcification, after adjustment for confounders.

The study by Maas et al. (2007) was conducted in women for whom the frozen blood samples and the baseline mammogram, on which calcium deposits along the breast arteries were searched for in one or both breasts, were retrieved. After exclusion of 18 subjects with reported use of vitamin K antagonists and of 29 subjects with no blood sample or baseline general questionnaires, 1,689 women were considered in the analysis. Mean K2 intakes were calculated for each quartile, and for women with or without breast arterial calcification. Adjustment for age, smoking, diabetes, energy-adjusted intakes of saturated, monounsaturated and polyunsaturated fatty acids and protein, and for intakes of calcium was done with univariate analysis of variance (ANOVA) (general linear model). The prevalence of breast arterial calcification was not statistically significantly different (OR 0.7, 95 % CI: 0.5-1.1) between the highest (9 %) and the lowest (13 %) quartile of vitamin K2 intake. After adjustment for confounders, mean vitamin K2 intake was not statistically significantly different between participants with or without breast arterial calcification. The Panel notes that this study showed no association between vitamin K2 intake and breast arterial calcification, after adjustment for confounders.

The Panel notes that one cross-sectional study reported that vitamin K2 intake was inversely related to the presence of coronary calcification (Beulens et al., 2009), while the other (Maas et al., 2007) showed no association between vitamin K2 intake and breast arterial calcification, after adjustment for confounders.

The proposed mechanism by which vitamin K2 could exert the claimed effect is by contributing to the vitamin K-dependent activation (carboxylation) of MGP, a matrix Gla-protein which has been identified in vascular tissue. Increased levels of carboxylated MGP would reduce vascular calcification and decrease the risk of vascular (including coronary) events.

There is some evidence for a role of MGP in preventing calcification of soft tissues. In an MGP knock-out mouse model, spontaneous calcification of soft tissues (mostly arteries) occurred (Luo et al., 1997). Also in the Keutel syndrome, which results from a mutation of the gene encoding the human MGP, patients display several of the same features as the knockout mice, including abnormal calcification of ear and nose cartilage, and of the respiratory tract (Munroe et al., 1999). However, whether changes in vitamin K2 intakes may induce changes in MGP carboxylation, which in turn could affect vascular function (e.g. calcification) or the risk of vascular events, has not been established.

Three additional randomised, placebo-controlled, parallel intervention studies investigated the effects of vitamin K2 supplementation on blood concentrations of (uncarboxylated/carboxylated) MGP (Braam and Vermeer, 2011, unpublished; Moschonis et al., 2011, unpublished; Vermeer, 2008, unpublished). The Panel notes that these studies do not provide any information about how, and to which extent, changes in (uncarboxylated/carboxylated) MGP may affect vascular function, and considers that no conclusions can be drawn from these studies for the scientific substantiation of the claim.

As regards the animal studies, one study (Spronk et al., 2003) investigated the effects of diets containing warfarin and vitamin K1, vitamin K2 (MK-4, 1.5 mg per g of food), or both, on calcification of the aorta and carotid arteries in male rats. The Panel considers that no conclusions can be drawn from a study using a fixed combination for the substantiation of a claim on vitamin K2 alone.

The second study (Schurgers et al., 2007) investigated the effects of diets with different contents of vitamin K1 or vitamin K2 on arterial calcium content and stiffness, total plasma MGP, MGP deposits in vascular tissues, and the content of vitamin K1 and K2 in the aorta, in male rats with preformed arterial calcification. Thirty rats received a six-week diet containing warfarin and 1.5 mg vitamin K1 per g of food ("W&K") to induce arterial calcification, while the controls (n=18) received vitamin K1 without warfarin. Six rats from the control group were killed to measure the baseline arterial calcium content, and after the six weeks of treatment, six additional control rats and six treated rats were killed to monitor the effect of treatment, while the remaining control rats continued their diet for six additional weeks. The remaining treated rats were divided into four groups (n=6 each), which either continued for six additional weeks the same "W&K" diet with warfarin and vitamin K1, or received diets without warfarin for six weeks, but either with vitamin K1 ("normal" and "high K1 groups"), or with 100 µg vitamin K2 per g of food ("high K2 group" receiving MK-4). Antibodies were raised against, respectively, total, carboxylated and uncarboxylated MGP. Calcium content was assessed in the abdominal aorta and left carotid artery, and the right carotid artery was used for monitoring distensibility and compliance. Immunohistochemistry was performed on the aortic arch and thoracic aorta. The Panel notes that although the outcomes assessed in this study were related to the claimed effect, no information was provided to establish the validity of this animal model for the scientific substantiation of the claim in humans.

The Panel considers that the evidence provided in these animal studies is not sufficient to predict the occurrence of an effect of the dietary intake of vitamin K2 on contribution to the normal function of the heart and blood vessels in humans.

In weighing the evidence, the Panel took into account the absence of human intervention studies from which conclusions could be drawn for the scientific substantiation of the claim, the inconsistency of the results reported in two cross-sectional studies regarding arterial calcification in women, that the results of two prospective cohort studies are in conflict regarding the risk of CHD associated with vitamin K2 intakes, that high intakes of vitamin K2 were associated with a significantly lower degree of aortic calcification in one prospective cohort study after adjustment for confounders, and that the evidence provided for a proposed mechanism is weak.

The Panel concludes that a cause and effect relationship has not been established between the dietary intake of vitamin K2 and contribution to the normal function of the heart and blood vessels.

CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food constituent, vitamin K2, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect, which is eligible for further assessment, is normal function of the heart and blood vessels. The proposed target population is the general population. Contribution to the normal function of the heart and blood vessels is a beneficial physiological effect.
- A cause and effect relationship has not been established between the dietary intake of vitamin K2 and contribution to the normal function of the heart and blood vessels.

DOCUMENTATION PROVIDED TO EFSA

Health claims pursuant to Article 13 of Regulation (EC) No 1924/2006 for further assessment (No: EFSA-Q-2012-00125). The scientific substantiation is based on the information provided by the Member States in the consolidated list of Article 13 health claims, references that EFSA has received from Member States or directly from stakeholders and the additional information provided by the competent Authority of the United Kingdom for further assessment of this claim (available at: http://www.efsa.europa.eu/en/topics/topic/article13.htm).

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APPENDICES

APPENDIX A

BACKGROUND AND TERMS OF REFERENCE AS PROVIDED BY THE EUROPEAN COMMISSION

The Regulation 1924/2006 on nutrition and health claims made on foods[7] (hereinafter "the Regulation") entered into force on 19th January 2007.

Article 13 of the Regulation foresees that the Commission shall adopt a Community list of permitted health claims other than those referring to the reduction of disease risk and to children's development and health. This Community list shall be adopted through the Regulatory Committee procedure and following consultation of the European Food Safety Authority (EFSA).

Health claims are defined as "any claim that states, suggests or implies that a relationship exists between a food category, a food or one of its constituents and health".

In accordance with Article 13 (1) health claims other than those referring to the reduction of disease risk and to children's development and health are health claims describing or referring to:

a) the role of a nutrient or other substance in growth, development and the functions of the body; or

b) psychological and behavioural functions; or

c) without prejudice to Directive 96/8/EC, slimming or weight-control or a reduction in the sense of hunger or an increase in the sense of satiety or to the reduction of the available energy from the diet.

To be included in the Community list of permitted health claims, the claims shall be:

(i) based on generally accepted scientific evidence; and

(ii) well understood by the average consumer.

Member States provided the Commission with lists of claims as referred to in Article 13 (1) by 31 January 2008 accompanied by the conditions applying to them and by references to the relevant scientific justification. These lists have been consolidated into the list which forms the basis for the EFSA consultation in accordance with Article 13 (3).

ISSUES THAT NEED TO BE CONSIDERED

IMPORTANCE AND PERTINENCE OF THE FOOD[8]

Foods are commonly involved in many different functions[9] of the body, and for one single food many health claims may therefore be scientifically true. Therefore, the relative importance of food e.g. nutrients in relation to other nutrients for the expressed beneficial effect should be considered: for functions affected by a large number of dietary factors it should be considered whether a reference to a single food is scientifically pertinent.

[7] OJ L12, 18/01/2007
[8] The term 'food' when used in this Terms of Reference refers to a food constituent, the food or the food category.
[9] The term 'function' when used in this Terms of Reference refers to health claims in Article 13(1)(a), (b) and (c).

It should also be considered if the information on the characteristics of the food contains aspects pertinent to the beneficial effect.

SUBSTANTIATION OF CLAIMS BY GENERALLY ACCEPTABLE SCIENTIFIC EVIDENCE

Scientific substantiation is the main aspect to be taken into account to authorise health claims. Claims should be scientifically substantiated by taking into account the totality of the available scientific data, and by weighing the evidence, and shall demonstrate the extent to which:

(a) the claimed effect of the food is beneficial for human health,

(b) a cause and effect relationship is established between consumption of the food and the claimed effect in humans (such as: the strength, consistency, specificity, dose-response, and biological plausibility of the relationship),

(c) the quantity of the food and pattern of consumption required to obtain the claimed effect could reasonably be achieved as part of a balanced diet,

(d) the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.

EFSA has mentioned in its scientific and technical guidance for the preparation and presentation of the application for authorisation of health claims consistent criteria for the potential sources of scientific data. Such sources may not be available for all health claims. Nevertheless it will be relevant and important that EFSA comments on the availability and quality of such data in order to allow the regulator to judge and make a risk management decision about the acceptability of health claims included in the submitted list.

The scientific evidence about the role of a food on a nutritional or physiological function is not enough to justify the claim. The beneficial effect of the dietary intake has also to be demonstrated. Moreover, the beneficial effect should be significant i.e. satisfactorily demonstrate to beneficially affect identified functions in the body in a way which is relevant to health. Although an appreciation of the beneficial effect in relation to the nutritional status of the European population may be of interest, the presence or absence of the actual need for a nutrient or other substance with nutritional or physiological effect for that population should not, however, condition such considerations.

Different types of effects can be claimed. Claims referring to the maintenance of a function may be distinct from claims referring to the improvement of a function. EFSA may wish to comment whether such different claims comply with the criteria laid down in the Regulation.

WORDING OF HEALTH CLAIMS

Scientific substantiation of health claims is the main aspect on which EFSA's opinion is requested. However, the wording of health claims should also be commented by EFSA in its opinion.

There is potentially a plethora of expressions that may be used to convey the relationship between the food and the function. This may be due to commercial practices, consumer perception and linguistic or cultural differences across the EU. Nevertheless, the wording used to make health claims should be truthful, clear, reliable and useful to the consumer in choosing a healthy diet.

In addition to fulfilling the general principles and conditions of the Regulation laid down in Article 3 and 5, Article 13(1)(a) stipulates that health claims shall describe or refer to "the role of a nutrient or other substance in growth, development and the functions of the body". Therefore, the requirement to describe or refer to the 'role' of a nutrient or substance in growth, development and the functions of the body should be carefully considered.

The specificity of the wording is very important. Health claims such as "Substance X supports the function of the joints" may not sufficiently do so, whereas a claim such as "Substance X helps maintain the flexibility of the joints" would. In the first example of a claim it is unclear which of the various functions of the joints is described or referred to contrary to the latter example which specifies this by using the word "flexibility".

The clarity of the wording is very important. The guiding principle should be that the description or reference to the role of the nutrient or other substance shall be clear and unambiguous and therefore be specified to the extent possible i.e. descriptive words/ terms which can have multiple meanings should be avoided. To this end, wordings like "strengthens your natural defences" or "contain antioxidants" should be considered as well as "may" or "might" as opposed to words like "contributes", "aids" or "helps".

In addition, for functions affected by a large number of dietary factors it should be considered whether wordings such as "indispensable", "necessary", "essential" and "important" reflects the strength of the scientific evidence.

Similar alternative wordings as mentioned above are used for claims relating to different relationships between the various foods and health. It is not the intention of the regulator to adopt a detailed and rigid list of claims where all possible wordings for the different claims are approved. Therefore, it is not required that EFSA comments on each individual wording for each claim unless the wording is strictly pertinent to a specific claim. It would be appreciated though that EFSA may consider and comment generally on such elements relating to wording to ensure the compliance with the criteria laid down in the Regulation.

In doing so the explanation provided for in recital 16 of the Regulation on the notion of the average consumer should be recalled. In addition, such assessment should take into account the particular perspective and/or knowledge in the target group of the claim, if such is indicated or implied.

TERMS OF REFERENCE

HEALTH CLAIMS OTHER THAN THOSE REFERRING TO THE REDUCTION OF DISEASE RISK AND TO CHILDREN'S DEVELOPMENT AND HEALTH

EFSA should in particular consider, and provide advice on the following aspects:

- Whether adequate information is provided on the characteristics of the food pertinent to the beneficial effect.

- Whether the beneficial effect of the food on the function is substantiated by generally accepted scientific evidence by taking into account the totality of the available scientific data, and by weighing the evidence. In this context EFSA is invited to comment on the nature and quality of the totality of the evidence provided according to consistent criteria.

- The specific importance of the food for the claimed effect. For functions affected by a large number of dietary factors whether a reference to a single food is scientifically pertinent.

In addition, EFSA should consider the claimed effect on the function, and provide advice on the extent to which:

- the claimed effect of the food in the identified function is beneficial.

- a cause and effect relationship has been established between consumption of the food and the claimed effect in humans and whether the magnitude of the effect is related to the quantity consumed.

- where appropriate, the effect on the function is significant in relation to the quantity of the food proposed to be consumed and if this quantity could reasonably be consumed as part of a balanced diet.

- the specific study group(s) in which the evidence was obtained is representative of the target population for which the claim is intended.

- the wordings used to express the claimed effect reflect the scientific evidence and complies with the criteria laid down in the Regulation.

When considering these elements EFSA should also provide advice, when appropriate:

- on the appropriate application of Article 10 (2) (c) and (d) in the Regulation, which provides for additional labelling requirements addressed to persons who should avoid using the food; and/or warnings for products that are likely to present a health risk if consumed to excess.

APPENDIX B

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of the food/food constituent, a positive assessment of its safety, nor a decision on whether the food/food constituent is, or is not, classified as foodstuffs. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wordings of the claims and the conditions of use as proposed in the Consolidated List may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 13(3) of Regulation (EC) No 1924/2006.

GLOSSARY AND ABBREVIATIONS

ANOVA	Analysis of variance
BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence interval
Gla	Glutamic acid
HDL	High density lipoproteins
HR	Hazard ratio
LDL	Low density lipoproteins
MGP	Matrix Gla Protein
MK	Menaquinone
OR	Odds ratio
RR	Risk ratio