



## **EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of health claims related to folate and maintenance of normal blood pressure (ID 176) pursuant to Article 13(1) of Regulation (EC) No 1924/2006**

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## SCIENTIFIC OPINION

### **Scientific Opinion on the substantiation of health claims related to folate and maintenance of normal blood pressure (ID 176) pursuant to Article 13(1) of Regulation (EC) No 1924/2006<sup>1</sup>**

**EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)<sup>2, 3</sup>**

European Food Safety Authority (EFSA), Parma, Italy

#### **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. This opinion addresses the scientific substantiation of health claims in relation to folate and maintenance of normal blood pressure. The scientific substantiation is based on the information provided by the Member States in the consolidated list of Article 13 health claims and references that EFSA has received from Member States or directly from stakeholders.

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

The claimed effect is “cardiovascular health”. The target population is assumed to be the general population. In the context of the proposed wordings, the Panel assumes that the claimed effect relates to the maintenance of normal blood pressure. The Panel considers that maintenance of normal blood pressure is a beneficial physiological effect.

In weighing the evidence, the Panel took into account that no human intervention studies from which conclusions could be drawn on an effect of folate intake on blood pressure were provided, and that two large prospective cohort studies which addressed the association between folate intake and incident hypertension in women had substantial weaknesses as the incidence of hypertension was self-reported and folate intake data (from diet and supplements) were collected by semi-quantitative food frequency questionnaires.

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<sup>1</sup> On request from the European Commission, Question No EFSA-Q-2008-963, adopted on 25 March 2011.

<sup>2</sup> Panel members: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Hannu Korhonen, Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley, Monika Neuhäuser-Berthold, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Stephan Strobel, Inge Tetens, Daniel Tomé, Hendrik van Loveren and Hans Verhagen. Correspondence: [nda@efsa.europa.eu](mailto:nda@efsa.europa.eu)

<sup>3</sup> Acknowledgement: The Panel wishes to thank for the preparatory work on this scientific opinion: The members of the Working Group on Claims 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. The members of the Claims Sub-Working Group on Cardiovascular Health/Oxidative Stress: Antti Aro, Marianne Geleijnse, Marina Heinonen, Ambroise Martin, Wilhelm Stahl and Henk van den Berg.

On the basis of the data presented, the Panel concludes that a cause and effects relationship has not been established between the dietary intake of folate and maintenance of normal blood pressure.

**KEY WORDS**

Folate, blood pressure, health claims.

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## INFORMATION AS PROVIDED IN THE CONSOLIDATED LIST

The consolidated list of health claims pursuant to Article 13 of Regulation (EC) No 1924/2006<sup>4</sup> submitted by Member States contains main entry claims with corresponding conditions of use and literature for similar health claims. EFSA has screened all health claims contained in the original consolidated list of Article 13 health claims which was received by EFSA in 2008 using six criteria established by the NDA Panel to identify claims for which EFSA considered sufficient information had been provided for evaluation and those for which more information or clarification was needed before evaluation could be carried out<sup>5</sup>. The clarifications which were received by EFSA through the screening process have been included in the consolidated list. This additional information will serve as clarification to the originally provided information. The information provided in the consolidated list for the health claims which are the subject of this opinion is tabulated in Appendix C.

## ASSESSMENT

### 1. Characterisation of the food/constituent (ID 176)

The food constituent that is the subject of the health claim is calcium L-methylfolate.

Calcium-L-methylfolate is a synthetic folate compound used in food supplements and food fortification; it is synthesised by reduction of folic acid to tetrahydrofolic acid followed by methylation and diastereoselective crystallisation (in water) of L-methylfolate as its calcium salt.

In the context of the references provided, the Panel assumes that the food constituent that is the subject of the claim is folate, which is the generic name for a number of derivatives of pteroylglutamic acid (PGA, folic acid). Natural (dietary) folates are mostly reduced folates, i.e. derivatives of tetrahydrofolate (THF) (SCF, 2000).

Different forms of folate, including calcium-L-methylfolate, are authorised for addition to foods (Annex II of the Regulation (EC) No 1925/2006<sup>6</sup> and Annex II of Directive 2002/46/EC<sup>7</sup>). This evaluation applies to folate naturally present in foods and those forms authorised for addition to foods (Annex II of the Regulation (EC) No 1925/2006 and Annex II of Directive 2002/46/EC).

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

### 2. Relevance of the claimed effect to human health (ID 176)

The claimed effect is “cardiovascular health”. The Panel assumes the target population is the general population.

In the context of the proposed wordings, the Panel assumes that the claimed effect relates to the maintenance of normal blood pressure.

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<sup>4</sup> 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.

<sup>5</sup> 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.

<sup>6</sup> 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.

<sup>7</sup> 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.

Blood pressure is the pressure (force per unit area) exerted by circulating blood on the walls of blood vessels. Elevated blood pressure, by convention above 140 mmHg (systolic) and/or 90 mmHg (diastolic), may compromise the normal arterial and cardiac function.

The Panel considers that maintenance of normal blood pressure is a beneficial physiological effect.

### 3. Scientific substantiation of the claimed effect (ID 176)

The majority of the references provided for the scientific substantiation of the claim included narrative reviews which did not contain original data that could be used for the scientific substantiation of the claim. Most of the human studies provided did not contain data on folate (or calcium L-methylfolate) intake, assessed the effects of folate or folic acid in combination with other food constituents (e.g. vitamin B6, vitamin E), or addressed health outcomes other than blood pressure (e.g. folate kinetics, homocysteine concentrations in relation to the risk of coronary heart disease and stroke, risk of cardiovascular disease, the MTHFR 677C→T polymorphism in relation to the risk of coronary heart disease, peripheral arterial disease, endothelial function, arterial stiffness and compliance, common carotid intima-media thickness, antioxidant status, markers of oxidative stress, insulin resistance, parameters of coronary blood circulation). The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claim.

Two double-blind, randomised, controlled, parallel group intervention studies investigated the effects of 5 mg folic acid daily for 3-4 weeks on blood pressure in cigarette smokers and in subjects with normal or high normal blood pressure (Mangoni et al., 2002; Williams et al., 2005). The Panel notes that these studies used daily doses of folic acid five times above the Tolerable Upper Intake Level (UL) for adults (1,000 µg) (SCF, 2000) and more than ten times the doses proposed in the conditions of use for this claim (400 µg). The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claim.

Forman et al. (2005) prospectively examined the association between folate intake and risk of incident hypertension in two large cohorts of younger and older women who were followed for eight years. The study cohorts consisted of 93,803 women aged 27 to 44 years in the Nurses' Health Study II (1991-1999) and 62,260 older women aged 43 to 70 years in the Nurses' Health Study I (1990-1998), and who did not have a history of hypertension. Baseline information on dietary folate and supplemental folic acid intakes was derived from semi-quantitative food frequency questionnaires and was updated every four years. The outcome variable was relative risk of incident self-reported hypertension during the eight years of follow-up. After adjusting for multiple potential confounders, younger women who consumed at least 1,000 µg/day of total folate (dietary plus supplemental intake) had a decreased risk of hypertension (relative risk [RR] 0.54; 95% CI = 0.45-0.66; p for trend <0.001) compared with those who consumed less than 200 µg/day. For older women the RR was 0.82 (95% CI = 0.69-0.97; p for trend = 0.05) for the same comparison. The Panel notes that incident hypertension was self-reported, and that dietary intake data were collected by semi-quantitative food frequency questionnaires.

In weighing the evidence, the Panel took into account that no human intervention studies from which conclusions could be drawn on an effect of folate intake on blood pressure were provided, and that two large prospective cohort studies which addressed the association between folate intake and incident hypertension in women had substantial weaknesses as the incidence of hypertension was self-reported and folate intake data (from diet and supplements) were collected by semi-quantitative food frequency questionnaires.

The Panel concludes that a cause and effects relationship has not been established between the dietary intake of folate and maintenance of normal blood pressure.

## CONCLUSIONS

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

- The food constituent, folate, which is the subject of the health claim is sufficiently characterised.
- The claimed effect is “cardiovascular health”. The target population is assumed to be the general population. Maintenance of normal blood pressure is a beneficial physiological effect.
- A cause and effect relationship has not been established between the dietary intake of folate and maintenance of normal blood pressure.

## DOCUMENTATION PROVIDED TO EFSA

Health claims pursuant to Article 13 of Regulation (EC) No 1924/2006 (No: EFSA-Q-2008-963). The scientific substantiation is based on the information provided by the Member States in the consolidated list of Article 13 health claims and references that EFSA has received from Member States or directly from stakeholders.

The full list of supporting references as provided to EFSA is available on: <http://www.efsa.europa.eu/panels/nda/claims/article13.htm>.

## REFERENCES

- Forman JP, Rimm EB, Stampfer MJ and Curhan GC, 2005. Folate intake and the risk of incident hypertension among US women. *JAMA*, 293, 320-329.
- Mangoni AA, Sherwood RA, Swift CG and Jackson SH, 2002. Folic acid enhances endothelial function and reduces blood pressure in smokers: a randomized controlled trial. *Journal of Internal Medicine*, 252, 497-503.
- SCF (Scientific Committee on Food), 2000. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Folate.
- Williams C, Kingwell BA, Burke K, McPherson J and Dart AM, 2005. Folic acid supplementation for 3 wk reduces pulse pressure and large artery stiffness independent of MTHFR genotype. *American Journal of Clinical Nutrition*, 82, 26-31.



## 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<sup>8</sup> (hereinafter "the Regulation") entered into force on 19<sup>th</sup> 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<sup>9</sup>

Foods are commonly involved in many different functions<sup>10</sup> 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.

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<sup>8</sup> OJ L12, 18/01/2007

<sup>9</sup> The term 'food' when used in this Terms of Reference refers to a food constituent, the food or the food category.

<sup>10</sup> 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.

**APPENDIX C**

Table 1. Main entry health claims related to folate, including conditions of use from similar claims, as proposed in the Consolidated List.

ID	Food or Food constituent	Health Relationship	Proposed wording
176	Calcium L-methylfolate (syn.: L-5-methyltetrahydrofolic acid, calcium salt; Vitamin B9), MetafolinTM	Cardiovascular health	<p>Helps keep arteries/blood vessels healthy;</p> <p>Contributes to healthy arteries/ blood vessels;</p> <p>Supports heart health by contributing to the normal functioning of the arteries/blood vessels;</p> <p>Helps maintain a normal blood pressure by supporting the elasticity of blood vessels/arteries.</p>
<p><b>Conditions of use</b></p> <p>- <math>\geq 400 \mu\text{g/d}</math></p>			

## GLOSSARY AND ABBREVIATIONS

CI	Confidence interval
MTHFR	Methylene tetrahydrofolate reductase
PGA	Pteroylglutamic acid
RR	Relative risk
THF	Tetrahydrofolate
UL	Tolerable Upper Intake Level