

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to folate and blood formation (ID 79), homocysteine metabolism (ID 80), energy-yielding metabolism (ID 90), function of the immune system (ID 91), function of blood vessels (ID 94, 175, 192), cell division (ID 193), and maternal tissue growth during pregnancy (ID 2882) pursuant to Article 13(1) of Regulation (EC) No 1924/2006¹

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

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 the following claimed effects: blood formation, homocysteine metabolism, energy-yielding metabolism, function of the immune system, function of blood vessels, cell division, and maternal tissue growth during pregnancy. 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 claims is folate, which is a well recognised nutrient and is measurable in foods by established methods. The Panel considers that the food constituent, folate, which is the subject of the health claims, is sufficiently characterised.

The Panel concludes that a cause and effect relationship has been established between the dietary intake of folate and normal blood formation, normal homocysteine metabolism, normal function of the immune system, normal cell division, and normal maternal tissue growth during pregnancy.

The Panel considers that, in order to bear the claims, a food should be at least a source of folate as per Annex to Regulation (EC) No 1924/2006. Such amounts can be easily consumed as part of a balanced

1 On request from the European Commission, Question No EFSA-Q-2008-866, EFSA-Q-2008-867, EFSA-Q-2008-877, EFSA-Q-2008-878, EFSA-Q-2008-881, EFSA-Q-2008-962, EFSA-Q-2008-979, EFSA-Q-2008-980, EFSA-Q-2008-3615 adopted on 02 July 2009.

2 Panel members: Jean-Louis Bresson, Albert Flynn, Marina Heinonen, Karin Hulshof, Hannu Korhonen, Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin, Bevan Moseley, Hildegard Przyrembel, Seppo Salminen, Sean (J.J.) Strain, Stephan Strobel, Inge Tetens, Henk van den Berg, Hendrik van Loveren and Hans Verhagen.
Correspondence: nda@efsa.europa.eu

For citation purposes: EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of health claims related to folate and blood formation (ID 79), homocysteine metabolism (ID 80), energy-yielding metabolism (ID 90), function of the immune system (ID 91), function of blood vessels (ID 94, 175, 192), cell division (ID 193), and maternal tissue growth during pregnancy (ID 2882) pursuant to Article 13(1) of Regulation (EC) No 1924/2006 on request from the European Commission. EFSA Journal 2009; 7(9):1213. [22 pp.].
doi:10.2903/j.efsa.2009.1213. Available online: www.efsa.europa.eu

diet. The target population is the general population for the following claimed effects: blood formation, homocysteine metabolism and function of the immune system. The target population is women planning to become pregnant and pregnant women for the following claimed effect: maternal tissue growth during pregnancy.

The Panel concludes that a cause and effect relationship has not been established between the dietary intake of folate and normal energy-yielding metabolism and function of blood vessels.

KEY WORDS

Folate, folic acid, blood formation, homocysteine, energy-yielding metabolism, immune system, blood vessels, cell division, pregnancy, health claims.

TABLE OF CONTENTS

Summary	1
Table of contents	3
Background as provided by the European Commission	4
Terms of reference as provided by the European Commission	4
EFSA Disclaimer.....	4
Acknowledgements	4
Information as provided in the consolidated list	5
Assessment	5
1. Characterisation of the food/constituent	5
2. Relevance of the claimed effect to human health.....	5
2.1. Blood formation (ID 79)	5
2.2. Homocysteine metabolism (ID 80)	5
2.3. Energy-yielding metabolism (ID 90)	6
2.4. Function of the immune system (ID 91)	6
2.5. Function of blood vessels (ID 94, 175, 192).....	6
2.6. Cell division (ID 193)	6
2.7. Maternal tissue growth during pregnancy (ID 2882).....	6
3. Scientific substantiation of the claimed effect	6
3.1. Blood formation (ID 79)	7
3.2. Homocysteine metabolism (ID 80)	7
3.3. Energy-yielding metabolism (ID 90)	7
3.4. Function of the immune system (ID 91)	7
3.5. Function of blood vessels (ID 94, 175, 192).....	8
3.6. Cell division (ID 193)	9
3.7. Maternal tissue growth during pregnancy (ID 2882).....	9
4. Panel's comments on the proposed wording	9
4.1. Blood formation (ID 79)	9
4.2. Homocysteine metabolism (ID 80)	9
4.3. Function of the immune system (ID 91)	9
4.4. Cell division (ID 193)	9
4.5. Maternal tissue growth during pregnancy (ID 2882).....	10
5. Conditions and possible restrictions of use	10
Conclusions	10
Documentation provided to EFSA	11
References	12
Appendices	13
Glossary / Abbreviations.....	22

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

ACKNOWLEDGEMENTS

The European Food Safety Authority wishes to thank the members of the Working Group on claims for the preparation of this opinion: Jean-Louis Bresson, Albert Flynn, Marina Heinonen, Hannu Korhonen, Martinus Løvik, Ambroise Martin, Hildegard Przyrembel, Seppo Salminen, Sean (J.J.) Strain, Inge Tetens, Henk van den Berg, Hendrik van Loveren and Hans Verhagen.

INFORMATION AS PROVIDED IN THE CONSOLIDATED LIST

The consolidated list of health claims pursuant to Article 13 of Regulation (EC) No 1924/2006³ submitted by Member States contains main entry claims with corresponding conditions of use and literature from similar health claims. The information provided in the consolidated list for the health claims subject to this opinion is tabulated in Appendix C.

ASSESSMENT

1. Characterisation of the food/constituent

The food constituent that is the subject of the health claims is folate. Folate is measurable in foods by established methods.

Folate is the generic name for a number of compounds having a similar activity as folic acid (pteroylglutamic acid, PGA). Folic acid (PGA) is a synthetic folate compound used in food supplements and in food fortification because of its stability, and becomes biologically active after reduction. Natural (dietary) folates are mostly reduced folates, i.e. derivatives of tetrahydrofolate (THF) (SCF, 2000).

Different forms of folate are authorised for addition to foods (Annex II of the Regulation (EC) No 1925/2006⁴ and Annex II of Directive 2002/46/EC⁵). 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 claims, is sufficiently characterised.

2. Relevance of the claimed effect to human health

2.1. Blood formation (ID 79)

The claimed effect is “blood formation”. The Panel assumes that the target population is the general population.

The Panel considers that normal blood formation is beneficial to human health.

2.2. Homocysteine metabolism (ID 80)

The claimed effect is “homocysteine metabolism”. The Panel assumes that the target population is the general population.

The Panel considers that normal homocysteine metabolism is beneficial to human health.

³ 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.

⁴ 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.

⁵ 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.

2.3. Energy-yielding metabolism (ID 90)

The claimed effect is “the role of water-soluble vitamins in energy metabolism / transformation of food into physiological energy”. The Panel assumes that the target population is the general population.

The Panel considers that normal energy-yielding metabolism is beneficial to human health.

2.4. Function of the immune system (ID 91)

The claimed effect is “the role of vitamins and minerals in immunity”. The Panel assumes that the target population is the general population.

The Panel considers that a normal function of the immune system is beneficial to human health.

2.5. Function of blood vessels (ID 94, 175, 192)

The claimed effects are “vascular function/cardiovascular health”, “cardiovascular health” and “folate helps keep arteries/ blood vessels healthy”. The Panel assumes that the target population is the general population.

The claimed effect “cardiovascular health” is not sufficiently defined in the list. From the proposed wordings the Panel assumes the claimed effect relates to normal function of the blood vessels.

The Panel considers that normal function of blood vessels is beneficial to human health.

2.6. Cell division (ID 193)

The claimed effect is “cell division”. The Panel assumes that the target population is the general population.

The Panel notes that cell division is a crucial process for tissue growth and development and for tissue maintenance through cell turnover.

The Panel considers that normal cell division is beneficial to human health.

2.7. Maternal tissue growth during pregnancy (ID 2882)

The claimed effect is “effect on a normal pregnancy”. The target population is women planning to become pregnant and pregnant women.

The Panel interprets the claimed effect “effect on a normal pregnancy” as normal maternal tissue growth during pregnancy.

The Panel considers that normal maternal tissue growth during pregnancy is beneficial to human health.

3. Scientific substantiation of the claimed effect

Folates play an important role in the transfer of C1-groups (i.e. methyl-, methylene- and formyl-groups), maintaining the methylation balance (SCF, 2000). Folate coenzymes are involved in numerous reactions that involve DNA synthesis, purine synthesis, generation of formate into the formate pool and amino acid interconversion (IoM, 1998).

3.1. Blood formation (ID 79)

In folate deficiency, a net decrease in 5,10-methylenetetrahydrofolate interrupts the reaction mediated by thymidylate synthase, which converts deoxyuridine monophosphate to deoxythymidine monophosphate. The excess deoxyuridine monophosphate is then phosphorylated to deoxyuridine triphosphate and is incorporated into DNA. This faulty incorporation is immediately recognised by an editorial enzyme and is excised. When this process is repeated several times, it leads to DNA fragmentation and to perturbation of the cell cycle giving rise to megaloblastosis. All proliferating cells exhibit megaloblastosis; however the changes are most striking in the blood and bone marrow (Chitambar and Anthony, 2006). The main clinical expression of folate deficiency is megaloblastic anemia characterised by large, abnormally nucleated erythrocytes that accumulate in the bone marrow. There are also decreased numbers of white cells and platelets as a result of the general impairment of cell division (Bailey and Gregory, 2006).

The Panel concludes that a cause and effect relationship has been established between the dietary intake of folate and normal blood formation.

3.2. Homocysteine metabolism (ID 80)

5-methyltetrahydrofolate is an important functional and regulatory component of the folate-dependent pathway for the production of methionine from homocysteine which is catalysed by methionine synthase. In this reaction, a methyl group is sequentially transferred from 5-methyltetrahydrofolate to the cobalamin coenzyme of the methionine synthase, and then to homocysteine to form methionine (Bailey and Gregory, 2006).

Under conditions of maximal metabolic efficiency, plasma concentrations of homocysteine range from 4 to 10 $\mu\text{mol/L}$. Metabolic blocks in homocysteine metabolism lead to accumulation of intracellular homocysteine with subsequent export into the blood. Depending on the magnitude of the metabolic impairment, plasma homocysteine can rise to varying degrees. Hyperhomocysteinemia is also caused by B vitamin deficiencies. Deficiencies of folate, vitamin B6 and vitamin B12 lead to impaired remethylation of homocysteine causing mild, moderate, or severe elevations in plasma homocysteine, depending on the severity of the deficiency, as well as coexistence of genetic or other factors that interfere with homocysteine metabolism (Miller, 2005).

The Panel concludes that a cause and effect relationship has been established between the dietary intake of folate and normal homocysteine metabolism.

3.3. Energy-yielding metabolism (ID 90)

Folate coenzymes are involved in the interconversion of serine to glycine and in the catabolism of histidine to glutamic acid (McPartlin, 2005).

The Panel notes that these reactions do not lead to intermediates that can be considered as significant source of energy for the body.

The Panel concludes that a cause and effect relationship has not been established between the dietary intake of folate and normal energy-yielding metabolism.

3.4. Function of the immune system (ID 91)

Folate plays a crucial role in nucleotide synthesis, and thus may affect immune cell proliferation and responsiveness. Folate deficiency has been shown to reduce proliferation of various cell types. Cells lacking folate accumulate in the S-phase owing to nucleotide imbalance and slow DNA synthesis; such cells also have increased uracil misincorporation and DNA damage. When folate is added back

to folate-deficient cells, there is a reversal of the S-phase accumulation, and proliferation is restored. Folate deficiency has been shown to reduce the proportion of circulating T lymphocytes and their proliferation in response to mitogen activation. In addition, folate deficiency induced in PHA-activated human T lymphocytes induced apoptosis and increased the ratio of CD4+ to CD8+ T cells because of a marked reduction in CD8+ cell proliferation. All these effects were reversible in vitro by either folate addition or nucleotide repletion, and suggest that folate status may affect the immune system by inhibiting the capacity of CD8+ T lymphocyte cells to proliferate in response to mitogen activation (Courtemanche et al., 2004).

The Panel concludes that a cause and effect relationship has been established between the dietary intake of folate and a normal function of the immune system.

3.5. Function of blood vessels (ID 94, 175, 192)

A total of 73 references were cited to substantiate the claimed effect. Six references were textbook or opinions of scientific bodies and 47 references were not directly related to the claimed effect but to blood homocysteine concentrations, insulin sensitivity, markers of oxidative stress or to the relationship between hyperhomocysteinemia and the risk of cardiovascular disease. The Panel notes that the references cited did not provide any scientific data that could be used to substantiate the claimed effect.

One meta-analysis, three review papers and 16 human studies investigating the relationship between folic acid intake and endothelial function were cited. 15 of the human studies were conducted with high doses of folic acid (5 mg/d, 10 mg/d or 20 mg/d). The Panel notes that the doses used in these studies were 5 to 20 fold the Tolerable Upper Intake Level of folic acid for adults and 12.5 to 50 times the proposed conditions of use. The Panel considers that no scientific conclusions can be drawn from these studies for the substantiation of the claimed effect at the proposed conditions of use.

In a randomised double blind placebo controlled parallel design intervention, 56 subjects with coronary artery disease not exposed to folate fortification were randomised to receive either a low dose (400 µg/d) (n= 20) or high dose (5 mg/d) of folic acid (n=22) or placebo (n=14) for 7 weeks before coronary artery bypass grafting. Vascular function was quantified by high-resolution magnetic resonance imaging at baseline and at the end of the treatment period. Images of the aorta and carotid arteries were used to determine vascular distensibility and pulse-wave velocity as indices of vascular stiffness. FMD was used as a measure of endothelial function. Supplementation with both low and high doses of folic acid significantly improved aortic and carotid distensibility, reduced aortic pulse-wave velocity, and increased FMD compared with placebo, whereas no significant differences were observed between the folic acid groups for any outcome variable (Shirodaria et al., 2007). The Panel notes that this study was performed in patients with coronary artery disease before coronary artery bypass grafting and no evidence has been provided that the finding in this small study of cardiovascular disease patients can be extrapolated to the general population.

The meta-analysis included 14 randomised controlled trials. One trial had two intervention groups and thus 15 intervention groups were analysed. In total, this meta-analysis was based on 732 persons treated with folic acid (either alone or in combination with vitamin B6, vitamin B12, or both) or placebo for a median duration of 8 weeks and with a median study size of 34 participants. Most study participants were middle-aged males (median age 55.8 years, 86% males). The median folic acid dose was 5000 µg/d (range: 400–10,000 µg/d). The primary outcome was the net change in flow-mediated dilatation (FMD) induced by the supplementation with folic acid (either alone or in combination with vitamin B6, vitamin B12, or both). Supplementation with folic acid significantly improved FMD when all studies were considered together. Study design, mean age of the study population, study duration, or addition of vitamin B6 or vitamin B12 had no effect on the estimated change in FMD following folic acid supplementation, whereas the dose of folic acid used was an independent predictor of the outcome. Trials using lower doses of folic acid (400 - 800 µg/d, 4 intervention

groups) did not show a significant beneficial effect of folic acid intake on FMD, whereas the studies using doses ≥ 5000 $\mu\text{g}/\text{d}$ (11 intervention groups) did (de Bree et al., 2007). The Panel notes that an effect of folic acid on endothelial function was only observed at doses that are 5 to 10 fold the Tolerable Upper Intake Level of folic acid for adults and 12.5 to 25 times the proposed conditions of use. The Panel considers that no scientific conclusions can be drawn from these studies for the substantiation the claimed effect at the proposed conditions of use.

The Panel concludes that a cause and effect relationship has not been established between the dietary intake of folate and normal function of blood vessels.

3.6. Cell division (ID 193)

During the S-phase of the cell division cycle the DNA of the cell is replicated. This DNA synthesis is dependent on the presence of 5,10-methylenetetrahydrofolate, a co-factor of the thymidylate synthase, which converts deoxyuridine monophosphate to deoxythymidine monophosphate (Chitambar and Anthony, 2006). An additional function of folate in the nucleotide production involves the de novo synthesis of adenine and guanine (Bailey and Gregory, 2006).

The Panel concludes that a cause and effect relationship has been established between the intake of folate and normal cell division.

3.7. Maternal tissue growth during pregnancy (ID 2882)

During pregnancy folate is needed for increasing the mother's red blood cell mass, for the formation of the placenta and for the growth of the foetus, the uterus, breasts and other maternal tissues (Chitambar and Anthony, 2006) owing to its role in cell division (see section 2.3.6).

The Panels concludes that a cause and effect relationship has been established between the dietary intake of folate and normal maternal tissue growth during pregnancy.

4. Panel's comments on the proposed wording

4.1. Blood formation (ID 79)

The Panel considers that the following wording reflects the scientific evidence: "Folate contributes to normal blood formation."

4.2. Homocysteine metabolism (ID 80)

The Panel considers that the following wording reflects the scientific evidence: "Folate contributes to normal homocysteine metabolism."

4.3. Function of the immune system (ID 91)

The Panel considers that the following wording reflects the scientific evidence: "Folate contributes to a normal function of the immune system."

4.4. Cell division (ID 193)

The Panel considers that the following wording reflects the scientific evidence: "Folate contributes to normal cell division."

4.5. Maternal tissue growth during pregnancy (ID 2882)

The Panel considers that the following wording reflects the scientific evidence: “Folate contributes to normal maternal tissue growth during pregnancy.”

5. Conditions and possible restrictions of use

The Panel considers that in order to bear the claims a food should be at least a source of folate as per Annex to Regulation (EC) 1924/2006. Such amounts can be easily consumed as part of a balanced diet. The target population is the general population for the following claimed effects: blood formation (ID 79), homocysteine metabolism (ID 80), function of the immune system (ID 91), and cell division (ID 193). The target population is women planning to become pregnant and pregnant women for the following claimed effect: maternal tissue growth during pregnancy (ID 2882). Tolerable Upper Intake Levels (UL) have been established for folic acid for children and adults. The Tolerable Upper Intake Level for adults has been set at 1000 µg/d (SCF, 2000).

CONCLUSIONS

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

- The food constituent, folate, which is the subject of the health claims, is sufficiently characterised.

Blood formation (ID 79)

- The claimed effect is “blood formation”. Target population is assumed to be the general population. Normal blood formation is beneficial to human health.
- A cause and effect relationship has been established between the dietary intake of folate and normal blood formation.
- The following wording reflects the scientific evidence: “Folate contributes to normal blood formation.”

Homocysteine metabolism (ID 80)

- The claimed effect is “homocysteine metabolism”. The target population is assumed to be the general population. Normal homocysteine metabolism is beneficial to human health.
- A cause and effect relationship has been established between the dietary intake of folate and normal homocysteine metabolism.
- The following wording reflects the scientific evidence: “Folate contributes to normal homocysteine metabolism.”

Energy-yielding metabolism (ID 90)

- The claimed effect is “the role of water-soluble vitamins in energy metabolism / transformation of food into physiological energy”. The target population is assumed to be the general population. Normal energy-yielding metabolism is beneficial to human health.
- A cause and effect relationship has not been established between the dietary intake of folate and normal energy-yielding metabolism.

Function of the immune system (ID 91)

- The claimed effect is “the role of vitamins and minerals in immunity”. The target population is assumed to be the general population.

- A normal function of the immune system is beneficial to human health. A cause and effect relationship has been established between the dietary intake of folate and a normal function of the immune system.
- The following wording reflects the scientific evidence: “Folate contributes to a normal function of the immune system.”

Function of the blood vessels (ID 94, 175, 192)

- The claimed effects are “vascular function/cardiovascular health”, “cardiovascular health” and “folate helps keep arteries/ blood vessels healthy”. The target population is assumed to be the general population. Normal function of the blood vessels is beneficial to human health.
- A cause and effect relationship has not been established between the dietary intake of folate and normal function of the blood vessels.

Cell division (ID 193)

- The claimed effect is “cell division”. The target population is assumed to be the general population. Normal cell division is beneficial to human health.
- A cause and effect relationship has been established between the dietary intake of folate and normal cell division.
- The following wording reflects the scientific evidence: “Folate contributes to normal cell division.”

Maternal tissue growth during pregnancy (ID 2882)

- The claimed effect is “effect on a normal pregnancy”. The target population is women planning to become pregnant and pregnant women. Normal maternal tissue growth during pregnancy is beneficial to human health.
- A cause and effect relationship has been established between the dietary intake of folate and normal maternal tissue growth during pregnancy.
- The following wording reflects the scientific evidence: “Folate contributes to normal maternal tissue growth during pregnancy.”

Conditions and possible restrictions of use

- In order to bear the claims a food should be at least a source of folate/folic acid as per Annex to Regulation (EC) No 1924/2006. Such amounts can be easily consumed as part of a balanced diet. The target population is the general population for the following claimed effects: blood formation (ID 79), homocysteine metabolism (ID 80) and function of the immune system (ID 91). The target population is women planning to become pregnant and pregnant women for the following claimed effect: maternal tissue growth during pregnancy (ID 2882).

DOCUMENTATION PROVIDED TO EFSA

Health claims pursuant to Article 13 of Regulation (EC) No 1924/2006 (No: EFSA-Q-2008-866, EFSA-Q-2008-867, EFSA-Q-2008-877, EFSA-Q-2008-878, EFSA-Q-2008-881, EFSA-Q-2008-962, EFSA-Q-2008-979, EFSA-Q-2008-980, EFSA-Q-2008-3615). 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

- Bailey LB and Gregory JF, 2006. Folate. In: Present knowledge in nutrition. Bowman BA and Russell RM (eds.). International Life Sciences Institute (ILSI), Washington, DC.
- Chitambar CR and Antony AC, 2006. Nutritional aspects of some hematological disease. In: Modern Nutrition in Health and Disease. Shils M, Shike M, Ross C, Caballero B, Cousins R (eds.). Baltimore, Philadelphia. Lippincott Williams & Wilkins, 1436-1461.
- Courtemanche C, Elson-Schwab I, Mashiyama ST, Kerry N, Ames BN, 2004. Folate deficiency inhibits the proliferation of primary human CD8+ T lymphocytes in vitro. *J Immunol* 173(5), 3186-3192.
- de Bree A, van Mierlo LA, Draijer R, 2007. Folic acid improves vascular reactivity in humans: a meta-analysis of randomized controlled trials. *Am. J. Clin. Nutr.* 86(3), 610-617.
- IoM (Institute of Medicine), 1998. Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin and choline. Washington DC. National Academies Press.
- McPartlin J, 2005. Folic acid. In: Encyclopedia of Human Nutrition. Caballero B, Allen L, Prentice A (eds.). Elsevier, Oxford, 257-264.
- Miller JW, 2005. Homocysteine. In: Encyclopedia of Human Nutrition. Caballero B, Allen L, Prentice A (eds.). Elsevier, Oxford, 462-469.
- SCF (Scientific Committee on Food), 2000. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Folate.
- Shirodaria C, Antoniadis C, Lee J, Jackson CE, Robson MD, Francis JM, Moat SJ, Ratnatunga C, Pillai R, Refsum H, Neubauer S, Channon KM, 2007. Global Improvement of Vascular Function and Redox State With Low-Dose Folic Acid: Implications for Folate Therapy in Patients With Coronary Artery Disease. *Circulation* 115(17), 2262-2270.

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 foods⁶ (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 FOOD⁷

Foods are commonly involved in many different functions⁸ 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.

⁶ OJ L12, 18/01/2007

⁷ The term 'food' when used in this Terms of Reference refers to a food constituent, the food or the food category.

⁸ 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
79	Folate/ Folic acid (Vitamin B9)	Blood formation	Folate/ Folic acid (Vitamin B9) is needed/important for blood formation
	<p>Conditions of use</p> <ul style="list-style-type: none"> – Schwangere–400 µg Folsäure pro Tag in Form von Nahrungsergänzungsmitteln – Tolerable Upper Intake Level: 1 mg / d; 400 Mikrogramm (µg) /d – Must meet minimum requirements for use of the claim source of Vitamin B9 (Folate/Folic acid) as per Annex to Regulation 1924/2006 Applicable to both children and adults – Number of nutrients/other substances that are essential to claimed effect: 3 Names of nutrient/other substances and Quantity in Average daily serving: 1.2micrograms Vitamin B12, 4.5mg Vitamin E, 210 micrograms Folic Acid Daily amount to be consumed to produce claimed effect: 2 litres – Fruit with folic acid content of 30 µg/100g, 60 µg/serving – Number of nutrients/other substances that are essential to claimed effect: 1 Names of nutrient/other substances and Quantity in Average daily serving: 30 microgram(s) folic acid/folate Daily amount to be consumed to produce claimed effect: 30 microgram(s) 		
80	Folate/ Folic acid (Vitamin B9)	Homocysteine metabolism	Folate/ Folic acid (Vitamin 9) helps maintain normal blood homocysteine levels
	<p>Conditions of use</p> <ul style="list-style-type: none"> – Tolerable Upper Intake Level: 1 mg / d, 400 Mikrogramm (µg)/d – Schwangere – Presence of a nutrient or other substance Number of nutrients/other substances that are essential to claimed effect: 1 Names of nutrient/other substances and Quantity in Average daily serving: 30 microgram(s) folic acid Daily amount to be consumed to produce claimed effect: 30 microgram(s) – Minimum 15% RDA per 100g or 100ml or per single servings as per 90/496/EEC – MUST AT LEAST BE A SOURCE OF MINERAL/S AS PER ANNEX TO REGULATION 1924/2006 – Only for products with at least 100 % RDA – RNI: 0.2mg, B6 RNI: 1.4 mg a day for men,1.2 mg a day for women, B12 RNI:1.5 µg" The product must contain at least 15% of the RDA PRESUMED NOT NECESSARY TO present a statement which conveys that there is a risk that excess folate consumption (over 1mg/day) may mask B12 deficiency leading to late diagnosis of clinical disease particularly in the elderly and vegans AS PRODUCT ALSO CONTAINS RNI OF B12 Folic Acid 		

	<p>Product Dosage 400µg/day B6 Product Dosage 2mg /day B12 Product Dosage 1µg/day</p> <ul style="list-style-type: none"> – Cereal-based beverages with folic acid content of 9-15µg/100g, 23-38µg/serving, 45-75µg/daily serving – Food supplement with 200 µg of folic acid, 2mg of vitamin B6 and 2µg of vitamin B 12 in the daily dose – Food supplement with 300µg of folic acid in the daily dose – Food supplement with 6-12mg of vitamin B6, 600-1200µg of folic acid and 3-6 µg of vitamin B12 in the daily dose – Source of 15% of RDA per 100g 		
90	Food or Food constituent	Health Relationship	Proposed wording
	Folic Acid	The role of water-soluble vitamins in energy metabolism / transformation of food into physiological energy	B-vitamins and vitamin C are essential for the energy metabolism / the transformation of food into energy
Conditions of use			
<ul style="list-style-type: none"> – Must meet minimum requirements for use of the claim "'source of [name of vitamin/s] and/or [name of mineral/s],'" as per Annex to Regulation 1924/2006. – Minimum 15% RDA (30 µg) dziennie. 			
91	Food or Food constituent	Health Relationship	Proposed wording
	Folic Acid	The role of vitamins and minerals in immunity	Vitamin C, E, A, D, B6, B12 folic acid, Selenium, Zinc, Copper and Iron are important for the immune system/natural defenses
Conditions of use			
<ul style="list-style-type: none"> – Minimum 15% RDA (30 µg) dziennie. – Witaminy na poziomie 100% RDA Cynk 15%RDA (2,25 mg) Żelazo 15%RDA (2,1 mg) Selen minimum 8,25 µg dziennie Miedź minimum 135 µg dziennie. – Must meet minimum requirements for use of the claim "source of [name of vitamin/s] and/or [name of mineral/s]" as per Annex to Regulation 1924/2006. 			
94	Food or Food constituent	Health Relationship	Proposed wording
	Folic Acid (Vitamin B9)	Vascular function / Cardiovascular health	Contributes to healthy arteries and vessels; Helps promote heart health.
Conditions of use			
<ul style="list-style-type: none"> – Must meet minimum requirements for use of the claim source of Vitamin B9 (Folate/Folic acid) as per Annex to Regulation 1924/2006 400 microgram/ day Only for products with at least 100 % RDA 			
175	Food or Food constituent	Health Relationship	Proposed wording
	Folic acid (syn.: Vitamin B9)	Cardiovascular health	<ul style="list-style-type: none"> • Helps keep arteries/blood vessels healthy; • Contributes

			to healthy arteries/ blood vessels; • Supports heart health by contributing to the normal functioning of the arteries/blood vessels; • Helps maintain a normal blood pressure by supporting the elasticity of blood vessels/arteries;
Conditions of use <ul style="list-style-type: none"> - 400 microgram/ day - Food supplement with 75 µg of folic acid in the daily dose - ≥ 400 µg/d 			
192	Food or Food constituent Name of Food product: Folic Acid/ folate	Health Relationship Health benefits of food: Folate helps keep arteries/ blood vessels healthy Target group: All adults aged 18 years and over	Proposed wording Exact wording of claim as it appears on product: Folate (Folic Acid) helps keep arteries healthy Examples of any alternative wording that may be used in relation to claim: Folate (Folic Acid) helps keep blood vessels healthy Folate promotes a healthy heart
	Conditions of use <ul style="list-style-type: none"> - Presence of a nutrient or other substance Number of nutrients/other substances that are essential to claimed effect: 1 Names of nutrient/other substances and Quantity in Average daily serving: 400 microgram(s) folic acid/folate Daily amount to be consumed to produce claimed effect: 400 microgram(s) 		
193	Food or Food constituent Name of Food product: Folate/ Folic Acid	Health Relationship Health benefits of food: Folic Acid is essential for cell division Target group: All adults aged 18 years and over	Proposed wording Exact wording of claim as it appears on product: Folic acid is essential for the healthy growth of cells Examples of any alternative wording that may be used in relation to claim: Folic acid is essential for cell division
	Conditions of use <ul style="list-style-type: none"> - Presence of a nutrient or other substance Number of nutrients/other substances that are essential to claimed effect: 1 Names of nutrient/other substances and Quantity in Average daily serving: 30 micrograms folic acid Daily amount to be consumed to produce claimed effect: 30 microgram(s) - Presence of a nutrient or other substance Number of nutrients/other substances that are essential to claimed effect: 1 Names of nutrient/other substances and Quantity in Average daily serving: 301 micrograms vitamin B9 (folate) Weight of average daily food serving: 301microgram(s) Daily amount to be consumed to produce claimed effect: 401 		

	<p>microgram(s) No Length of time after consumption for claimed effect to become apparent: 4 weeks</p> <ul style="list-style-type: none"> – Presence of a nutrient or other substance Number of nutrients/other substances that are essential to claimed effect: 1 Names of nutrient/other substances and Quantity in Average daily serving: 36 micrograms vitamin B9 Weight of average daily food serving: 90 gram(s) Daily amount to be consumed to produce claimed effect: 500 gram(s) Number of food portions this equates to in everyday food portions: 		
2882	Food or Food constituent	Health Relationship	Proposed wording
	Folate/Folic acid	Effect on a normal pregnancy target group: women planning to become pregnant and pregnant	Folate/Folic acid has the favourable effect on a normal pregnancy
	<p>Conditions of use</p> <ul style="list-style-type: none"> – minimum 400 µg per day folate – Only for combinations with at least 14 mg Iron and 400 µg Folic Acid. Agency guidance for supplements is that products containing >20 mg of Iron should carry the label advisory statement ""[This amount of Iron] may cause mild stomach upset in sensitive individuals"" 		

GLOSSARY / ABBREVIATIONS

DNA	Deoxyribonucleic acid
FMD	Flow-mediated dilatation
NK	Natural killer cells
PHA	Phytohemagglutinin
UL	Tolerable Upper Intake Levels