SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to betaine and contribution to normal homocysteine metabolism (ID 4325) 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

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 betaine and contribution to normal homocysteine metabolism. 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 betaine. The Panel considers that betaine is sufficiently characterised.

The claimed effect is "heart health and vascular system". The target population is assumed to be the general population. In the context of the proposed wordings and the references provided, the Panel assumes that the claimed effect relates to the maintenance of normal blood concentrations of homocysteine by contributing to normal homocysteine metabolism. The Panel considers that contribution to normal homocysteine metabolism is a beneficial physiological effect.

In weighing the evidence, the Panel took into account that betaine can act as a methyl donor in the remethylation of homocysteine in the liver by the enzyme betaine-homocysteine methyltransferase, and that human intervention studies consistently show a significant decrease in plasma concentrations of homocysteine following betaine administration.

The Panel concludes that a cause and effect relationship has been established between the consumption of betaine and contribution to normal homocysteine metabolism.

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[1] On request from the European Commission, Question No EFSA-Q-2010-00278, adopted on 28 January 2011.

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The Panel considers that in order to obtain the claimed effect, 1.5 g of betaine should be consumed daily. The target population is the general population.

The Panel notes that daily doses of betaine ≥4 g may significantly increase total and LDL-cholesterol concentrations in the blood.

KEY WORDS

Betaine, homocysteine metabolism, 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[4] 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[5]. 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 4325)

The food constituent that is the subject of the health claim is betaine.

Betaine, i.e. N,N,N-trimethylglycine, is formed by oxidation of choline in mammals including humans, and can also be found in food. Dietary intakes of betaine range approximately from 0.5 to 2 g per day. Betaine is measurable in foods by established methods.

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

2. Relevance of the claimed effect to human health (ID 4325)

The claimed effect is "heart health and vascular system". The Panel assumes that the target population is the general population.

In the context of the proposed wordings and the references provided, the Panel assumes that the claimed effect relates to the maintenance of normal blood concentrations of homocysteine by contributing to normal homocysteine metabolism.

The Panel considers that contribution to normal homocysteine metabolism is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect (ID 4325)

Most of the references provided in the consolidated list were narrative reviews or textbooks that did not provide original scientific data that could be used to substantiate the claimed effect. One meta-analysis was not related to betaine. The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claimed effect.

It is well established that betaine can act as a methyl donor in the remethylation of homocysteine in the liver by the enzyme betaine-homocysteine methyltransferase.

[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] Briefing document for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims: http://www.efsa.europa.eu/en/ndameetings/docs/nda100601-ax01.pdf

In a randomised, double-blind, placebo-controlled intervention study, 42 obese subjects (28 women) treated with a hypocaloric diet were randomly assigned to a betaine-supplemented group (6 g/day) or a control group given placebo for 12 weeks after a 4-week run-in period aiming at energy balance (Schwab et al., 2002). Plasma homocysteine concentrations significantly decreased in the betaine group compared to placebo ($p=0.030$ for the interaction of time and treatment). Total and LDL-cholesterol concentrations significantly increased in the betaine group compared to placebo ($p=0.009$ and $p=0.011$ for the interaction of time and treatment, respectively). No significant differences were observed between groups with respect to changes in body weight or body fat.

Olthof et al. (2003) investigated the effect of betaine supplementation in the range of dietary intakes on fasting and post-methionine-loading plasma homocysteine concentrations in a double-blind, placebo-controlled, randomised intervention. Four groups of 19 healthy subjects with the highest plasma total homocysteine concentrations (range 8.4 to 22.2 μmol/L) among the 132 subjects screened (but within the normal range) consumed either 0.75 g of betaine (plus 2.25 g of placebo), 1.5 g of betaine (plus 1.5 g of placebo), 3 g of betaine or 3 g of placebo twice daily (at breakfast and evening meal) dissolved in a glass of water. Daily doses of anhydrous betaine were 0, 1.5, 3 and 6 g in the four intervention groups, respectively. A methionine-loading test was performed during the run-in period (day 3), on day 1 of betaine supplementation, and after 2 and 6 weeks of betaine supplementation. Blood samples were collected at these time points after an overnight fast and six hours after the methionine load. Fasting plasma concentrations of homocysteine after 6 weeks of daily betaine intakes of 1.5, 3 and 6 g were 12 % ($p<0.01$), 15 % ($p<0.002$) and 20 % ($p<0.0001$) lower than in the placebo group, respectively. The increase in plasma homocysteine concentrations after the methionine-loading on the first day of betaine supplementation with 1.5, 3 and 6 g of betaine per day was 16 % ($p<0.06$), 23 % ($p<0.008$) and 35 % ($p<0.0002$) lower than in the placebo group, respectively, and after 6 weeks of supplementation it was 23 % ($p<0.02$), 30 % ($p<0.003$) and 40 % ($p<0.0002$) lower than in the placebo group, respectively.

A randomised, double-blind, cross-over intervention in humans was designed to assess the pharmacokinetics of orally administered betaine and its acute effect on plasma homocysteine concentrations (Schwab et al., 2006). A total of 10 normal weight volunteers (three females) received betaine at doses of 1, 3 and 6 g on single occasions seven days apart mixed with 150 mL of orange juice after a 12 h overnight fast. A significant, dose-dependant, inverse relationship was observed between the intake of betaine and blood concentrations of homocysteine. The Panel notes that no conclusions can be drawn from this study on the sustained effects of betaine consumption on blood homocysteine concentrations, but that it supports the findings observed in the longer term studies described above.

The Panel notes that whereas doses of 6 g per day of betaine appear to increase total and LDL-cholesterol concentrations in the blood (Olthof et al., 2005; Schwab et al., 2002), this effect does not appear to be significant at lower daily doses (≤4 g per day) (Olthof et al., 2005; Schwab et al., 2010).

In weighing the evidence, the Panel took into account that betaine can act as a methyl donor in the remethylation of homocysteine in the liver by the enzyme betaine-homocysteine methyltransferase, and that human intervention studies consistently show a significant decrease in plasma concentrations of homocysteine following betaine administration.

The Panel concludes that a cause and effect relationship has been established between the consumption of betaine and contribution to normal homocysteine metabolism.

4. Panel's comments on the proposed wording (ID 4325)

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

5. Conditions and possible restrictions of use (ID 4325)

The Panel considers that, in order to obtain the claimed effect, 1.5 g of betaine should be consumed daily. The target population is the general population.

The Panel notes that daily doses of betaine ≥4 g may significantly increase total and LDL-cholesterol concentrations in the blood.

CONCLUSIONS

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

- The food constituent, betaine, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect is "heart health and vascular system". The target population is assumed to be the general population. In the context of the proposed wordings and the references provided, it is assumed that the claimed effect relates to the maintenance of normal blood concentrations of homocysteine by contributing to normal homocysteine metabolism. Contribution to normal homocysteine metabolism is a beneficial physiological effect.
- A cause and effect relationship has been established between the consumption of betaine and contribution to normal homocysteine metabolism.
- The following wording reflects the scientific evidence: "Betaine contributes to normal homocysteine metabolism".
- In order to obtain the claimed effect, 1.5 g of betaine should be consumed daily. The target population is the general population. The Panel notes that daily doses of betaine ≥4 g may significantly increase total and LDL-cholesterol concentrations in the blood.

DOCUMENTATION PROVIDED TO EFSA

Health claims pursuant to Article 13 of Regulation (EC) No 1924/2006 (No: EFSA-Q-2010-00278). 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.

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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[6] (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[7]

Foods are commonly involved in many different functions[8] 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 betaine, including conditions of use from similar claims, as proposed in the Consolidated List.

ID	Food or Food constituent	Health Relationship	Proposed wording
4325	Betaine	Heart health and vascular system	Contributes to the maintenance of a healthy heart by its ablity to promote healthy levels of homocysteine/contributes to the normal functioning of the cardiovascular system
	Conditions of use - 2-30 g per day		