European Food Safety Authority

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to choline and contribution to normal lipid metabolism (ID 3186), maintenance of normal liver function (ID 1501), contribution to normal homocysteine metabolism (ID 3090), maintenance of normal neurological function (ID 1502), contribution to normal cognitive function (ID 1502), and brain and neurological development (ID 1503) 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 related to choline and contribution to normal lipid metabolism, maintenance of normal liver function, contribution to normal homocysteine metabolism, maintenance of normal neurological function, contribution to normal cognitive function, and brain and neurological development. 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 choline. The Panel considers that choline is sufficiently characterised.

[1] On request from the European Commission, Question No EFSA-Q-2008-2238, EFSA-Q-2008-2239, EFSA-Q-2008-2240, EFSA-Q-2008-3822, EFSA-Q-2008-3918, adopted on 28 January 2011.

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[3] 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. The members of the Claims Sub-Working Group on Mental/Nervous System: Jacques Rigo, Astrid Schloerscheidt, Barbara Stewart-Knox, Sean (J.J.) Strain, and Peter Willatts.

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Contribution to normal lipid metabolism

The claimed effect is "choline is needed for lipids metabolism". The target population is assumed to be the general population. The Panel considers that contribution to normal lipid metabolism is a beneficial physiological effect.

It is well established that choline functions as a precursor of phospholipids, and plays a role in the structural integrity of cell membranes. Phosphatidylcholine is the predominant phospholipid in cell membranes. It is also well established that choline plays a role in lipid and cholesterol transport and metabolism.

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

Maintenance of normal liver function

The claimed effect is "maintaining healthy liver functioning". The target population is assumed to be the general population. The Panel notes that the claimed effect refers to the maintenance of normal liver function. The Panel considers that maintenance of normal liver function is a beneficial physiological effect.

It is well established that choline deficiency is associated with liver damage (elevated serum alanine aminotransferase activity) and the development of fatty liver (hepatosteatosis) in humans fed choline-free total parenteral nutrition solutions, as well as in men and post-menopausal women (but not in pre-menopausal women) fed choline-deficient diets or a choline-deficient diet with adequate amounts of methionine, folate and occasionally vitamin B12; these effects can be reversed by the administration of dietary choline.

The Panel concludes that a cause and effect relationship has been established between the consumption of choline and maintenance of normal liver function.

Contribution to normal homocysteine metabolism

The claimed effect is "reduction in homocysteine levels". 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 refers 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 choline can be a precursor for the formation of betaine, that betaine can act as a methyl donor in the remethylation of homocysteine in the liver by the enzyme betaine-homocysteine methyltransferase, that choline depleted diets tend to increase plasma concentrations of homocysteine, that a human intervention study showed a significant decrease in plasma concentrations of homocysteine following choline administration, and that two observational studies supported the inverse association between dietary choline and blood concentrations of homocysteine.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has been established between the consumption of choline and contribution to normal homocysteine metabolism.

Maintenance of normal neurological function

The claimed effect is "cognitive, memory functioning; neurological functioning". The target population is assumed to be the general population. The Panel considers that maintenance of normal neurological function is a beneficial physiological effect.

No references were provided from which conclusions could be drawn for the scientific substantiation of the claimed effect.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of choline and the maintenance of neurological function.

Contribution to normal cognitive function

The claimed effect is "cognitive, memory functioning; neurological functioning". The target population is assumed to be the general population. The Panel considers that contribution to normal cognitive function is a beneficial physiological effect.

No references were provided from which conclusions could be drawn for the scientific substantiation of the claimed effect.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of choline and contribution to normal cognitive function.

Brain and neurological development

The claimed effect is "development". In the context of the proposed wordings and the clarifications provided by Member States, the Panel assumes that the claimed effect is related to brain and neurological development, which is interpreted by the Panel as children's development.

The Panel notes that claims related to children's development and health are outside the scope of Article 13 of Regulation (EC) No 1924/2006.

Conditions and possible restrictions of use

The Panel notes that no dietary reference values for choline have been established in the EU. There are no reliable intake data and there are no indications of inadequate choline intakes available in the EU. The Panel also notes that dietary references values (adequate intakes) have been established outside the EU for different population subgroups. A nutrient content claim has been authorised in the United States based on the adequate intake for adult males (550 mg of choline per day).

KEY WORDS

Choline, liver, neurological function, cognition, homocysteine, lipid 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

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

Choline (2-hydroxyethyl-N,N,N-trimethylammonium chloride) is a quaternary ammonium cation generally present in foods either with a chloride counterion (chloride salt) or bound to an acetyl group (acetylcholine), to a cytidine diphosphate group (citicoline) or, mainly, to a phosphatidyl group (lecithin) as in milk, liver, eggs and peanuts. Choline is also synthesised in the body. In supplements, choline is mostly present as choline chloride or as phosphatidylcholine, isolated from soy or egg yolk.

Choline is measurable in foods by established methods. This evaluation applies to choline present in foods, and to those forms consumed as food supplements.

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

2. Relevance of the claimed effect to human health

2.1. Contribution to normal lipid metabolism (ID 3186)

The claimed effect is "choline is needed for lipids metabolism". The Panel assumes that the target population is the general population.

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

2.2. Maintenance of normal liver function (ID 1501)

The claimed effect is "maintaining healthy liver functioning". The Panel assumes that the target population is the general population.

The Panel notes that the claimed effect refers to the maintenance of normal liver function.

[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

The Panel considers that maintenance of normal liver function is a beneficial physiological effect.

2.3. Contribution to normal homocysteine metabolism (ID 3090)

The claimed effect is "reduction in homocysteine levels". 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 refers 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.

2.4. Maintenance of normal neurological function (ID 1502)

The claimed effect is "cognitive, memory functioning; neurological functioning". The Panel assumes that the target population is the general population.

The Panel considers that maintenance of normal neurological function is a beneficial physiological effect.

2.5. Contribution to normal cognitive function (ID 1502)

The claimed effect is "cognitive, memory functioning; neurological functioning". The Panel assumes that the target population is the general population.

Cognitive function includes memory, attention (concentration), learning, intelligence and problem solving. These are well defined constructs and can be measured by validated psychometric cognitive tests.

The Panel considers that contribution to normal cognitive function is a beneficial physiological effect.

2.6. Brain and neurological development (ID 1503)

The claimed effect is "development".

In the context of the proposed wordings and the clarifications provided by Member States, the Panel assumes that the claimed effect is related to brain and neurological development, which is interpreted by the Panel as children's development.

The Panel notes that claims related to children's development and health are outside the scope of Article 13 of Regulation (EC) No 1924/2006.

3. Scientific substantiation of the claimed effect

Choline is a dietary component which is also formed endogenously in the body by methylation of phosphatidylethanolamine using S-adenosylmethionine as the methyl donor. Choline functions as a precursor of acetylcholine, phospholipids and betaine, and plays a role in the structural integrity of cell membranes, in methyl metabolism, in cholinergic neurotransmission, and in lipid and cholesterol transport and metabolism. Demand for dietary choline is dependent on the metabolic methyl-group exchange relationships between choline and methionine, folate and vitamin B12. With this type of

nutrient interdependence, the designation of the essential nature of a nutrient will depend on whether *de novo* synthesis rates are adequate to meet the demand when other nutrients are available in amounts sufficient to sustain normal growth and function. In men with adequate folate and vitamin B12 status fed a choline-deficient diet, endogenous synthesis of choline may not be sufficient to cover needs, whereas little information is available with respect to other population subgroups (e.g. women, children and elderly subjects). The primary criterion to estimate adequate intakes of choline in the United States is the prevention of liver damage, as assessed by measuring serum alanine aminotransferase activity in the blood (IoM, 1998).

No dietary reference values for choline have been established in the EU. There are no reliable intake data, and no indications of inadequate choline intakes, available in the EU.

3.1. Contribution to normal lipid metabolism (ID 3186)

The six references provided in the consolidated list were one textbook and five narrative reviews on the metabolic effects of choline deficiency, on the absolute choline dependence of cultured cells, and on the dietary requirements of choline.

It is well established that choline functions as a precursor of phospholipids, and plays a role in the structural integrity of cell membranes (IoM, 1998). Phosphatidylcholine is the predominant phospholipid (>50 %) in the cell membranes. It is also well established that choline plays a role in lipid and cholesterol transport and metabolism. Dietary choline deficiency is associated with liver damage (elevated serum alanine aminotransferase activity) and the development of fatty liver (hepatosteatosis) in humans fed choline-deficient total parenteral nutrition solutions, as well as in men and post-menopausal women (but not in pre-menopausal women) fed choline-deficient diets (da Costa et al., 2005; Fischer et al., 2007; IoM, 1998; Kohlmeier et al., 2005; Zeisel, 2006). These effects can be reversed by the administration of dietary choline (Buchman et al., 1992; 1995; da Costa et al., 2005). Most of the choline-deficient diets used in these studies were adequate for methionine and folate, and for vitamin B12 in some cases. The effect of choline-deficient diets on lipid transport and metabolism, assessed by the amount of fat accretion in the liver, appears to depend on genetic variations of, for example, the 5,10-methylenetetrahydrofolate dehydrogenase, the phosphatidylethanolamine N-methyltransferase, and/or the choline dehydrogenase genes, as well as on oestrogen status (i.e. *de novo* choline synthesis of phosphatidylcholine is up-regulated by oestrogen) (da Costa et al., 2006; Kohlmeier et al., 2005).

No studies on specific effects of supplemental choline on lipid metabolism were included in the references provided.

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

3.2. Maintenance of normal liver function (ID 1501)

It is well established that choline deficiency is associated with liver damage (elevated serum alanine aminotransferase activity) and the development of fatty liver (hepatosteatosis) in humans fed choline-free total parenteral nutrition solutions, as well as in men and post-menopausal women (but not in pre-menopausal women) fed choline-deficient diets (Kohlmeier et al., 2005) or a choline-deficient diet with adequate amounts of methionine, folate and occasionally vitamin B12 (da Costa et al., 2005; Fischer et al., 2007; IoM, 1998; Zeisel, 2006). These effects can be reversed by the administration of dietary choline (Buchman et al., 1992; 1995; da Costa et al., 2005). The effect of choline-deficient diets on fat accretion in the liver appears to depend on genetic variations of, for example, the 5,10-methylenetetrahydrofolate dehydrogenase, the phosphatidylethanolamine N-methyltransferase,

and/or the choline dehydrogenase genes, as well as on oestrogen status (i.e. *de novo* choline synthesis of phosphatidylcholine is up-regulated by oestrogen) (da Costa et al., 2006; Kohlmeier et al., 2005).

Prevention of elevated serum alanine aminotransferase activities and/or fat accretion in the liver, assessed by appropriate imaging techniques (computed tomography, magnetic resonance imaging), have been proposed as the primary criterion to estimate adequate intakes for choline (IoM, 1998).

The Panel concludes that a cause and effect relationship has been established between the consumption of choline and maintenance of normal liver function.

3.3. Contribution to normal homocysteine metabolism (ID 3090)

It is well established that choline can function as a precursor for the formation of betaine, and that betaine can act as a methyl donor in the remethylation of homocysteine in the liver by the enzyme betaine-homocysteine methyltransferase (IoM, 1998).

A claim on betaine and contribution to normal homocysteine metabolism has already been assessed with a favourable outcome (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2011).

Most of the references provided in the consolidated list were narrative reviews from textbooks and scientific journals referring to the biochemical functions and metabolism of choline, or human and animal studies addressing the effects of choline depletion or supplementation relative to the status of other methyl donors (e.g. folate, vitamin B12 and betaine) on health outcomes other than homocysteine concentrations or metabolism (e.g. liver steatosis, muscle function and cancer).

Two human intervention studies on the effects of choline supplementation on blood concentrations of homocysteine were provided (da Costa et al., 2005; Olthof et al., 2005).

In a placebo-controlled cross-over study, Olthof et al. (2005) investigated the effect of supplemental choline (2.6 g/day as phosphatidylcholine) for two weeks on plasma homocysteine concentrations after an overnight fast, as well as after an oral methionine load in 26 men with mildly elevated homocysteine concentrations (14.7±3.4 μmol/L). Phosphatidylcholine supplementation for two weeks significantly decreased mean fasting plasma homocysteine concentrations by 18 % (-3.0 μmol/L; 95 % CI: -3.9, -2.1 μmol/L). A single dose of phosphatidylcholine containing 1.5 g choline significantly reduced the postmethionine-loading increase in homocysteine by 15 % (-4.8 μmol/L; 95 % CI: -6.8, -2.8 μmol/L) on the first day of supplementation, and phosphatidylcholine supplementation for two weeks significantly reduced the postmethionine-loading increase in homocysteine by 29 % (-9.2 μmol/L; 95 % CI: -11.3, -7.2 μmol/L). All changes were relative to placebo. The Panel notes that the doses of choline used in this study are several times above the proposed conditions of use.

In one small (pilot) depletion study, eight men were fed a "choline-sufficient" diet providing 550 mg choline per day for 10 days followed by a choline-deficient diet (<50 mg/day) for 42 days, or until the subjects were clinically judged to be choline deficient (i.e. evaluated as the development of hepatic steatosis assessed by magnetic resonance imaging), whichever came first (da Costa et al., 2005). Plasma concentrations of homocysteine were assessed in fasting and four hours after an oral methionine load (100 mg/kg body weight) on day 10 of the diet containing 550 mg choline per day, and after 42 days of the choline-deficient diet (or when deficiency was diagnosed). The diets met or exceeded the estimated average requirement for methionine plus cysteine and the daily reference intake for vitamin B6, vitamin B12, and folate (400 dietary folate equivalents per day). Four subjects developed hepatic steatosis during the choline depletion phase, and four subjects did not by day 42. In all eight human subjects, plasma choline and betaine concentrations fell 30 % and 47 %, respectively, at the end of the depletion phase ($P<0.005$). Subjects who were judged to be clinically depleted had

decreases in plasma choline and betaine concentrations which were not different from those observed in subjects not deemed to be clinically depleted. At the end of the depletion phase, plasma concentrations of homocysteine at fast and four hours after an oral methionine load significantly increased only in subjects clinically choline-depleted, as compared to the "choline sufficient" phase.

Two human observational studies addressed the association between dietary choline and blood concentrations of homocysteine (Cho et al., 2006; Dalmeijer et al., 2008).

In a cohort of the Framingham Offspring Study (Cho et al., 2006) an inverse association was observed between choline, betaine, and choline plus betaine intakes measured by validated food frequency questionnaires (FFQ) and plasma total homocysteine concentrations in 1,960 subjects (1,040 women) independent of age, sex, smoking, alcohol intake, caffeine intake, hypertensive medication use, serum creatinine concentrations and intakes of folate, vitamin B6 and vitamin B12. The energy-adjusted mean (±SD) intakes of choline and betaine were 313±61 mg/day (314 mg per day for women and 312 mg per day for men) and 208±90 mg per day (216 mg per day for women and 200 mg per day for men), respectively.

In a prospective cohort study (Dalmeijer et al., 2008) which investigated the association between dietary intakes of folate, betaine and choline and the risk of cardiovascular disease (CVD) in a cohort of 16,165 women, aged 49-70 years, without prior CVD, intakes of folate, betaine and choline were assessed using a validated FFQ at baseline. Median follow-up period was 97 months. Homocysteine concentrations were assessed in the blood of a randomly selected sample of women (n=910). High folate and choline intakes were statistically significantly associated with lower homocysteine concentrations, whereas no statistically significant association was observed for betaine. Mean intakes of betaine, choline and folate were 214±74, 300±51 and 195±40 mg/day, respectively.

In weighing the evidence, the Panel took into account that choline can be a precursor for the formation of betaine, that betaine can act as a methyl donor in the remethylation of homocysteine in the liver by the enzyme betaine-homocysteine methyltransferase, that choline depleted diets tend to increase plasma concentrations of homocysteine, that a human intervention study showed a significant decrease in plasma concentrations of homocysteine following choline administration, and that two observational studies supported the inverse association between dietary choline and blood concentrations of homocysteine.

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

3.4. Maintenance of normal neurological function (ID 1502)

The references provided included narrative reviews and textbooks which did not provide any original data for the scientific substantiation of the claimed effect, and conference abstracts which did not provide sufficient detail for a scientific evaluation. A number of the remaining references did not address relevant endpoints (e.g. choline metabolism, memory and attention) or did not evaluate choline (e.g. citicoline and phosphatidylserine). The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claimed effect.

The Panel notes that no human studies have been provided from which conclusions can be drawn for the scientific substantiation of the claimed effect.

Ten animal studies provided primary data to substantiate the claimed effect. These studies evaluated the effects of choline supplementation and deprivation on choline plasma concentrations, acetylcholine synthesis and release, and nicotinic receptor regulation. The Panel considers that while effects shown in animal studies may be used as supportive evidence, human studies are required for

the substantiation of a claim, and that evidence provided in animal studies alone is not sufficient to predict the occurrence of an effect of choline consumption on the maintenance of normal neurological function in humans.

The Panel concludes that a cause and effect relationship has not been established between the consumption of choline and the maintenance of normal neurological function.

3.5. Contribution to normal cognitive function (ID 1502)

The references provided included narrative reviews which did not provide any original data, and conference abstracts which did not provide sufficient detail for a scientific evaluation. A number of the remaining references did not report on relevant endpoints (e.g. choline metabolism and functions, choline uptake into the brain, and deficiency symptoms unrelated to cognition) or did not evaluate choline (e.g. citicoline and phosphatidylserine). Some of the human intervention studies provided used lecithin preparations. The Panel notes that these interventions did not control for dietary compounds other than choline (e.g. phospholipids and fatty acids) which could contribute to the claimed effect. The Panel notes that no conclusions can be drawn from these references for the scientific substantiation of the claimed effect.

The study by Sitaram et al. (1978) evaluated the effect of a single dose of choline chloride (10 g) against placebo (not defined but matched for colour and taste) given in random order on two separate days on a serial learning test and a selective reminding test in 10 healthy male and female volunteers. The Panel notes that the dose of choline which was used in the study was much greater than the minimum dose of 20 mg, the indicated "therapeutic" dose of 300 mg, or the "excess" consumption of 3.5 g per day given in the conditions of use. The Panel considers that no conclusions can be drawn from this reference for the scientific substantiation of the claimed effect.

The study by Buchman et al. (2001) was a pilot study in patients (n=11) receiving long-term parenteral nutrition (more than 80 % of their nutritional needs). The effect of choline supplementation on verbal and visual memory was evaluated after 24 weeks of parenteral nutrition regimen supplemented with 2 g of choline chloride (n=5) *vs.* no supplementation (n=6). The Panel notes that 24 endpoints were tested in this pilot study and that no correction was made for multiple testing. The Panel considers that no conclusions can be drawn from this small pilot study for the scientific substantiation of the claimed effect.

Nine of the animal studies provided evaluated the effect of choline supplementation on various memory tests in rats. The Panel considers that evidence provided in animal studies is not sufficient to predict the occurrence of an effect of choline consumption on contribution to normal cognitive function in humans.

The Panel concludes that a cause and effect relationship has not been established between the consumption of choline and contribution to normal cognitive function.

4. Panel's comments on the proposed wording

4.1. Contribution to normal lipid metabolism (ID 3186)

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

4.2. Maintenance of normal liver function (ID 1501)

The Panel considers that the following wording reflects the scientific evidence: "Choline contributes to the maintenance of normal liver function".

4.3. Contribution to normal homocysteine metabolism (ID 3090)

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

5. Conditions and possible restrictions of use

The Panel notes that no dietary reference values for choline have been established in the EU. There are no reliable intake data and there are no indications of inadequate choline intakes available in the EU. The Panel also notes that dietary references values (adequate intakes) have been established outside the EU for different population subgroups (IoM, 1998). A nutrient content claim has been authorised in the United States based on the adequate intake for adult males (550 mg of choline per day).

CONCLUSIONS

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

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

Contribution to normal lipid metabolism (ID 3186)

- The claimed effect is "choline is needed for lipids metabolism". The target population is assumed to be the general population. Contribution to normal lipid metabolism is a beneficial physiological effect.
- A cause and effect relationship has been established between the consumption of choline and contribution to normal lipid metabolism.
- The following wording reflects the scientific evidence: "Choline contributes to normal lipid metabolism".

Maintenance of normal liver function (ID 1501)

- The claimed effect is "maintaining healthy liver functioning". The target population is assumed to be the general population. Maintenance of normal liver function is a beneficial physiological effect.
- A cause and effect relationship has been established between the consumption of choline and maintenance of normal liver function.
- The following wording reflects the scientific evidence: "Choline contributes to the maintenance of normal liver function".

Contribution to normal homocysteine metabolism (ID 3090)

- The claimed effect is "reduction in homocysteine levels". The target population is assumed to be the general population. Contribution to normal homocysteine metabolism is a beneficial physiological effect.

- A cause and effect relationship has been established between the consumption of choline and maintenance of normal homocysteine metabolism.
- The following wording reflects the scientific evidence: "Choline contributes to normal homocysteine metabolism".

Maintenance of normal neurological function (ID 1502)

- The claimed effect is "cognitive, memory functioning; neurological functioning". The target population is assumed to be the general population. Maintenance of normal neurological function is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of choline and maintenance of normal neurological function.

Contribution to normal cognitive function (ID 1502)

- The claimed effect is "cognitive, memory functioning; neurological functioning". The target population is assumed to be the general population. Contribution to normal cognitive function is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of choline and contribution to normal cognitive function.

Brain and neurological development (ID 1503)

- The claimed effect is "development". Brain and neurological development is interpreted as children's development.
- Claims related to children's development and health are outside the scope of Article 13 of Regulation (EC) No 1924/2006.

Conditions and possible restrictions of use

- No dietary reference values for choline have been established in the EU. There are no reliable intake data and there are no indications of inadequate choline intakes available in the EU. Dietary references values (adequate intakes) have been established outside the EU for different population subgroups. A nutrient content claim has been authorised in the United States based on the adequate intake for adult males (550 mg of choline per day).

DOCUMENTATION PROVIDED TO EFSA

Health claims pursuant to Article 13 of Regulation (EC) No 1924/2006 (No: EFSA-Q-2008-2238, EFSA-Q-2008-2239, EFSA-Q-2008-2240, EFSA-Q-2008-3822, EFSA-Q-2008-3918). 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 (EC) No 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 choline, including conditions of use from similar claims, as proposed in the Consolidated List.

ID	Food or Food constituent	Health Relationship	Proposed wording
1501	Choline	Maintaining healthy liver functioning.	Choline, as a component of phosphatidylcholine, aids in fat transport away from the liver, thereby maintaining healthy liver functioning." "Choline helps transport fat away from the liver, thereby maintaining healthy liver functioning." "Adequate choline intakes help maintain healthy liver functioning." "An adequate choline intake helps maintain a healthy liver."
	Conditions of use - The product must contain at least 15% of the AI (AI for adult males and females varies is 550 and 425 mg/day, respectively). To also present a statement that excess choline consumption (=3.5 g/day), may be associated with hypotension and/or a fishy body odour. - Tagesdosis > 50 mg.		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1502	Choline	Cognitive, memory functioning Neurological functioning <u>Clarification provided</u> Neurological/cognitive/memory functioning/better brain performance by taking part in nerve impulse transmission, constituent of neurotransmitters. Improves memory. Improves learning skills and concentration. Prevention of degenerative processess in the central nervous system.	Choline supports normal neurological functioning. Choline supports nerve impulse transmission. Choline supports cognitive functioning. Choline helps maintain memory and brain function.
	Conditions of use – Sportler–Tagesdosis Cholin: 100 mg – 45 mg;(15% of the lower therapeutic dose 300 mg). (see PDR for Nutritional Suppl. page		

	90.); – The product must contain at least 15% of the AI (AI for adult males and females varies is 550 and 425 mg/day, respectively). To also present a statement that excess choline consumption (=3.5 g/day), may be associated with hypotension and/or a fishy body. – Minimum 20 mg dziennie		
	Comments from Member States HU Comments: EFSA has accepted similar relationships, under HR_ID 710, 1631, 1983 without comment.		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1503	Choline	Development <u>Clarification provided</u> Essential for brain and nervous system function. Stimulates development of central nervous system and improves memory. (Choline is an essential nutrient, closely linked to the B-vitamins complex. Despite the fact that humans can synthesize it in small amounts, choline must be consumed in the diet to maintain health. As such, it must be considered an essential nutrient and it is therefore considered essential" for all functions in which it participates)	Choline is essential for normal development, particular of brain and nervous system
	Conditions of use – 20 mg per day – Amount of consumption: 20 Milligramm (mg)/Tag – Only for products with at least 20 mg		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
3090	Choline	Reduction in homocysteine levels	Choline supports a healthy heart. Choline supports cardiovascular health.
	Conditions of use - The product must contain at least 15% of the AI (AI for adult males and females varies is 550 and 425 mg/day, respectively). To also present a statement that excess choline consumption (=3.5 g/day), may be associated with hypotension and/or a fishy body odour.		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
3186	Choline	Choline is needed for lipids metabolism.	Choline improves body metabolism.
	Conditions of use		

	- Twice a day 202,6 mg

GLOSSARY AND ABBREVIATIONS

AI	Adequate intake
CI	Confidence interval
CVD	Cardiovascular disease
EU	European Union
FFQ	Food frequency questionnaire
SD	Standard deviation