SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to L-arginine and "immune system functions" (ID 455, 1713), growth or maintenance of muscle mass (ID 456, 1712, 4681), normal red blood cell formation (ID 456, 664, 1443, 1712), maintenance of normal blood pressure (ID 664, 1443), improvement of endothelium-dependent vasodilation (ID 664, 1443, 4680), "physical performance and condition" (ID 1820), "système nerveux" (ID 608), maintenance of normal erectile function (ID 649, 4682), contribution to normal spermatogenesis (ID 650, 4682), "function of the intestinal tract" (ID 740), and maintenance of normal ammonia clearance (ID 4683) 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 L-arginine and "immune system functions", growth or maintenance of muscle mass, normal red blood cell formation, maintenance of normal blood pressure, improvement of endothelium-dependent vasodilation, "physical performance and condition", "système nerveux",

[1] On request from the European Commission, Question No EFSA-Q-2008-1242, EFSA-Q-2008-1243, EFSA-Q-2008-1395, EFSA-Q-2008-1436, EFSA-Q-2008-1437, EFSA-Q-2008-1451, EFSA-Q-2008-1527, EFSA-Q-2008-2180, EFSA-Q-2008-2448, EFSA-Q-2008-2449, EFSA-Q-2008-2553, EFSA-Q-2010-00633, EFSA-Q-2010-00634, EFSA-Q-2010-00635, EFSA-Q-2010-00636, 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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maintenance of normal erectile function, contribution to normal spermatogenesis, "function of the intestinal tract", and maintenance of normal ammonia clearance. 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 L-arginine. The Panel considers that L-arginine is sufficiently characterised.

"Immune system functions"

The claimed effect is "for immune system functions". The target population is assumed to be the general population.

Given the multiple roles of the immune system, the specific aspect of immune function that is the subject of the claim needs to be specified, but it has not been indicated in the information provided.

The Panel considers that the claimed effect is general and non-specific, and does not refer to any specific health claim as required by Regulation (EC) No 1924/2006.

Growth or maintenance of muscle mass

The claimed effects are "for muscle integrity and haematopoiesis (red blood cells building)", "structural aminoacid for muscular growth", and "increases muscle mass". The target population is assumed to be the general population. In the context of the proposed wordings, the Panel assumes that the claimed effects refer to the growth or maintenance of muscle mass by decreasing muscle breakdown, increasing muscle synthesis, or both. The Panel considers that growth or maintenance of muscle mass is a beneficial physiological effect.

A claim on protein and growth and maintenance of muscle has already been assessed with a favourable outcome.

Arginine is a component of dietary protein, and both endogenous and exogenous arginine contribute to protein synthesis. No evidence has been provided that arginine in addition to normal protein intake has an additional role in muscle mass.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of L-arginine and growth or maintenance of muscle mass, apart from the well established role of protein on the claimed effect.

Normal red blood cell formation

The claimed effects are "vascular system (blood pressure, circulation, vessels)", "vascular health; blood circulation", and "for muscle integrity and haematopoiesis (red blood cells building)". The target population is assumed to be the general population. In the context of the proposed wordings and the clarifications provided by Member States, the Panel assumes that the claimed effects refer to the normal formation of red blood cells. The Panel considers that normal red blood cell formation 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 L-arginine and normal red blood cell formation.

Maintenance of normal blood pressure

The claimed effects are "vascular system (blood pressure, circulation, vessels)" and "vascular health; blood circulation". The target population is assumed to be the general population. In the context of the proposed wordings and the clarifications provided by Member States, the Panel assumes that the claimed effects refer to the maintenance of normal blood pressure. The Panel considers that maintenance of normal blood pressure is a beneficial physiological effect.

In weighing the evidence, the Panel took into account that although a small scale short-term (one-week) only partially controlled intervention study observed an effect of arginine consumption on blood pressure, two small long-term studies did not observe a significant effect, and that the results from the studies assessing the acute effects of arginine consumption on blood pressure are inconsistent.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of L-arginine and maintenance of normal blood pressure.

Improvement of endothelium-dependent vasodilation

The claimed effects are "vascular system (blood pressure, circulation, vessels)", "vascular health; blood circulation", and "normal blood circulation as a nitric oxide precursor". The target population is assumed to be the general population. In the context of the proposed wordings and the clarifications provided by Member States, the Panel assumes that the claimed effects refer to the improvement of endothelium-dependent vasodilation. The Panel considers that an improvement of endothelium-dependent vasodilation may be a beneficial physiological effect.

In weighing the evidence, the Panel took into account that one study did not show an effect of L-arginine consumption on endothelium-dependent vasodilation, and that in a second study the observed changes in endothelium-dependent vasodilation could have been due to an acute effect of arginine rather than to a sustained 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 L-arginine and improvement of endothelium-dependent vasodilation.

"Physical performance and condition"

The claimed effect is "physical performance and condition". The target population is assumed to be the general population.

The claimed effect is not sufficiently defined, and no further details were given in the proposed wordings. No further clarifications were provided by Member States.

The Panel considers that the claimed effect is general and non-specific, and does not refer to any specific health claim as required by Regulation (EC) No 1924/2006.

"Système nerveux"

The claimed effect is "système nerveux". The target population is assumed to be the general population.

The claimed effect is not sufficiently defined, and no further details were given in the proposed wordings. No further clarifications were provided by Member States.

The Panel considers that the claimed effect is general and non-specific, and does not refer to any specific health claim as required by Regulation (EC) No 1924/2006.

Maintenance of normal erectile function

The claimed effects are "erection" and "supporting spermatogenesis and local pelvic microcirculation". The target population is assumed to be the general male population. The Panel considers that maintenance of normal erectile function is a beneficial physiological effect.

In weighing the evidence, the Panel took into account that the two human intervention studies which investigated the effect of L-arginine consumption on erectile function did not show a significant effect of arginine on erectile function.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of L-arginine and maintenance of normal erectile function.

Contribution to normal spermatogenesis

The claimed effects are "spermatogenesis" and "supporting spermatogenesis and local pelvic microcirculation". The target population is assumed to be the general male population. The Panel considers that contribution to normal spermatogenesis 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 L-arginine and contribution to normal spermatogenesis.

"Function of the intestinal tract"

The claimed effect is "function of the intestinal tract". The target population is assumed to be the general population.

The claimed effect is not sufficiently defined, and no further details were given in the proposed wordings or the clarifications provided by Member States.

The Panel considers that the claimed effect is general and non-specific, and does not refer to any specific health claim as required by Regulation (EC) No 1924/2006.

Maintenance of normal ammonia clearance

The claimed effect is "ureogenesis by increasing ammonia clearance in the body". The target population is assumed to be the general population. The Panel considers that maintenance of normal ammonia clearance is a beneficial physiological effect.

Arginine participates in the detoxification of ammonia via the urea cycle, which takes place in the liver. Arginine may be obtained from the diet or from endogenous synthesis, and dietary arginine contributes to the claimed effect.

The Panel concludes that a cause and effect relationship has been established between the consumption of L-arginine in a protein adequate diet and maintenance of normal ammonia clearance.

No evidence has been provided that the protein supply in the diet of the European population is not sufficient to fulfil this function of the amino acid.

The Panel considers that no conditions of use can be defined for L-arginine.

KEY WORDS

Arginine, immune system, muscle mass, red blood cell formation, blood pressure, endothelium-dependent vasodilation, physical performance and condition, système nerveux, erectile function , spermatogenesis, intestinal tract, ammonia clearance, 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 claims is L-arginine.

Arginine is an alpha-amino acid present in foods from animal and vegetable origin. The L-form is the most commonly found form in nature and in food supplements. L-arginine is also known as (S)-2-amino-5-guanidinopentanoic acid and (S)-2-amino-5-[(aminoiminomethyl)amino] pentanoic acid. The terms L-arginine and arginine are frequently used interchangeably. The content of L-arginine in foods can be measured by established methods.

Arginine is a conditionally indispensable amino acid provided by mixed dietary protein intakes from different sources. Arginine can also be consumed in the form of food supplements as L-arginine.

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

2. Relevance of the claimed effect to human health

2.1. "Immune system functions" (ID 455, 1713)

The claimed effect is "for immune system functions". The Panel assumes that the target population is the general population.

Given the multiple roles of the immune system, the specific aspect of immune function that is the subject of the claim needs to be specified, but it has not been indicated in the information provided.

The Panel considers that the claimed effect is general and non-specific, and does not refer to any specific health claim as required by Regulation (EC) No 1924/2006.

[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

2.2. Growth or maintenance of muscle mass (ID 456, 1712, 4681)

The claimed effects are "for muscle integrity and haematopoiesis (red blood cells building)", "structural aminoacid for muscular growth", and "increases muscle mass". The Panel assumes that the target population is the general population.

In the context of the proposed wordings, the Panel assumes that the claimed effects refer to the growth or maintenance of muscle mass by decreasing muscle breakdown, increasing muscle synthesis, or both. Failure to increase muscle mass during growth and development, and the loss of muscle mass at any age, will reduce muscle strength and power.

The Panel considers that growth or maintenance of muscle mass is a beneficial physiological effect.

2.3. Normal red blood cell formation (ID 456, 664, 1443, 1712)

The claimed effects are "vascular system (blood pressure, circulation, vessels)", "vascular health; blood circulation", and "for muscle integrity and haematopoiesis (red blood cells building)". The Panel assumes that the target population is the general population.

In the context of the proposed wordings and the clarifications provided by Member States, the Panel assumes that the claimed effects refer to normal formation of red blood cells.

Panel considers that normal red blood cell formation is a beneficial physiological effect.

2.4. Maintenance of normal blood pressure (ID 664, 1443)

The claimed effects are "vascular system (blood pressure, circulation, vessels)" and "vascular health; blood circulation". The Panel assumes that the target population is the general population.

In the context of the proposed wordings and the clarifications provided by Member States, the Panel assumes that the claimed effects refer to the maintenance of normal blood pressure.

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

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

2.5. Improvement of endothelium-dependent vasodilation (ID 664, 1443, 4680)

The claimed effects are "vascular system (blood pressure, circulation, vessels)", "vascular health; blood circulation", and "normal blood circulation as a nitric oxide precursor". The Panel assumes that the target population is the general population.

In the context of the proposed wordings and the clarifications provided by Member States, the Panel assumes that the claimed effects refer to the improvement of endothelium-dependent vasodilation.

The Panel considers that an improvement of endothelium-dependent vasodilation may be a beneficial physiological effect.

2.6. "Physical performance and condition" (ID 1820)

The claimed effect is "physical performance and condition". The Panel assumes that the target population is the general population.

The claimed effect is not sufficiently defined, and no further details were given in the proposed wordings. No further clarifications were provided by Member States.

The Panel considers that the claimed effect is general and non-specific, and does not refer to any specific health claim as required by Regulation (EC) No 1924/2006.

2.7. "Système nerveux" (ID 608)

The claimed effect is "système nerveux". The Panel assumes that the target population is the general population.

The claimed effect is not sufficiently defined, and no further details were given in the proposed wordings. No clarifications were provided by Member Sates.

The Panel considers that the claimed effect is general and non-specific, and does not refer to any specific health claim as required by Regulation (EC) No 1924/2006.

2.8. Maintenance of normal erectile function (ID 649, 4682)

The claimed effects are "erection" and "supporting spermatogenesis and local pelvic microcirculation". The Panel assumes that the target population is the general male population.

In the context of the proposed wordings and the references provided, the Panel assumes that the claimed effects refer to the maintenance of normal erectile function.

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

2.9. Contribution to normal spermatogenesis (ID 650, 4682)

The claimed effects are "spermatogenesis" and "supporting spermatogenesis and local pelvic microcirculation". The Panel assumes that the target population is the general male population.

In the context of the proposed wordings and the references provided, the Panel assumes that the claimed effects refer to normal spermatogenesis.

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

2.10. "Function of the intestinal tract" (ID 740)

The claimed effect is "function of the intestinal tract". The Panel assumes that the target population is the general population.

The claimed effect is not sufficiently defined and no further details were given in the proposed wordings or the clarifications provided by Member States.

The Panel considers that the claimed effect is general and non-specific, and does not refer to any specific health claim as required by Regulation (EC) No 1924/2006.

2.11. Maintenance of normal ammonia clearance (ID 4683)

The claimed effect is "ureogenesis by increasing ammonia clearance in the body". The Panel assumes that the target population is the general population.

In the context of the proposed wordings, the Panel assumes that the claimed effect refers to the maintenance of normal ammonia clearance in the body.

The Panel considers that maintenance of normal ammonia clearance is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

3.1. Growth or maintenance of muscle mass (ID 456, 1712, 4681)

A claim on protein and growth and maintenance of muscle has already been assessed with a favourable outcome (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2010).

Arginine is a component of dietary protein, and both endogenous and exogenous arginine contribute to protein synthesis.

The references provided for the scientific substantiation of the claim included a textbook, narrative reviews, a web page, a monograph and opinion papers with no reference to the role of arginine on growth or maintenance of muscle mass, intervention studies on foods/food constituents other than L-arginine, and studies on the effects of arginine consumption on health outcomes other than growth or maintenance of muscle mass (e.g. immunity, endothelial function and hormonal modification). The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claim.

No references were provided which addressed the effects of arginine on growth or maintenance of muscle. No evidence has been provided that arginine in addition to normal protein intake has an additional role in muscle mass.

The Panel concludes that a cause and effect relationship has not been established between the consumption of L-arginine and growth or maintenance of muscle mass, apart from the well established role of protein on the claimed effect.

3.2. Normal red blood cell formation (ID 456, 664, 1443, 1712)

The references provided for the scientific substantiation of the claim included narrative reviews and opinion papers with no reference to the role of arginine on red blood cell formation, references on food constituents other than arginine, intervention studies using intravenous arginine administration, which is not relevant to human nutrition, and studies on the effects of arginine consumption on health outcomes other than red blood cell formation. The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claim.

The Panel concludes that a cause and effect relationship has not been established between the consumption of L-arginine and normal red blood cell formation.

3.3. Maintenance of normal blood pressure (ID 664, 1443)

The references provided for the scientific substantiation of the claim included narrative reviews and opinion papers with no original data on the effects of arginine intake on blood pressure, references on food constituents other than arginine, intervention studies using intravenous arginine administration, which is not relevant to human nutrition, and studies on the effects of arginine administration on health outcomes other than blood pressure (e.g. endothelial function, clinical course of myocardial infarction, insulin sensitivity, wound healing, immune parameters and erectile function). The Panel

considers that no conclusions can be drawn from these references for the scientific substantiation of the claim.

Miller (2006) investigated the effects of L-arginine (1,050 mg, as sustained-release preparation) twice daily (total 2.1 g daily) for one week on blood pressure in 29 healthy subjects in an open-label, single-arm intervention. The Panel notes the short duration and uncontrolled nature of the study, and considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

Clarkson et al. (1996) performed a randomised, double-blind, cross-over study in 27 hypercholesterolaemic subjects aged 19-40 years. Subjects taking HMG CoA reductase inhibitors in a stable dose for >6 months who met the entry criteria for blood cholesterol concentrations (>162 mg/dL) were recruited. Subjects on vasoactive medications were excluded. Subjects received 3x7 g L-arginine daily or placebo during four-week periods, separated by a four-week wash-out period. Plasma arginine concentrations rose from 115 to 231 μmol/L during L-arginine intake. No significant changes in supine blood pressure during the L-arginine or placebo treatment phases were observed. Blood pressure values (systolic/diastolic) before and after treatment did not show any difference. The Panel notes that this study does not show an effect of L-arginine consumption on blood pressure.

Lerman et al. (1998) performed a randomised, double-blind, placebo-controlled parallel intervention to assess the effect of 3 g/day of L-arginine on blood pressure in 26 patients (age ≈49 years) with non-obstructive coronary artery disease. Patients were on cardiovascular treatment during the study, but all medication (except for study treatment) was discontinued one week prior to the measurements. During six months of treatment, no statistically significant difference was observed in mean arterial blood pressure. Data on systolic and diastolic blood pressure were not reported. The Panel notes that this study does not show an effect of L-arginine consumption on blood pressure.

Siani et al. (2000) performed a randomised, single-blind, cross-over intervention study in six healthy men, aged ≈39 years, who received three isocaloric diets during one week each with no wash-out period between the diets. Diet 1 (control) was relatively low in L-arginine (3.4–4 g/day). Diet 2 was an L-arginine-enriched diet (10 g/day) based on natural foods, mainly lentils and nuts. Diet 3 was identical to the control diet, but was supplemented with 10 g/day of an oral L-arginine preparation given three times a day. During Diet 2, potassium and fibre intakes were considerably higher (+0.9 g and +25 g, respectively) than during Diets 1 and 3, because of dietary changes. Blood pressure was significantly lower after the L-arginine diets compared to Diet 1 (control), i.e. -6.2 mmHg (95% CI, -0.5 to -11.8) systolic and -5.0 mmHg (95% CI, -2.8 to -7.2) diastolic for Diet 2, and -6.2 mmHg (95% CI, -1.8 to -10.5) systolic and -6.8 mmHg (95% CI, -3.0 to -10.6) diastolic for Diet 3. The Panel notes the small number of subjects included in the study, the lack of assessment of carry-over effects between interventions, and the short duration of the intervention, which does not allow conclusions to be drawn on the sustainability of the effect. The Panel considers that only limited conclusions can be drawn from this study for the scientific substantiation of the claimed effect.

Evans et al. (2004) studied the effect on blood pressure of different doses of arginine (3, 9, 21 and 30 g/day) given for consecutive periods of one-week each to 12 healthy subjects. No significant changes in systolic or diastolic blood pressure were observed during the study. The Panel notes that this study does not show an effect of L-arginine consumption on blood pressure.

Three randomised, placebo-controlled, human intervention studies assessed the acute effects of L-arginine intake on blood pressure (i.e. arginine consumption lasting up to three days, Huynh and Tayek, 2002; Lekakis et al., 2002; Nagaya et al., 2001). Whereas L-arginine consumption acutely decreased brachial systolic and diastolic blood pressure (Huynh and Tayek, 2002) and mean pulmonary arterial blood pressure (Nagaya et al., 2001) in two studies, no effect on brachial systolic or diastolic blood pressure was observed in the third study (Lekakis et al., 2002). The Panel considers that results obtained in these studies are inconsistent with respect to the acute effects of arginine

consumption on blood pressure, and that no conclusions can be drawn from these studies for a sustained effect of L-arginine on blood pressure.

In weighing the evidence, the Panel took into account that although a small scale short-term (one-week) only partially controlled intervention study observed an effect of arginine consumption on blood pressure (Siani et al., 2000), two small longer-term studies did not observe a significant effect (Clarkson et al., 1996; Lerman et al., 1998), and that the results from the studies assessing the acute effects of arginine consumption on blood pressure are inconsistent.

The Panel concludes that a cause and effect relationship has not been established between the consumption of L-arginine and maintenance of normal blood pressure.

3.4. Improvement of endothelium-dependent vasodilation (ID 664, 1443, 4680)

The references provided for the scientific substantiation of the claim included narrative reviews and opinion papers with no original data on the effects of arginine intake on vasodilation, references on food constituents other than arginine, intervention studies using intravenous arginine administration, which is not relevant to human nutrition, and studies on the effects of arginine administration on health outcomes other than endothelium-dependent vasodilation (e.g. blood pressure, clinical course of myocardial infarction, insulin sensitivity, wound healing, immune parameters and erectile function). The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claim.

In one study in hypertensive patients, only the acute effect of arginine intake on endothelium-dependent vasodilation was assessed, and no information on sustained effects was provided (Lekakis et al., 2002). The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claimed effect.

Miller (2006) investigated the effects of L-arginine (1,050 mg, as sustained-release preparation) twice daily (total 2.1 g daily) for one week on endothelial function in 29 healthy subjects in an open-label, single-arm intervention. The Panel considers that no conclusions can be drawn from this uncontrolled study for the scientific substantiation of the claim.

Lerman et al. (1998) performed a six-month randomised, double-blind, placebo-controlled parallel intervention to assess the effect of 3 g/day of L-arginine on coronary blood flow and epicardial coronary artery diameter in response to selective infusion of acetylcholine in 26 patients (age ≈49 years) with non-obstructive coronary artery disease. Patients were on cardiovascular treatment during the study, but all medication (except for study treatment) was discontinued at least 72 hours prior to the measurements. None of the subjects received cholesterol-lowering medications. All the patients were referred for the evaluation of stable exertional chest pain suspected to be of cardiac origin. Before the coronary angiogram, 10 patients (77 %) from each group underwent a non-invasive functional test, which was positive and consistent with myocardial ischemia in six patients from group 1 and five patients from group 2. Measures of peripheral endothelial function, for example flow-mediated dilation of the brachial artery, were not obtained in this study. The Panel considers that the evidence provided does not establish that patients with non-obstructive coronary artery disease including myocardial ischemia are representative of the general population with respect to the endothelial function of the coronary arteries. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claimed effect.

Blum et al. (2000) provided 9 g/day of L-arginine or placebo to ten healthy post-menopausal women (aged 55±5 years) in a randomised cross-over study. Intervention periods lasted one month and were separated by a one-month wash-out period. The study was powered to detect a difference of 1.7 % in flow-mediated (endothelium-dependent) dilation after hyperaemia between the study periods. Plasma L-arginine concentrations significantly increased during the intervention, whereas no significant changes were observed in serum nitric oxide or soluble cell adhesion molecules (E-selectin, ICAM-1

and VCAM-1). No significant differences between treatment periods were observed on endothelium-dependent vasodilation. The Panel notes that this study does not show an effect of L-arginine consumption on the improvement of endothelium-dependent vasodilation.

Clarkson et al. (1996) performed a randomised, double-blind, cross-over study in 27 hypercholesterolaemic subjects aged 19-40 years. Those taking HMG CoA reductase inhibitors in a stable dose for >6 months who met the entry criteria for blood cholesterol concentrations (>162 mg/dL) were recruited. Subjects on vasoactive medication were excluded. Subjects received 3x7 g L-arginine daily or placebo during four-week periods, separated by a four-week wash-out period. The non-invasive assessment of endothelium-dependent dilation was performed before and at the end of each treatment period. Post-treatment studies were performed between 1 and 2 h after the last dose of L-arginine or placebo. Plasma arginine concentrations rose from 115 to 231 μmol/L during L-arginine intake. There was a significant improvement in flow-mediated dilation in subjects while taking L-arginine (1.7±1.3 % to 5.6±3.0 %) compared with placebo (2.3±1.9 % to 2.3±2.4 %). The change with L-arginine was 3.9±3.0 % *vs.* 0.1±2.2 % with placebo ($p<0.001$). No significant differences were observed in endothelium-independent vasodilation (i.e. in response to nitroglycerine). Flow-mediated dilation improved, by more than 2 %, in 67 % of the subjects who consumed L-arginine. The Panel notes that the observed changes in endothelium-dependent vasodilation could have been due to an acute effect of arginine occurring 1-2 hours after intake in the second flow-mediated dilation test. The Panel also notes that the evidence provided does not establish that acute changes in endothelium-dependent vasodilation constitute a beneficial physiological effect *per se*.

In weighing the evidence, the Panel took into account that one study did not show an effect of L-arginine consumption on endothelium-dependent vasodilation, and that in a second study the observed changes in endothelium-dependent vasodilation could have been due to an acute effect of arginine rather than to a sustained effect.

The Panel concludes that a cause and effect relationship has not been established between the consumption of L-arginine and improvement of endothelium-dependent vasodilation.

3.5. Maintenance of normal erectile function (ID 649, 4682)

The references provided for the scientific substantiation of the claim included general reviews, a web page, a monograph, human intervention studies, animal studies and *in vitro* experiments on food/food constituents other than L-arginine, and/or effects other than erectile function (i.e. oligoasthenospermia, asthenospermia and sperm motility). The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claim.

Two human intervention studies examined the effect of L-arginine glutamate or L-arginine aspartate alone or in combination with other compounds (i.e. yohimbine hydrochloride and pine bark extract) on erectile function. The Panel considers that no conclusions can be drawn from studies using a fixed combination for the substantiation of a claim on arginine alone.

Chen et al. (1999), in a randomised, double-blind, placebo-controlled study investigated the ability of L-arginine to improve erections in 50 male subjects with confirmed organic erectile dysfunction of >6 months duration. The first two weeks of the study were a single-blind, placebo run-in phase; at the end of this period the patients were randomised and received 5 g of L-arginine monohydrochloride or placebo daily for six weeks. A penile haemodynamic test assessing peak systolic velocity, end diastolic velocity and resistance index was used as an objective measure of erectile function. Subjective measures included the O'Leary questionnaire, which contained 11 questions on sexual drive, erectile function and overall sexual satisfaction, and a questionnaire on sexual function which addressed the number and quality of the erections, libido and sexual performance. No significant

differences between groups were observed in either the objective measures or the subjective estimates of erectile function. The Panel notes that this study does not show an effect of L-arginine consumption on erectile function.

Klotz et al. (1999), in a randomised, placebo-controlled, cross-over study, investigated the effects of 500 mg L-arginine three times daily in 32 subjects with erectile dysfunction of >12 months duration. Between changes in treatment, the subjects had a wash-out phase of one week. Efficacy was assessed using the validated Köln Questionnaire of Erectile Dysfunction (KEED). No significant differences on erectile function between groups were observed. The Panel notes that this study does not show an effect of L-arginine consumption on erectile function.

The remaining reference was a study on the long-term oral administration of L-arginine on rat erectile response (Moody et al., 1997). 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 is not sufficient to predict the occurrence of an effect of arginine consumption on normal erectile function in humans.

In weighing the evidence, the Panel took into account that the two human intervention studies which investigated the effect of L-arginine consumption on erectile function did not show a significant effect of arginine on erectile function.

The Panel concludes that a cause and effect relationship has not been established between the consumption of L-arginine and maintenance of normal erectile function.

3.6. Contribution to normal spermatogenesis (ID 650, 4682)

The references provided for the scientific substantiation of the claim included general reviews, a web page, a monograph, human intervention studies, animal studies and *in vitro* experiments on foods/food constituents other than L-arginine, and/or effects other than spermatogenesis (i.e. erectile function). The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claim.

One human intervention study (De Aloysio et al., 1982) investigated the effect of arginine aspartate (providing arginine and aspartic acid) in subjects with asthenospermia or oligoasthenospermia. The Panel considers that no conclusions can be drawn from a study using a fixed combination for the substantiation of a claim on arginine alone.

In a randomised human intervention study by Aydin et al. (1995), 45 subjects with various degrees of oligospermia and asthenospermia were treated with L-arginine (2x5 g/day, n=15), the anti-inflammatory agent indomethacin (75 mg/day, n=15) or the enzyme kallikrein (100 Ku/day, n=15) for three months to encompass a complete cycle of spermatogenesis. The Panel notes the absence of an appropriate control group in this study, and considers that no conclusions can be drawn from this reference for the scientific substantiation of the claimed effect.

In the study described by Scibona et al. (1994) L-arginine-HCL (80 mL of 10 % L-arginine-HCL administered for 6 months daily) was administered to 40 asthenospermic subjects to assess its effects on sperm motility. The Panel notes the absence of a control group in this study, and considers that no conclusions can be drawn from this uncontrolled study for the scientific substantiation of the claimed effect.

In an *in vitro* study the effects on sperm motility of adding L-arginine to sperm cell suspensions from idiopathic or diabetic asthenozoospermic subjects was assessed (Morales et al., 2003). The Panel considers that evidence provided in *in vitro* studies is not sufficient to predict the occurrence of an effect of arginine consumption on normal spermatogenesis in humans.

The Panel concludes that a cause and effect relationship has not been established between the consumption of L-arginine and contribution to normal spermatogenesis.

3.7. Maintenance of normal ammonia clearance (ID 4683)

Arginine participates in the detoxification of ammonia via the urea cycle, which takes place in the liver. Arginine may be obtained from the diet or from endogenous synthesis, and dietary arginine contributes to the claimed effect.

The references provided for the scientific substantiation of the claim included a monograph, a general review, two *in vitro* experiments on the control of the urea cycle by factors other than arginine, and one animal study demonstrating the synthesis of urea from arginine and uric acid in the kidney of the frog. The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the claimed effect.

No references were provided which addressed the effects of arginine on ammonia clearance.

The Panel concludes that a cause and effect relationship has been established between the consumption of L-arginine in a protein adequate diet and maintenance of normal ammonia clearance. However, no evidence has been provided that the protein supply in the diet of the European population is not sufficient to fulfil this function of the amino acid.

4. Panel's comments on the proposed wording

4.1. Maintenance of normal ammonia clearance (ID 4683)

The Panel considers that the following wording reflects the scientific evidence: "arginine contributes to the maintenance of normal ammonia clearance".

5. Conditions and possible restrictions of use

5.1. Maintenance of normal ammonia clearance (ID 4683)

The Panel considers that no conditions of use can be defined for L-arginine.

CONCLUSIONS

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

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

"Immune system functions" (ID 455, 1713)

- The claimed effect is "for immune system functions". The target population is assumed to be the general population.
- The claimed effect is general and non-specific, and does not refer to any specific health claim as required by Regulation (EC) No 1924/2006.

Growth or maintenance of muscle mass (ID 456, 1712, 4681)

- The claimed effects are "for muscle integrity and haematopoiesis (red blood cells building)", "structural aminoacid for muscular growth", and "increases muscle mass. The target population is assumed to be the general population. In the context of the proposed wordings, it is assumed that the claimed effects refer to the growth or maintenance of muscle mass by decreasing muscle breakdown, increasing muscle synthesis, or both. Growth or maintenance of muscle mass is a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of L-arginine and growth or maintenance of muscle mass, apart from the well established role of protein on the claimed effect.

Normal red blood cell formation (ID 456, 664, 1443, 1712)

- The claimed effects are "vascular system (blood pressure, circulation, vessels)", "vascular health; blood circulation", and "for muscle integrity and haematopoiesis (red blood cells building)". The target population is assumed to be the general population. In the context of the proposed wordings and the clarifications provided by Member States, it is assumed that the claimed effects refer to normal formation of red blood cells. Normal red blood cell formation is a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of L-arginine and normal red blood cell formation.

Maintenance of normal blood pressure (ID 664, 1443)

- The claimed effects are "vascular system (blood pressure, circulation, vessels)" and "vascular health; blood circulation". The target population is assumed to be the general population. In the context of the proposed wordings and the clarifications provided by Member States, it is assumed that the claimed effects refer to the maintenance of normal blood pressure. Maintenance of normal blood pressure is a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of L-arginine and maintenance of normal blood pressure.

Improvement of endothelium-dependent vasodilation (ID 664, 1443, 4680)

- The claimed effects are "vascular system (blood pressure, circulation, vessels)", "vascular health; blood circulation", and "normal blood circulation as a nitric oxide precursor". The target population is assumed to be the general population. In the context of the proposed wordings and the clarifications provided by Member States, it is assumed that the claimed effects refer to the improvement of endothelium-dependent vasodilation. Improvement of endothelium-dependent vasodilation may be a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of L-arginine and improvement of endothelium-dependent vasodilation.

"Physical performance and condition" (ID 1820)

- The claimed effect is "physical performance and condition". The target population is assumed to be the general population.

- The claimed effect is general and non-specific, and does not refer to any specific health claim as required by Regulation (EC) No 1924/2006.

"Système nerveux" (ID 608)

- The claimed effect is "système nerveux". The target population is assumed to be the general population.

- The claimed effect is general and non-specific, and does not refer to any specific health claim as required by Regulation (EC) No 1924/2006.

Maintenance of normal erectile function (ID 649, 4682)

- The claimed effects are "erection" and "supporting spermatogenesis and local pelvic microcirculation". The target population is assumed to be the general male population. Maintenance of normal erectile function is a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of L-arginine and maintenance of normal erectile function.

Contribution to normal spermatogenesis (ID 650, 4682)

- The claimed effects are "spermatogenesis" and "supporting spermatogenesis and local pelvic microcirculation". The target population is assumed to be the general male population. Contribution to normal spermatogenesis is a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of L-arginine and contribution to normal spermatogenesis.

"Function of the intestinal tract" (ID 740)

- The claimed effect is "function of the intestinal tract". The target population is assumed to be the general population.

- The claimed effect is general and non-specific, and does not refer to any specific health claim as required by Regulation (EC) No 1924/2006.

Maintenance of normal ammonia clearance (ID 4683)

- The claimed effect is "ureogenesis by increasing ammonia clearance in the body". The target population is assumed to be the general population. Maintenance of normal ammonia clearance is a beneficial physiological effect.

- A cause and effect relationship has been established between the consumption of L-arginine in a protein adequate diet and maintenance of normal ammonia clearance.

- No evidence has been provided that the protein supply in the diet of the European population is not sufficient to fulfil this function of the amino acid.

- The following wording reflects the scientific evidence: "Arginine contributes to the maintenance of normal ammonia clearance".

- No conditions of use can be defined for L-arginine.

DOCUMENTATION PROVIDED TO EFSA

Health claims pursuant to Article 13 of Regulation (EC) No 1924/2006 (No: EFSA-Q-2008-1242, EFSA-Q-2008-1243, EFSA-Q-2008-1395, EFSA-Q-2008-1436, EFSA-Q-2008-1437, EFSA-Q-2008-1451, EFSA-Q-2008-1527, EFSA-Q-2008-2180, EFSA-Q-2008-2448, EFSA-Q-2008-2449, EFSA-Q-2008-2553, EFSA-Q-2010-00633, EFSA-Q-2010-00634, EFSA-Q-2010-00635, EFSA-Q-2010-00636). 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 L-arginine, including conditions of use from similar claims, as proposed in the Consolidated List.

ID	Food or Food constituent	Health Relationship	Proposed wording
455	Arginine	For immune system functions. Clarification provided Arginine is necessary for the synthesis of proteins within the body tissues (it supports tissue repair and growth acceleration), it plays an important role in cell division and is necessary for the proper functioning of the immune system, by accelerating wounds healing.	Conditionally-essential amino acid that plays an important role in the growth and immune system. It supports tissue growth acceleration.
	Conditions of use - Immunonutrition. - 75 – 150 mg. - The glycemic response is not more than half that of glucose. see Reference list for details. - Tagesdosis L-Arginin: 2000 mg–Erwachsene.		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
456	Arginine	For muscle integrity and haematopoiesis (red blood cells building)	It has positive effects on muscle integrity and on haematopoiesis (for red blood cells building)
	Conditions of use - 75-150 mg - Sportler–Tagesdosis L-Arginin-Pyroglutamat: 500 mg		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
608	Arginine.	Système nerveux.	Acide aminé régulateur du cortisol, médiateur du stress.
	Conditions of use - 400mg/j.		
	No clarification provided by Member States		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
649	L-arginine.	Erection.	L-arginine helps to induce and improve erection.
	Conditions of use		

	- 500 mg for 8 weeks.		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
650	L-arginine.	Spermatogenesis.	L-arginine influence positively on spermatogenesis (sperms formation and mobility).
	Conditions of use - 500 mg for 3 month.		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
664	L-Arginine	Vascular system;(blood pressure, circulation, vessels) Clarification provided For the vascular health/ normal blood circulation/the healthy blood pressure and the haematopoiesis.	Arginine can contribute to the maintenance of the healthy blood circulation. Clarification provided Arginine can contribute to the maintenance of the healthy blood circulation. Arginine can contribute to the maintance of the normal blood circulation, such as the healthy blood pressure and the haematopoiesis.
	Conditions of use - 1500 mg per day. 75-150 mg - 225 mg daily; (15 % of the lower (1500 mg) therapeutic dose)		
	Comments from Member States add. example of wording from HU		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
740	Arginin. Clarification provided l-arginin.	Verdauungstrakt. Clarification provided Function of the intestinal tract.	[In german :] stärkt die Darmmucosa. Clarification provided Strengthens the gut mucosa.
	Conditions of use - Immunonutrition.		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1443	Arginine	Vascular health; blood circulation Clarification provided Vascular health; normal blood circulation; Contributes to a better endothelial dilatation of the blood vessel walls. Improves endothlial function. Helps maintain a healthy	Support of normal blood circulation

		blood-circulation, blood pressure and the haematopoiesis.	
	Conditions of use - 225 mg daily;(15 % of the lower (1500 mg) therapeutic dose - 1,4 g - 1500 mg per day (75-150 mg) - Tagesdosis > 200 mg - 500 mg pro Tag		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1712	Arginine	For muscle integrity and haematopoiesis (red blood cells building)	It has positive effects on muscle integrity and on haematopoiesis (for red blood cells building).
	Conditions of use - 75 – 150 mg		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1713	Arginine.	For immune system functions. Clarification provided Arginine is necessary for the synthesis of proteins within the body tissues (it supports tissue repair and growth acceleration), it plays an important role in cell division and is necessary for the proper functioning of the immune system, by accelerating wounds healing.	Essential amino acid that plays an important role in the immune system.
	Conditions of use - 75 – 150 mg.		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1820	L-arginine hydrochloride	Physical performance and condition	Power for muscles. Increases nitric oxide production.
	Conditions of use - Food supplement with 1000-3000mg of L-arginine hydrochloride (=830-2490mg of L-arginine) in the daily dose.		
	No clarification provided by Member States		

ID	Food or Food constituent	Health Relationship	Proposed wording
4680	L/arginine	Normal blood circulation as a nitric oxide precursor	Contributes to the synthesis of creatinine and nitric oxide, with important role in dilatation and relaxation of blood vessels.
	Conditions of use - 1000-2000 mg/day		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
4681	L/arginine	Structural aminoacid for muscular growth Increases muscle mass	Helps the organism to maintain and to recover after prolonged physical effort. / Helps in muscular atrophy. / Invigorator of the muscle mass. / Helps in the harmonious growth and development of the young organisms. / Helps to stimulate the production of Human Growth Hormone. / Helps in the development of the muscle mass.
	Conditions of use - 1000-2000 mg/day		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
4682	L/arginine.	Supporting spermatogenesis and local pelvic microcirculation.	Helps to improve blood circulation on pelvic level. / Helps protein synthesis and cellular replication with important role in the spermatogenesis process.
	Conditions of use - 1000-2000 mg/day.		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
4683	L/arginine.	Ureogenesis by increasing ammonia clearance in the body.	Interferes in the ureogenesis, helping the elimination of ammonia.
	Conditions of use - 1000-2000 mg/day.		

GLOSSARY AND ABBREVIATIONS

CI	Confidence interval
HMG CoA reductase	3-Hydroxy-3-methyl-glutaryl-CoA reductase
ICAM-1	Inter-Cellular Adhesion Molecule 1
VCAM-1	Vascular Cell Adhesion Molecule 1