EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of health claims related to L-glutamine and growth or maintenance of muscle mass (ID 719, 722, 3185), faster restoration of muscle glycogen stores after strenuous exercise (ID 434, 699, 701, 723, 1569), skeletal muscle tissue repair (ID 721), maintenance of normal neurological function (ID 662, 700), increased attention (ID 700, 1570), improvement of working memory (ID 700, 1570), maintenance of defence against pathogenic gastro-intestinal microorganisms (ID 452), gut protein synthesis (ID 701), decreasing gut permeability (ID 701), and stimulating immunological responses (ID 1568) pursuant to Article 13(1) of Regulation (EC) No 1924/2006

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to L-glutamine and growth or maintenance of muscle mass (ID 719, 722, 3185), faster restoration of muscle glycogen stores after strenuous exercise (ID 434, 699, 701, 723, 1569), skeletal muscle tissue repair (ID 721), maintenance of normal neurological function (ID 662, 700), increased attention (ID 700, 1570), improvement of working memory (ID 700, 1570), maintenance of defence against pathogenic gastro-intestinal microorganisms (ID 452), gut protein synthesis (ID 701), decreasing gut permeability (ID 701), and stimulating immunological responses (ID 1568) 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-glutamine and growth or maintenance of muscle mass, faster restoration of muscle glycogen stores after strenuous exercise, skeletal muscle tissue repair, maintenance of normal

[1] On request from the European Commission, Question No EFSA-Q-2008-1221, EFSA-Q-2008-1239, EFSA-Q-2008-1449, EFSA-Q-2008-1486, EFSA-Q-2008-1487, EFSA-Q-2008-1488, EFSA-Q-2008-1506, EFSA-Q-2008-1508, EFSA-Q-2008-1509, EFSA-Q-2008-1510, EFSA-Q-2008-2305, EFSA-Q-2008-2306, EFSA-Q-2008-2307, EFSA-Q-2008-3917, adopted on 25 March 2011.

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

[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 Gut/Immune: Jean-Louis Bresson, Maria Carmen Collado, Miguel Gueimonde, Daisy Jonkers, Martinus Løvik, Bevan Moseley, Maria Saarela, Seppo Salminen, Yolanda Sanz, Stephan Strobel, Daniel Tomé and Hendrik van Loveren. The members of the Claims Sub-Working Group on Weight Management/Satiety/Glucose and Insulin Control/Physical Performance: Kees de Graaf, Joanne Harrold, Mette Hansen, Mette Kristensen, Anders Sjödin and Inge Tetens. 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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neurological function, increased attention and improvement of working memory, maintenance of defence against pathogenic gastro-intestinal microorganisms, gut protein synthesis, decreasing gut permeability, and stimulating immunological responses. 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-glutamine. The Panel considers that L-glutamine is sufficiently characterised.

Growth or maintenance of muscle mass

The claimed effects are "increasing cell swelling, volumization", "muscle protein metabolism" and "improves muscles metabolism". 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. The Panel considers that growth or maintenance of muscle mass is a beneficial physiological effect.

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

No references were provided which addressed the effects of L-glutamine consumption on growth or maintenance of 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-glutamine and growth or maintenance of muscle mass, apart from the well established role of protein on the claimed effect.

Faster restoration of muscle glycogen stores after strenuous exercise

The claimed effects are "supporting glycogen replenishment", "muscle function", "metabolic stress, protein synthesis, gut permeability, carbohydrate metabolism", and "supporting glucose homeostasis". The target population is assumed to be adults performing strenuous exercise. In the context of the proposed wordings, clarifications from Member States and references provided, the Panel assumes that the claimed effects refer to the faster restoration of glycogen stores in skeletal muscle after strenuous exercise. The Panel considers that faster restoration of muscle glycogen stores after strenuous exercise might be a beneficial physiological effect.

In weighing the evidence, the Panel took into account that the two studies from which conclusions could be drawn for the scientific substantiation of the claim did not show an effect of L-glutamine consumption on the restoration of muscle glycogen stores after strenuous exercise.

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-glutamine and faster restoration of muscle glycogen stores after strenuous exercise.

Skeletal muscle tissue repair

The claimed effect is "supporting exercise recovery". The target population is assumed to be adults performing resistance exercise. In the context of the proposed wordings, the Panel assumes that the claimed effect refers to the rebuilding of structural protein within the skeletal muscle tissue after exercise that has caused muscle damage. The Panel considers that skeletal muscle tissue repair is a beneficial physiological effect.

No references were provided which addressed the effects of L-glutamine consumption on skeletal muscle tissue repair in humans.

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-glutamine and skeletal muscle tissue repair.

Maintenance of normal neurological function

The claimed effects are "mental health" and "nervous system". 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 neurological function. The Panel considers that the 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 claim.

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-glutamine and maintenance of normal neurological function.

Increased attention

The claimed effect is "mental health". The target population is assumed to be the general population. In the context of the proposed wordings, the Panel assumes that the claimed effect refers to increased attention. The Panel considers that increased attention is a beneficial physiological effect.

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

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-glutamine and increased attention.

Improvement of working memory

The claimed effect is "mental health". The target population is assumed to be the general population. In the context of the proposed wordings, the Panel assumes that the claimed effect refers to improvement of working memory. The Panel considers that improvement of working memory is a beneficial physiological effect.

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

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-glutamine and improvement of working memory.

Maintenance of defence against pathogenic gastro-intestinal microorganisms

The claimed effect is "maintains healthy gastrointestinal tract and immune functions in stressful conditions". 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 effect refers to the maintenance of defence against pathogenic gastro-intestinal microorganisms. The Panel considers that maintenance of defence against pathogenic gastro-intestinal microorganisms is a beneficial physiological effect.

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

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-glutamine and maintenance of defence against pathogenic gastro-intestinal microorganisms.

Gut protein synthesis

The claimed effect is "metabolic stress, protein synthesis, gut permeability, carbohydrate metabolism". The target population is assumed to be the general population. In the context of the clarifications provided by Member States, the Panel assumes that the claimed effect refers to gut protein synthesis. The Panel considers that gut protein synthesis is not a beneficial physiological effect *per se*, but needs to be linked to a beneficial physiological or clinical outcome. The Panel notes that no evidence has been provided on the context in which the claimed effect could be considered as a beneficial physiological 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-glutamine and a beneficial physiological effect related to gut protein synthesis.

Decreasing gut permeability

The claimed effect is "metabolic stress, protein synthesis, gut permeability, carbohydrate metabolism". The target population is assumed to be the general population. In the context of the clarifications provided by Member States, the Panel assumes that the claimed effect refers to decreasing gut permeability. The Panel considers that decreasing gut permeability is not a beneficial physiological effect *per se*, but needs to be linked to a beneficial physiological or clinical outcome. The Panel notes that no evidence has been provided on the context in which the claimed effect could be considered as a beneficial physiological 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-glutamine and a beneficial physiological effect related to decreasing gut permeability.

Stimulating immunological responses

The claimed effect is "immune health". The target population is assumed to be the general population. In the context of the clarifications provided by Member States, the Panel assumes that the claimed effect refers to stimulating various immunological responses such as increasing mononuclear cell proliferation, cytokine production and nasal IgA after exercise. The evidence provided does not establish that stimulation of mononuclear cell proliferation, cytokine production and nasal IgA is a beneficial physiological effect *per se*.

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-glutamine and a beneficial physiological effect related to the stimulation of mononuclear cell proliferation, cytokine production and nasal IgA.

KEY WORDS

L-glutamine, muscle mass, glycogen stores, tissue repair, neurological function, attention, working memory, defence, gastro-intestinal, microorganisms, gut, 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-glutamine.

Glutamine is a conditionally indispensable amino acid provided by mixed dietary protein intakes from different sources. It can also be consumed as a food supplement. The content of L-glutamine in foods can be measured by established methods.

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

2. Relevance of the claimed effect to human health

2.1. Growth or maintenance of muscle mass (ID 719, 722, 3185)

The claimed effects are "increasing cell swelling/volumization", "muscle protein metabolism" and "improves muscles metabolism". 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. 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.

2.2. Faster restoration of muscle glycogen stores after strenuous exercise (ID 434, 699, 701, 723, 1569)

The claimed effects are "supporting glycogen replenishment", "muscle function", "metabolic stress, protein synthesis, gut permeability, carbohydrate metabolism" and "supporting glucose homeostasis". The Panel assumes that the target population is adults performing strenuous exercise.

[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] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), 2011. General guidance for stakeholders on the evaluation of Article 13.1, 13.5 and 14 health claims. EFSA Journal, 9(4):2135, 24 pp.

In the context of the proposed wordings, clarifications from Member States and references provided, the Panel assumes that the claimed effects refer to the faster restoration of glycogen stores in skeletal muscle after strenuous exercise.

The Panel considers that faster restoration of muscle glycogen stores after strenuous exercise might be a beneficial physiological effect.

2.3. Skeletal muscle tissue repair (ID 721)

The claimed effect is "supporting exercise recovery". The Panel assumes that the target population is adults performing resistance exercise.

In the context of the proposed wordings, the Panel assumes that the claimed effect refers to the rebuilding of structural protein within the skeletal muscle tissue after exercise that has caused muscle damage.

The Panel considers that skeletal muscle tissue repair is a beneficial physiological effect.

2.4. Maintenance of normal neurological function (ID 662, 700)

The claimed effect is "nervous system" and "mental health". 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 neurological function.

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

2.5. Increased attention (ID 700, 1570)

The claimed effect is "mental health". 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 increased attention (concentration).

The Panel considers that increased attention is a beneficial physiological effect.

2.6. Improvement of working memory (ID 700, 1570)

The claimed effect is "mental health". 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 improvement of working memory.

The Panel considers that improvement of working memory is a beneficial physiological effect.

2.7. Maintenance of defence against pathogenic gastro-intestinal microorganisms (ID 452)

The claimed effect is "maintains healthy gastrointestinal tract and immune functions in stressful conditions". 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 effect refers to the maintenance of defence against pathogenic gastro-intestinal microorganisms.

The Panel considers that maintenance of defence against pathogenic gastro-intestinal microorganisms is a beneficial physiological effect.

2.8. Gut protein synthesis (ID 701)

The claimed effect is "metabolic stress, protein synthesis, gut permeability, carbohydrate metabolism". The Panel assumes that the target population is the general population.

In the context of the clarifications provided by Member States, the Panel assumes that the claimed effect refers to gut protein synthesis.

The Panel considers that gut protein synthesis is not a beneficial physiological effect *per se*, but needs to be linked to a beneficial physiological or clinical outcome. The Panel notes that no evidence has been provided on the context in which the claimed effect could be considered as a beneficial physiological effect.

The Panel concludes that a cause and effect relationship has not been established between the consumption of L-glutamine and a beneficial physiological effect related to gut protein synthesis.

2.9. Decreasing gut permeability (ID 701)

The claimed effect is "metabolic stress, protein synthesis, gut permeability, carbohydrate metabolism". The Panel assumes that the target population is the general population.

In the context of the clarifications provided by Member States, the Panel assumes that the claimed effect refers to decreasing gut permeability.

The Panel considers that decreasing gut permeability is not a beneficial physiological effect *per se*, but needs to be linked to a beneficial physiological or clinical outcome. The Panel notes that no evidence has been provided on the context in which the claimed effect could be considered as a beneficial physiological effect.

The Panel concludes that a cause and effect relationship has not been established between the consumption of L-glutamine and a beneficial physiological effect related to decreasing gut permeability.

2.10. Stimulating immunological responses (ID 1568)

The claimed effect is "immune health". The Panel assumes that the target population is the general population.

In the context of the clarifications provided by Member States, the Panel assumes that the claimed effect refers to stimulating various immunological responses such as increasing mononuclear cell proliferation, cytokine production and nasal IgA after exercise.

The Panel considers that the evidence provided does not establish that stimulation of mononuclear cell proliferation, cytokine production and nasal IgA is a beneficial physiological effect *per se*.

The Panel concludes that a cause and effect relationship has not been established between the consumption of L-glutamine and a beneficial physiological effect related to the stimulation of mononuclear cell proliferation, cytokine production and nasal IgA.

3. Scientific substantiation of the claimed effect

The references provided for the scientific substantiation of these claims included textbooks and narrative reviews which did not provide original data for the scientific substantiation of the claim. Human, animal and *in vitro* studies on food constituents other than L-glutamine alone (e.g. branched-chain aminoacids (BCAA); N-acetyl-cysteine; mixtures of whey protein plus BCAA or arginine plus L-glutamine; mixtures of soy lecithin, sodium dihydrogen phosphate, thiamin, pyridoxine and L-glutamine; mixtures of glycine, niacin, and glutamine), on glutamine given intravenously, on health outcomes (e.g. treatment of chronic disease or pathological conditions, morbidity and mortality in pre-term infants, use in enteral nutrition) unrelated to the claimed effects, or on the effects of intense training on plasma and tissue concentrations of L-glutamine, were also provided. The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claims.

3.1. Growth or maintenance of muscle mass (ID 719, 722, 3185)

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

Glutamine is a component of dietary protein, and both endogenous and exogenous glutamine contribute to protein synthesis.

No references which addressed the effects of L-glutamine consumption on growth or maintenance of muscle mass were provided. No evidence has been provided that L-glutamine 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-glutamine and growth or maintenance of muscle mass, apart from the well established role of protein on the claimed effect.

3.2. Faster restoration of muscle glycogen stores after strenuous exercise (ID 434, 699, 701, 723, 1569)

Two references which assessed the effects of L-glutamine consumption on muscle glycogen stores after exercise were provided.

In the study by Bowtell et al. (1999) seven male subjects participated in three trials, in each of which they received one of three different drinks by systematic rotation: 18.5 % (wt/vol) glucose polymer solution (containing glucose, maltose, maltotriose, tetrasaccharide, pentasaccharide and "higher sugars"), a solution containing 8 g glutamine, or 18.5 % glucose polymers containing 8 g glutamine. Tests were undertaken one month apart. On each test day, subjects followed a validated standard exercise protocol designed to deplete of glycogen both type I and type II muscle fibres. A muscle biopsy was taken from the quadriceps femoris muscle within 15 min of the end of exercise. Within 20 min, a 2 h constant [1-^{13}C]glucose intravenous infusion started at a rate of 8.5 mg/kg/h for the first 30 min after a 9 mg/kg bolus of [1-^{13}C]glucose. Subjects then consumed the test drinks (330 mL) within 2 min of the start of the infusion. Second and third quadriceps femoris muscle biopsies were taken after 1 and 2 h of recovery. No significant differences with respect to the average rate of net muscle glycogen storage during the 2 h of recovery after exercise were observed between the test drinks. The Panel notes that this study does not show an effect of L-glutamine on the restoration of muscle glycogen stores after strenuous exercise.

In the study by Van Hall et al. (2000) eight trained subjects were studied during 3 h of recovery while consuming one of four drinks in random order. Drinks were ingested in three 500 mL boluses. Each bolus of the control drink contained 0.8 g/kg body weight of glucose. The other drinks contained the same amount of glucose and either 0.3 g/kg body weight of glutamine, or a wheat hydrolysate (26 % glutamine), or a whey hydrolysate (6.6 % glutamine). On each test day (7 days apart), subjects followed a validated standard exercise protocol for glycogen depletion. A biopsy was taken from the quadriceps muscle 15 min after the end of exercise, and the first bolus was taken immediately thereafter. The other boluses followed after 1 and 2 h of recovery. A second muscle biopsy was taken after 3 h of recovery. The rate of glycogen re-synthesis in skeletal muscle was not significantly different between the four test drinks. The Panel notes that this study does not show an effect of L-glutamine on the restoration of muscle glycogen stores after strenuous exercise.

In weighing the evidence, the Panel took into account that the two studies from which conclusions could be drawn for the scientific substantiation of the claim did not show an effect of L-glutamine consumption on the restoration of muscle glycogen stores after strenuous exercise.

The Panel concludes that a cause and effect relationship has not been established between the consumption of L-glutamine and faster restoration of muscle glycogen stores after strenuous exercise.

3.3. Skeletal muscle tissue repair (ID 721)

No references which addressed the effects of L-glutamine consumption on skeletal muscle tissue repair in humans were provided.

The Panel concludes that a cause and effect relationship has not been established between the consumption of L-glutamine and skeletal muscle tissue repair.

3.4. Maintenance of normal neurological function (ID 662, 700)

No references which addressed the effects of L-glutamine consumption on neurological function were provided.

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

3.5. Increased attention (ID 700, 1570)

No references which addressed the effects of L-glutamine consumption on measures of attention were provided.

The Panel concludes that a cause and effect relationship has not been established between the consumption of L-glutamine and increased attention.

3.6. Improvement of working memory (ID 700, 1570)

No references which addressed the effects of L-glutamine consumption on measures of working memory were provided.

The Panel concludes that a cause and effect relationship has not been established between the consumption of L-glutamine and improvement of working memory.

3.7. Maintenance of defence against pathogenic gastro-intestinal microorganisms (ID 452)

Rohde et al. (1996) investigated the effects of physical exercise (i.e. triathlon) on immune markers and serum amino acid concentrations in eight male tri-athletes. The Panel notes that this study did not report on L-glutamine intakes.

Castell et al. (1996) studied ultra-marathon (n=27), marathon (n=88), middle-distance (10 and 15 km; n=41) runners and rowers (n=45) undergoing training. Both males and females were included. Glutamine (5 g in 330 mL mineral water) or placebo (maltodextrin) were given immediately after and 2 h after a test exercise on a double-blind basis. Randomisation is not mentioned. The athletes were given a questionnaire to monitor infections according to specified symptoms for seven days after the test exercise. Gastro-intestinal infections were included for analysis in addition to airway infections. The incidence of infections in the seven-day period was only reported for marathon and ultra-marathon runners. The Panel notes the lack of information about randomisation, that no detailed information about the questionnaires used for the diagnosis of infections was provided, that the number of non-responders and the gender distribution were not indicated, and that it is unclear why some sub-groups of athletes were excluded from the statistical analysis. The Panel considers that owing to important methodological limitations no conclusions can be drawn from this study 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-glutamine and maintenance of defence against pathogenic gastro-intestinal microorganisms.

CONCLUSIONS

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

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

Growth or maintenance of muscle mass (ID 719, 722, 3185)

- The claimed effects are “increasing cell swelling/volumization”, “muscle protein metabolism” and “improves muscles metabolism”. The target population is assumed to be the general population. 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-glutamine and growth or maintenance of muscle mass, apart from the well established role of protein on the claimed effect.

Faster restoration of muscle glycogen stores after strenuous exercise (ID 434, 699, 701, 723, 1569)

- The claimed effects are “supporting glycogen replenishment”, “muscle function”, “metabolic stress, protein synthesis, gut permeability, carbohydrate metabolism”, and “supporting glucose homeostasis”. The target population is assumed to be adults performing strenuous exercise. Faster restoration of muscle glycogen stores after strenuous exercise might be a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of L-glutamine and faster restoration of muscle glycogen stores after strenuous exercise.

Skeletal muscle tissue repair (ID 721)

- The claimed effect is "supporting exercise recovery". The target population is assumed to be adults performing resistance exercise. Skeletal muscle tissue repair is a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of L-glutamine and skeletal muscle tissue repair.

Maintenance of normal neurological function (ID 662, 700)

- The claimed effects are "nervous system" and "mental health". 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 L-glutamine and maintenance of normal neurological function.

Increased attention (ID 700, 1570)

- The claimed effect is "mental health". The target population is assumed to be the general population. In the context of the proposed wordings, it is assumed that the claimed effect refers to increased attention. Increased attention is a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of L-glutamine and increased attention.

Improvement of working memory (ID 700, 1570)

- The claimed effect is "mental health". The target population is assumed to be the general population. In the context of the proposed wordings, it is assumed that the claimed effect refers to improvement of working memory. Improvement of working memory is a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of L-glutamine and improvement of working memory.

Maintenance of defence against pathogenic gastrointestinal microorganisms (ID 452)

- The claimed effect is "maintains healthy gastrointestinal tract and immune functions in stressful conditions". The target population is assumed to be the general population. Maintenance of defence against pathogenic gastro-intestinal microorganisms is a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of L-glutamine and maintenance of defence against pathogenic gastro-intestinal microorganisms.

Gut protein synthesis (ID 701)

- The claimed effect is "metabolic stress, protein synthesis, gut permeability, carbohydrate metabolism". The target population is assumed to be the general population. Gut protein synthesis is not a beneficial physiological effect *per se*, but needs to be linked to a beneficial physiological or clinical outcome. No evidence has been provided on the context in which the claimed effect could be considered as a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of L-glutamine and a beneficial physiological effect related to gut protein synthesis.

Decreasing gut permeability (ID 701)

- The claimed effect is "metabolic stress, protein synthesis, gut permeability, carbohydrate metabolism". The target population is assumed to be the general population. Decreasing gut permeability is not a beneficial physiological effect *per se*, but needs to be linked to a beneficial physiological or clinical outcome. No evidence has been provided on the context in which the claimed effect could be considered as a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of L-glutamine and a beneficial physiological effect related to decreasing gut permeability.

Stimulating immunological responses (ID 1568)

- The claimed effect is "immune health". The target population is assumed to be the general population. In the context of the clarifications provided by Member States, it is assumed that the claimed effect refers to stimulating various immunological responses such as increasing mononuclear cell proliferation, cytokine production and nasal IgA after exercise. The evidence provided does not establish that stimulation of mononuclear cell proliferation, cytokine production and nasal IgA is a beneficial physiological effect *per se*.

- A cause and effect relationship has not been established between the consumption of L-glutamine and a beneficial physiological effect related to the stimulation of mononuclear cell proliferation, cytokine production and nasal IgA.

DOCUMENTATION PROVIDED TO EFSA

Health claims pursuant to Article 13 of Regulation (EC) No 1924/2006 (No: EFSA-Q-2008-1221, EFSA-Q-2008-1239, EFSA-Q-2008-1449, EFSA-Q-2008-1486, EFSA-Q-2008-1487, EFSA-Q-2008-1488, EFSA-Q-2008-1506, EFSA-Q-2008-1508, EFSA-Q-2008-1509, EFSA-Q-2008-1510, EFSA-Q-2008-2305, EFSA-Q-2008-2306, EFSA-Q-2008-2307, EFSA-Q-2008-3917). The scientific substantiation is based on the information provided by the Member States in the consolidated list of Article 13 health claims and references that EFSA has received from Member States or directly from stakeholders.

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

REFERENCES

Bowtell JL, Gelly K, Jackman ML, Patel A, Simeoni M and Rennie MJ, 1999. Effect of oral glutamine on whole body carbohydrate storage during recovery from exhaustive exercise. Journal of Applied Physiology, 86, 1770-1777.

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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 glutamine, including conditions of use from similar claims, as proposed in the Consolidated List.

ID	Food or Food constituent	Health Relationship	Proposed wording
434	Glutamine	Supporting glycogen replenishment	Glutamine may support muscle glycogen replenishment followingexhaustive exercise.
	Conditions of use - Amount of consumption (value): 50 Milligramm (mg). Amount of consumption (plaintext): mg/kg KG p.Tag. Upper limit (value): 900 Milligramm (mg). Other condition: mg/kg täglich - The product must contain at least 5 gram Glutamine per serving. Claim to be used for foods for active individuals		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
452	L-glutamine	Maintains healthy gastrointestinal tract and immune functions in stressful conditions Clarification provided Supports a healthy immune system: decrease in infections among treated athletes, mechanism may be linked to neutrophils	Glutamine supports a healthy digestive system and contributes to strengthen the natural defences
	Conditions of use - Healthy adults concerned with maintaining healthy gastrointestinal tract and immune functions in stressful conditions. AMOUNT RECOMMENDATION: Min 5 g glutamine per day		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
662	L-Glutamine	Nervous system Clarification provided Influence on nervous system: for the better performance of the nervous system and the brain /constituent of gluthathione, purines, amino sugars, precursor of GABA (g-amino butyric acid)	Glutamine contributes to the healthy function of the nervous system and the brain.
	Conditions of use - Schulkinder, Erwachsene. Amount of consumption: 1000 Milligramm (mg) - Amount of consumption: 100 mg/Tag. Other condition: Mind. 100 mg täglich - Other condition: Vor allem in Kombination mit anderen Aminosäuren wie z.B. Serin sowie den Vitaminen B12, B1, B2 und B6		

	- 225 mg,;15% of the lower (1500 mg) therapeutic dose ;(Martindale pp. 1785-86)		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
699	Glutamine	Muscle function Clarification provided Increases blood glutamine levels, which is reduced during exercise	Skeletal muscle represents the greatest store of glutamine in the body/muscle tissue is an important source of glutamine/high intensity exercise decreases plasma glutamine levels anaerobic training can deplete the glutamine pool/prolonged exercise such as marathon running decreases glutamine levels/supplementation can maintain glutamine levels during intense exercise/can abolish the exercise related decline restores blood glutamine levels post exercise/helps maintain optimal health after training/helps keep athletes healthy after intense exercise/optimizing blood glutamine levels helps enhance muscle adaptation to intense exercise /reduced glutamine levels decreases the adaptive response to intense exercise/helps enhance glycogen storage/helps increase carbohydrate storage
	Conditions of use - 50 - 900 mg/kg per day		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
700	Glutamine	Mental health	- Constituent of gluthathione, purines, amino sugars, precursor of GABA (g-amino butyric acid)/supports concentration and mental performance under conditions of mental or physical exertion/ - helps to maintain working memory and brain performance in aging adults/plays an important

			role in healthy nerve function through the central nervous system including the brain
	Conditions of use - Min 100 mg per day		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
701	Glutamine and glutamine peptide	Metabolic stress/protein synthesis/gut permeablity/carbohydrate metabolism Clarification provided Contributes to gut protein synthesis. Decreases permeability of gut cells. Increases/Replenishes carbohydrate stores in the muscle and the liver	Extra dietary supply of glutamine restores plasma glutamine levels after metabolic stress/contributes to gut protein synthesis/help decrease permeability of gut cells/helps to replenish carbohydrate stores in the muscle and the liver
	Conditions of use - min.5 g glutamine per day		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
719	Glutamine	Increasing cell swelling / volumization	Glutamine may improve intestinal water and electrolyte absorption Glutamine can help volumize muscle cells Glutamine may increase cell swelling (volume)
	Conditions of use - The product must contain at least 5 gram Glutamine per serving - Claim to be used for foods for active individuals		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
721	Glutamine	Supporting exercise recovery	Glutamine is considered essential for repair and recovery Glutamine can aid In muscle tissue repair
	Conditions of use - The product must contain at least 5 gram Glutamine per serving - Claim to be used for foods for active individuals		

ID	Food or Food constituent	Health Relationship	Proposed wording
722	Glutamine	Muscle protein metabolism	Glutamine supports muscle cells Glutamine supports muscle protein metabolism
	Conditions of use - The product must contain at least 5 gram Glutamine per serving - Claim to be used for foods for active individuals		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
723	Glutamine	Supporting glucose homeostasis	Glutamine may support glucose homeostasis during and after exercise
	Conditions of use - The product must contain at least 5 gram Glutamine per serving - Claim to be used for foods for active individuals		
	No clarification provided by Member States		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1568	Glutamine	Immune health <u>Clarification provided</u> Immune health. Supports the immune system: Glutamine supplementation increases mononuclear cell proliferation, cytokine production and nasal IgA after exercise.	Supports the immune system -is an important nutrient for those cells requiring rapid renewal such as immune cells (e.g. lymphocytes) -is an important fuel for rapidly dividing cells, including those of the immune system -supplementation contributes to immune function -contributes to the immune response to exercise
	Conditions of use - 50-400 mg/kg per day. The product must contain at least 5 gram Glutamine per serving. Claim to be used for foods for active individuals - Immunonutrition		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1569	Glutamine	Muscle function <u>Clarification provided</u> Supports muscle function: Exercise decreases plasma glutamine concentrations. Glutamine supplementation can maintain plasma	Skeletal muscle represents the greatest store of glutamine in the body -muscle tissue is an important source of glutamine -high intensity exercise decreases plasma glutamine

		glutamine concentrations during intense exercise: Abolishing the decline in plasma glutamine and enhancing plasma glutamine levels. Glutamine supplementation reduces the risk of infections after training, helping athletes avoid infections after intense exercise. After exercise glutamine supplementation may enhance glycogen and carbohydrate storage in skeletal muscle following exercise. Reducing the decline in blood glutamine levels after training reduces breakdown of body tissue	levels -anaerobic training can deplete the glutamine pool -prolonged exercise such as marathon running decreases glutamine levels -supplementation can maintain glutamine levels during intense exercise -can abolish the exercise related decline in glutamine stores -enhances glutamine levels -restores blood glutamine levels post exercise -helps maintain optimal health after training -helps keep athletes healthy after intense exercise -optimizing blood glutamine levels helps enhance muscle adaptation to intense exercise -reduced glutamine levels decreases the adaptive response to intense exercise -helps enhance glycogen storage -helps increase carbohydrate storage
	Conditions of use - 50 - 900 mg/kg per day - Sportler–Tagesdosis L-Glutamin: 500 mg–		
	Comments from Member States Note the Cion from submitter: Submitter initally sent these as separte claims to the CIAA, the claims have since become amalgamated into one. Please separate and health relationships amended as indicated		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
1570	Glutamine	Mental health	- supports concentration and mental performance under conditions of mental or physical exertion - helps to maintain working memory and brain performance in aging adults

	Conditions of use - 225 mg,;15% of the lower (1500 mg) therapeutic dose ;(Martindale pp. 1785-86) - Min 100 mg per day - Tagesdosis L-Glutaminsäure: 500 mg– Erwachsene - Gesamtbevölkerung		
ID	**Food or Food constituent**	**Health Relationship**	**Proposed wording**
3185	Glutaminian	glutamine improves muscles metabolism	- glutamine improves body metabolism
	Conditions of use - (twice a day 170,2 mg)		

GLOSSARY AND ABBREVIATIONS

BCAA Branched-chain amino acids