European Food Safety Authority

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of health claims related to glutamine and immune health (ID 733) and integrity of the intestinal lining and normal intestinal permeability (ID 1602) pursuant to Article 13(1) of Regulation (EC) No 1924/2006[1]

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

European Food Safety Authority (EFSA), Parma, Italy

SUMMARY

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies was asked to provide a scientific opinion on a list of health claims pursuant to Article 13 of Regulation 1924/2006. This opinion addresses the scientific substantiation of health claims in relation to glutamine and the following claimed effects: "immune health" and integrity of the intestinal lining and normal intestinal permeability. 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 glutamine (as L-glutamine). The Panel considers that glutamine (as L-glutamine), is sufficiently characterised.

Immune health

The claimed effect is not sufficiently defined and in the context of the proposed wording it refers to "support of the immune system" and "contribution to the immune function/response to exercises", which are also not sufficiently defined.

In weighing the evidence, the Panel took into account that the claimed effects are general and do not refer to any specific health claim as required by Regulation (EC) No 1924/2006; that the only intervention study on glutamine in relation to a clinical immune-related outcome, which indicated an effect of glutamine supplementation on reduced occurrence of infections post-exercise, had several methodological weaknesses i.e. self-reported infections and lack of clarity regarding completeness of reporting; that other intervention studies showed no or minor effects on laboratory parameters only, and that the cross-sectional data provides only limited evidence for a causal role of glutamine on the outcomes measured

On the basis of the data available, the Panel concludes that a cause and effect relationship has not been established between the consumption of L-glutamine and the claimed effects.

1 On request from the European Commission, Question No EFSA-Q-2008-1520, EFSA-Q-2008-2338, adopted on 02 July 2009.

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Integrity of the intestinal lining and normal intestinal permeability

The claimed effect "intestinal health" is not sufficiently defined but in the context of the proposed wording, the Panel assumes that the claimed effect refers to the aspects of: "promoting/maintaining integrity of the intestinal lining, preventing (increased) intestinal permeability". The Panel considers that maintaining integrity of the intestinal lining and normal intestinal permeability is beneficial to human health.

In weighing the evidence the Panel took into account that the rat and the *in vitro* studies provide limited evidence to support the claimed effect in humans, and that the results of two studies in patient populations cannot be extrapolated to the general population.

On the basis of the data available, the Panel concludes that a cause and effect relationship has not been established between the consumption of L-glutamine and maintaining integrity of the intestinal lining and normal intestinal permeability.

KEY WORDS

Glutamine, L-glutamine, immune, intestinal, permeability, health claims.

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The members of the Working Group on Claims: Jean-Louis Bresson, Albert Flynn, Marina Heinonen, Hannu Korhonen, Martinus Løvik, Ambroise Martin, Hildegard Przyrembel, Seppo Salminen, Sean (J.J.) Strain, Inge Tetens, Henk van den Berg, Hendrik van Loveren and Hans Verhagen.

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INFORMATION AS PROVIDED IN THE CONSOLIDATED LIST

The consolidated list of health claims pursuant to Article 13 of Regulation 1924/2006[3] submitted by Member States contains main entry claims with corresponding conditions of use and literature from similar health claims. The information provided in the consolidated list for the health claims subject to this opinion is given in Table 1.

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
733	Glutamine	Immune health	Supports the immune system is a vital nutrient for those cells requiring rapid renewal such as immune cells (e.g. lymphocytes) is an essential fuel for rapidly dividing cells, including those of the immune system supplementation contributes to immune function contributes to the immune response to the exercise.
	Conditions of use - 50-400 mg/kg per day		
	Food or Food constituent	**Health Relationship**	**Proposed wording**
1602	L-Glutamine	Intestinal health	Glutamine helps promote and maintain integrity of the intestinal lining. Glutamine may help prevent intestinal permeability. Glutamine may help support a healthy gastro-intestinal tract.
	Conditions of use - A stimulatory effect has been noted at high doses, some people may experience diarrhoea at high doses		

ASSESSMENT

1. Characterisation of the food/constituent

The food constituent that is the subject of the health claim is glutamine (as L-glutamine).

Glutamine is the most abundant naturally occurring amino acid in the human body. Dietary sources of L-glutamine include beef, chicken, fish, eggs, milk, dairy products, wheat, cabbage, beets, beans, spinach, and parsley. L-glutamine can be measured in foods by established methods.

The Panel considers that the food constituent, glutamine (as L-glutamine), which is the subject of the health claim is sufficiently characterised.

[3] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

2. Relevance of the claimed effect to human health

2.1. Immune health (ID 733)

The claimed effect is "immune health". The Panel assumes that the target population is sportsmen and sportswomen, and other members of the general population engaged in strenuous physical activities.

"Immune health" is not sufficiently defined. In the context of the proposed wording, the Panel assumes that the claimed effect refers to "support of the immune system" and "contribution to the immune function/response to exercise".

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

2.2. Integrity of the intestinal lining and normal intestinal permeability (ID 1602)

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

"Intestinal health" is not sufficiently defined. In the context of the proposed wording, the Panel assumes that the claimed effect refers to the aspects of "promoting/maintaining integrity of the intestinal lining, preventing (increased) intestinal permeability".

Maintenance of a normal epithelial barrier in the intestines and avoidance of excess intestinal permeability is required for normal intestinal function.

The Panel considers that maintaining integrity of the intestinal lining and normal intestinal permeability is beneficial to human health.

3. Scientific substantiation of the claimed effect

3.1. Immune health (ID 733)

Among the 55 references cited to substantiate the claimed effect, 38 were either general reviews or did report on outcomes other than immune function or immune system-related laboratory parameters (e.g. metabolic or muscle performance). The Panel notes that these references did not provide scientific data that could be used to substantiate the claimed effect. Of the remaining 17 studies on L-glutamine with immune system-related outcomes, nine are human interventions and eight are cross-sectional studies.

Human intervention studies

Castell et al. (1996) studied infections in men and women participating in various sport activities (marathon, ultra-marathon, mid-distance running and rowing) shown to be associated with increased incidence of infections after competition. Castell and Newsholme (1997) report on the same studies. On a double-blind basis, in altogether 8 separate series, athletes were either given 5 g L-glutamine (72 subjects) or placebo (maltodextrin, 79 participants) in two drinks immediately after and 2 hrs after strenuous exercise. In the glutamine group, 80.8±4.2% of subjects reported no infections during the next seven days, whereas in the placebo group only 48.8±7.4% of participants did ($p<0.001$). The Panel notes that the criteria for self-reported infections were not specified. Further, it is not clear from the papers whether the reporting was complete or whether there were any drop-outs.

Castell and Newsholme (1997) and Castell et al. (1997) also report on various immune cell and soluble mediator parameters. Whereas a significant difference in the $CD4^+/CD8^+$ (helper/suppressor) ratio was observed in one study between the glutamine and placebo groups (n=12), no differences were observed with regard to a number of cellular and soluble mediator parameters in the other study (n= 18).

Hiscock et al. (2003) studied eight healthy, highly trained men in a randomised, double-blind, crossover study and found that the normal increase in post-exercise IL-6 levels was further enhanced by glutamine supplementation. Krieger et al. (2004) studied 13 healthy runners given oral glutamine supplementation (0.1 g/kg) or placebo. Salivary IgA concentration and output were found to be unchanged by training and glutamine supplementation. In contrast, mean nasal IgA across the study period was significantly higher in runners receiving glutamine than in those receiving placebo. Krzywkowski et al. (2001) studied ten male athletes in a randomised, placebo-controlled, double-blind crossover study. Glutamine supplementation had no effect on a number of cellular parameters, except for a small reduction in exercise-induced neutrocytosis. Rohde et al. (1998a, 1998b) in two placebo-controlled intervention studies (16 runners and 8 cyclists, respectively) found no effect of glutamine supplementation on a number of lymphocyte subpopulations and functional parameters. Walsh et al. (2000) studied seven well-trained men who performed exercise in what appears to have been a placebo-controlled, crossover study. Glutamine supplementation had no effect on post-exercise leukocytosis or neutrophil function.

The Panel notes that, although glutamine supplementation generally prevented the fall in plasma glutamine concentrations during exercise, consistent effects on the immune system-related laboratory parameters measured were not observed. The Panel also notes that no scientific conclusions can be drawn for the substantiation of the claimed effect from the other five studies that used interventions other than glutamine, such as branched-chain amino acids (Bassit et al., 2000, 2002) and carbohydrate diet (Bacurau et al., 2002; Gleeson et al., 1998; Mitchell et al., 1998).

Cross-sectional studies

Bailey et al. (2003) reported on 55 high-altitude mountain climbers, and observed an association between severity of mountain sickness symptoms (n=10), symptoms of infection and plasma concentrations of glutamine. Hack et al. (1997) investigated healthy untrained subjects performing either aerobic or anaerobic exercise training programs for 8 weeks; the decrease in plasma concentrations of glutamine showed a strong positive correlation to the exercise-induced reduction in CD4+ T cells. Robson et al. (1999) studied 18 healthy cycling males and concluded that reductions in neutrophil function observed after exercise appear unrelated to the plasma glutamine concentration.

The Panel notes that human cross-sectional studies provide only limited evidence for a causal role of glutamine on the outcomes measured (co-variation).

In weighing the evidence, the Panel took into account that the claimed effects are general and do not refer to any specific health claim as required by Regulation (EC) No 1924/2006; that the only intervention study on glutamine in relation to a clinical immune-related outcome, which indicated an effect of glutamine supplementation on reduced occurrence of infections post-exercise, had several methodological weaknesses i.e. self-reported infections and lack of clarity regarding completeness of reporting; that other intervention studies showed no or minor effects on laboratory parameters only, and that the cross-sectional data provides only limited evidence for a causal role of glutamine on the outcomes measured .

The Panel concludes that a cause and effect relationship has not been established between the consumption of L-glutamine and “support of the immune system” and “contribution to the immune function/response to exercise”.

3.2. Integrity of the intestinal lining and normal intestinal permeability (ID 1602)

Six references were cited to substantiate the claimed effect.

Two randomised placebo-controlled intervention trials in breast cancer patients receiving chemotherapy (Li et al., 2006) and in patients after portal hypertension surgery (Tang et al., 2007), respectively, were provided. The Panel notes that the evidence provided does not establish that the results of these studies can be extrapolated to the general population.

One reference reports on an experimental study in rats receiving total parenteral nutrition (Li et al., 1994), and one reference describes an *in vitro* study on proliferation and protein kinases in intestinal epithelial cell lines (Rhoads et al., 1997). The Panel considers that the evidence provided in the animal and *in vitro* studies does not predict an effect of glutamine consumption on the claimed effect in humans.

One general review of L-glutamine and a second review on glutamine and the intestinal tract were cited. The Panel notes that no scientific conclusions can be drawn from these references for the substantiation of the claimed effect.

In weighing the evidence the Panel took into account that the rat and the *in vitro* studies provide limited evidence to support the claimed effect in humans, and that the results of two studies in patient populations cannot be extrapolated to the general population.

The Panel concludes that a cause and effect relationship has not been established between the consumption of L-glutamine and maintaining integrity of the intestinal lining and normal intestinal permeability.

CONCLUSIONS

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

- The food constituent, glutamine (as L-glutamine), which is the subject of the health claim is sufficiently characterised.

Immune health (ID 733)

- The claimed effect is "immune health". The target population is assumed to be sportsmen and sportswomen and other members of the general population engaged in strenuous physical activities. The claimed effects are general and non-specific and do not refer to any specific health claim as required by Regulation (EC) No 1924/2006.
- A cause-and-effect relationship has not been established between the consumption of L-glutamine and the claimed effects.

Integrity of the intestinal lining and normal intestinal permeability (ID 1602)

- The claimed effect is "intestinal health". The target population is assumed to be the general population. Maintaining integrity of the intestinal lining and normal intestinal permeability is beneficial to human health.
- A cause and effect relationship has not been established between the consumption of L-glutamine and maintaining integrity of the intestinal lining and normal intestinal permeability.

DOCUMENTATION PROVIDED TO EFSA

Health claims pursuant to Article 13 of Regulation (EC) No 1924/2006 (No: EFSA-Q-2008-1520, EFSA-Q-2008-2338). 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[4] (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[5]

Foods are commonly involved in many different functions[6] 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.

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,

[4] OJ L12, 18/01/2007
[5] The term 'food' when used in this Terms of Reference refers to a food constituent, the food or the food category.
[6] The term 'function' when used in this Terms of Reference refers to health claims in Article 13(1)(a), (b) and (c).

(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.