



EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Scientific Opinion on the substantiation of a health claim related to citrulline-malate and faster recovery from muscle fatigue after exercise pursuant to Article 13(5) of Regulation (EC) No 1924/2006

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to citrulline-malate and faster recovery from muscle fatigue after exercise pursuant to Article 13(5) of Regulation (EC) No 1924/2006¹

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)^{2,3}

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from Biocodex, submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Belgium, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to citrulline-malate and faster recovery from muscle fatigue after exercise. The Panel considers that citrulline-malate is sufficiently characterised. The claimed effect proposed by the applicant is “improved recovery from muscle fatigue”. Faster recovery from muscle fatigue by contributing to the restoration of muscle function after exercise is a beneficial physiological effect. The applicant identified, as being pertinent to the health claim, a total of 35 references, all of which, except for one human study and one animal study, were submitted by the applicant in a previous application for the same food and the same claim. No conclusions could be drawn from the animal study, which was carried out with citrulline only and not with citrulline-malate. The human study was concerned with blood lactate concentrations after exercise and did not assess muscle function. The evidence provided by the applicant did not establish that a faster reduction of blood lactate concentrations through a dietary intervention leads to faster recovery from muscle fatigue by contributing to the restoration of muscle function after exercise. No conclusions could be drawn from the human study for the scientific substantiation of the claim. A health claim on citrulline-malate and faster recovery from muscle fatigue after exercise has already been assessed by the Panel with an unfavourable outcome. The additional information submitted by the applicant did not provide evidence that could be used for the scientific substantiation of the claim.

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KEY WORDS

citrulline-malate, muscle function, physical exercise, muscle fatigue, health claims

¹ On request from the Competent Authority of Belgium following an application by Biocodex, Question No EFSA-Q-2013-00659, adopted on 9 April 2014.

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SUMMARY

Following an application from Biocodex, submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Belgium, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to citrulline-malate and faster recovery from muscle fatigue after exercise.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application included a request for the protection of proprietary data.

The food constituent that is the subject of the health claim is citrulline-malate, which is a mixture of L-citrulline and D,L-malic acid, forming a salt. The Panel considers that citrulline-malate is sufficiently characterised.

The claimed effect proposed by the applicant is “improved recovery from muscle fatigue”. The target population proposed by the applicant is healthy children above six years of age and adults. The Panel considers that faster recovery from muscle fatigue by contributing to the restoration of muscle function after exercise is a beneficial physiological effect.

The applicant identified a total of 35 references as being pertinent to the health claim. All of these references except for one human study and one animal study were submitted by the applicant in a previous application for the same food and the same claim, which was assessed by the Panel with an unfavourable outcome as there were no human studies from which conclusions could be drawn for the scientific substantiation of the claim.

The animal study was carried out with citrulline only and not with citrulline-malate, which is the subject of the health claim. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

The primary outcome of the human study was percent changes in blood lactate concentrations within 30 minutes after exercise. Secondary outcomes included blood lactate concentrations at other time points and perceived fatigue assessed by a non-validated self-rated questionnaire. Muscle function was not assessed.

The Panel considers that the evidence provided by the applicant does not establish that a faster reduction of blood lactate concentrations through a dietary intervention leads to faster recovery from muscle fatigue by contributing to the restoration of muscle function after exercise. The Panel considers that no conclusions can be drawn from this human study for the scientific substantiation of the claim.

A health claim on citrulline-malate and faster recovery from muscle fatigue after exercise pursuant to Article 13(5) of Regulation (EC) No 1924/2006 has already been assessed by the Panel with an unfavourable outcome. The additional information submitted by the applicant did not provide evidence that could be used for the scientific substantiation of the claim.

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BACKGROUND

Regulation (EC) No 1924/2006⁴ harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction of disease risk and to children's development and health) which are based on newly developed scientific evidence, or which include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3).

According to Article 18 of this Regulation, an application for inclusion in the Community list of permitted claims referred to in Article 13(3) shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

STEPS TAKEN BY EFSA

- The application was received on 11/07/2013.
- The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application included a request for the protection of proprietary data.
- On 08/08/2013, during the validation process of the application, EFSA sent a request to the applicant to provide missing information.
- On 03/09/2013, EFSA received the missing information as submitted by the applicant.
- The scientific evaluation procedure started on 24/09/2013.
- On 22/11/2013, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application and the clock was stopped on 03/12/2013, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
- On 17/12/2013, EFSA received the requested information and the clock was restarted, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
- During its meeting on 09/04/2014, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to citrulline-malate and faster recovery from muscle fatigue after exercise.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to: citrulline-malate and faster recovery from muscle fatigue after 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.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of citrulline-malate, a positive assessment of its safety, nor a decision on whether citrulline-malate is, or is not, classified as a foodstuff. 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 wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: Biocodex, 7 avenue Gallieni, 94250 Gentilly, France.

The application includes a request for the protection of proprietary data (Creff, 1982; Dauverchain, 1982; Fornaris et al., 1984; Vanuxem et al., 1986, 1990; Briand et al., 1986, 1992; Thuillier-Brustion et al., 1990, 1991; Verleye et al., 1995; Goubel et al., 1995a, 1995b, 1997; Bendahan et al., 1997, 2001, 2002; Moinard et al., 2008; Giannesini et al., 2009), in accordance with Article 21 of Regulation (EC) No 1924/2006.

Food/constituent as stated by the applicant

According to the applicant, the food is citrulline-malate, which is a mixture of L-citrulline and D,L-malic acid.

Health relationship as claimed by the applicant

According to the applicant, the consumption of citrulline-malate helps to relieve muscular fatigue.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: "Maintenance of ATP levels through reduction of lactates in excess for an improved recovery from muscle fatigue".

Specific conditions of use as proposed by the applicant

The applicant has proposed a daily intake of 2-3 g for children and 3-6 g for adults.

The target population is healthy children above six years of age and adults.

The applicant recommends that the citrulline-malate be diluted in a glass of water. Owing to the acidity of the product, citrulline-malate should be taken with meals. It should not be consumed during pregnancy and lactation. The duration of consumption should not exceed four weeks. If the feeling of weakness or fatigue persists, a doctor should be consulted.

ASSESSMENT

1. Characterisation of the food/constituent

The food constituent that is the subject of the health claim is citrulline-malate, which is a mixture of L-citrulline and D,L-malic acid (1:1), forming a salt.

According to the applicant, the starting materials for citrulline-malate are D,L-malic acid (provided by a supplier) and L-citrulline, which is obtained enzymatically from L-arginine by the applicant. D,L-Malic acid and L-citrulline are dissolved in purified water and mixed to yield a 50 % citrulline-malate solution, and packaged in ampoules. An alternative dosage form described by the applicant is an effervescent powder, supplied in sachets. Details on the manufacturing process, composition, batch-to-batch variability and stability information have been provided by the applicant. The content of citrulline-malate in foods can be measured by established methods.

L-Citrulline is a non-proteinogenic alpha-amino acid. It is an intermediate in the urea cycle, where it is made from L-ornithine and carbamoyl phosphate. Malate (L-malic acid) is a dicarboxylic hydroxyacid and an intermediate in the citric acid cycle where it is formed by hydration of fumarate. Malic acid contributes to the sour taste of fruits and is also used as a food additive (E 296).

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

2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant is “improved recovery from muscle fatigue”. The target population proposed by the applicant is healthy children above six years of age and adults.

Fatigue can be defined as the loss of peak force or power output. Faster recovery from muscle fatigue by contributing to the restoration of muscle function (e.g. muscle strength) in subsequent exercise bouts or sessions is a beneficial physiological effect. Outcome measures of muscle function are appropriate for the assessment of the claimed effect in humans (EFSA NDA Panel, 2012b).

The Panel considers that faster recovery from muscle fatigue by contributing to the restoration of muscle function after exercise is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

The applicant performed a literature search in PubMed and in the applicant’s own archives, using various combinations of the search terms “malate”, “malic acid”, “citrulline”, “human”, “lactate”, “ATP”, “NH₃”, “ammonium”, “energy”, “exercise”, “muscle”, “fatigue”, “weakness” and “tiredness”. Studies were excluded if they were published before 1990 (except for the studies claimed as proprietary by the applicant), had health outcomes not considered pertinent by the applicant for the claim, included a specific disease such as diabetes or kidney failure, or were concerned with mechanisms unrelated to fatigue.

The applicant identified a total of 35 references as being pertinent to the health claim. These included 19 human studies (Colin, 1972; Creff, 1972, 1982; Vallat, 1972; Commandré, 1973; Mande, 1978; Dauverchain, 1982; Fornaris et al., 1984; Taillade, 1984; Vanuxem et al., 1990; Callis et al., 1991; Bendahan et al., 1997, 2001, 2002; Moinard et al., 2008; Sureda et al., 2009, 2010; Pérez-Guisado and Jakeman, 2010; López-Cabral et al., 2012; López-Cabral, 2013, unpublished study report), six animal studies (Callis et al., 1991; Verley et al., 1995; Osowska et al., 2006; Giannesini et al., 2009; Giannesini et al., 2011; Takeda et al., 2011), seven *in vitro* studies (Briand et al., 1986, 1992; Thuillier-Brustion et al., 1990, 1991; Goubel et al., 1995a, b, 1997), and four reviews (Vanuxem et al., 1986; Rabier and Kamoun, 1995; Gibala et al., 1997; Curis et al., 2005). One of these references (Callis et al., 1991) reported on outcomes in humans and animals.

All the references above except for one human study (López-Cabral et al., 2012; López-Cabral, 2013, unpublished study report) and one animal study (Takeda et al., 2011) were submitted by the applicant in a previous application for the same food and the same claim, which was assessed by the Panel with an unfavourable outcome as there were no human studies from which conclusions could be drawn for the scientific substantiation of the claim (EFSA NDA Panel, 2012a).

The animal study (Takeda et al., 2011) was carried out with citrulline only and not with citrulline-malate, which is the subject of the health claim. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

The human study (López-Cabral et al., 2012; López-Cabral, 2013, unpublished study report) was a double-blind, randomised, placebo-controlled, parallel study in 72 athletes (age range 13-20 years) who were randomised to receive 3 g citrulline-malate (n = 25), 6 g citrulline-malate (n = 24) or a placebo (n = 23) for 13 days. The primary outcome of the study was percent changes in blood lactate concentrations within 30 minutes after exercise. Secondary outcomes included blood lactate concentrations at other time points and perceived fatigue assessed by a non-validated self-rated questionnaire. Muscle function was not assessed.

EFSA requested the applicant to clarify how this study, which did not include any direct measure of muscle function, could contribute to the scientific substantiation of the claim. The applicant argued that elevated blood lactate concentrations are associated with impaired muscle function and exercise

performance (Margaria et al., 1971; Hermansen and Stensvold, 1972; Belcastro and Bonen, 1975; Freund and Gendry, 1978; McGrail et al., 1978; Stamford et al., 1978; Stanley et al., 1986; Näveri et al., 1997; Grassi et al., 1999; Thomas et al., 2004; Goodwin et al., 2007; Ichiwata et al., 2010). The applicant also argued that subjects undergoing physical training to increase their aerobic capacity have lower blood lactate concentrations and a delayed onset of muscle fatigue during exercise (Karlsson and Jacobs, 1982; Kumagai et al., 1982; Hagberg and Coyle, 1983; Sjodin and Svedenhag, 1985; Jacobs, 1986; Taivassalo, 1996, 1998, 1999; Messonnier et al., 2006), as well as better physical performance at the “lactate threshold” (Hagberg and Coyle, 1983; Grant et al., 1997; Baldari et al., 2007; Lorenzo et al., 2011). The applicant also provided one human intervention study reporting that the administration of NaHCO₃ resulted in improved physical performance without altering blood lactate concentrations (Costill et al., 1984). The Panel considers that, while there is consensus on the contribution of training in reducing blood lactate concentrations during and after exercise and on delaying muscle fatigue during exercise, no evidence was provided that lowering blood lactate through a dietary intervention can prevent or alleviate loss of muscle function during exercise or can lead to a faster recovery from muscle fatigue by contributing to the restoration of muscle function after exercise.

The Panel considers that the evidence provided by the applicant does not establish that a faster reduction of blood lactate concentrations after exercise through a dietary intervention leads to faster recovery from muscle fatigue by contributing to the restoration of muscle function. The Panel also notes that there is no consensus on the role of lactate in the recovery from muscle fatigue (Allen and Westerblad, 2004; Cairns, 2006; Allen et al., 2008; Sola-Penna, 2008; Ament and Verkerke, 2009; Finsterer, 2012).

The Panel considers that no conclusions can be drawn from the human study (López-Cabral et al., 2012; López-Cabral, 2013, unpublished study report) for the scientific substantiation of the claim.

A health claim on citrulline-malate and faster recovery from muscle fatigue after exercise pursuant to Article 13(5) of Regulation (EC) No 1924/2006 has already been assessed by the Panel with an unfavourable outcome (EFSA NDA Panel, 2012a). The additional information submitted by the applicant did not provide evidence that could be used for the scientific substantiation of the claim.

CONCLUSIONS

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

- The food, citrulline-malate, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect proposed by the applicant is “improved recovery from muscle fatigue”. The target population proposed by the applicant is healthy children above six years of age and adults. Faster recovery from muscle fatigue by contributing to the restoration of muscle function after exercise is a beneficial physiological effect.
- A health claim on citrulline-malate and faster recovery from muscle fatigue after exercise pursuant to Article 13(5) of Regulation (EC) No 1924/2006 has already been assessed by the Panel with an unfavourable outcome. The additional information submitted by the applicant did not provide evidence that could be used for the scientific substantiation of the claim.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on citrulline-malate and faster recovery from muscle fatigue after exercise pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0394_BE). July 2013. Submitted by Biocodex.

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