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L-carnitine and contribution to normal lipid metabolism

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L-carnitine and contribution to normal lipid metabolism: evaluation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006

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Peter Willatts, Ambroise Martin, Sean (J.J.) Strain and Alfonso Siani

Abstract

Following an application from Lonza Ltd., submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Germany, 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 L-carnitine and normal lipid metabolism. The food that is proposed as the subject of the health claim is L-carnitine. The Panel considers that L-carnitine is sufficiently characterised. The claimed effect proposed by the applicant is 'normal lipid metabolism'. The target population proposed by the applicant is the general population. The Panel considers that contribution to normal lipid metabolism is a beneficial physiological effect. The applicant proposes that the claim submitted with this application is based on the essentiality of a nutrient. The Panel considers that the evidence provided does not establish that dietary L-carnitine is required to maintain normal lipid metabolism in the target population, for which the claim is intended. The Panel concludes that a cause and effect relationship has not been established between the consumption of L-carnitine and contribution to normal lipid metabolism in the target population.

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Keywords: L-carnitine, lipid metabolism, health claim

Requestor: Competent Authority of Germany following an application by Lonza Ltd.

Question number: EFSA-Q-2017-00564

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Summary

Following an application from Lonza Ltd., submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Germany, the European Food Safety Authority (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 L-carnitine and contribution to normal lipid metabolism.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence.

The general approach of the NDA Panel for the evaluation of health claims applications is outlined in the EFSA general guidance for stakeholders on health claim applications and the guidance on the scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health.

The food proposed by the applicant as the subject of the health claim is L-carnitine. The Panel considers that, the food/constituent, which is the subject of the health claim, L-carnitine, is sufficiently characterised.

The claimed effect proposed by the applicant is 'normal lipid metabolism'. The target population proposed by the applicant is the general population. The Panel considers that contribution to normal lipid metabolism is a beneficial physiological effect.

The applicant proposes that the claim submitted with this application is based on the essentiality of a nutrient.

The Panel acknowledges that L-carnitine is needed for the transport of long-chain fatty acids across the mitochondrial membrane, and therefore for their use as energy substrate. The Panel notes, however, that the human body is able to synthesise L-carnitine from methionine and lysine, and that there is consensus that L-carnitine is not an essential nutrient. No dietary reference values have been set for L-carnitine.

The Panel notes that L-carnitine is considered an indispensable nutrient for (both preterm and term) infants because of a temporarily insufficient synthesising capacity, and that this is the reason why a minimum L-carnitine content in infant formula has been established. The Panel also notes, however, that this insufficient capacity to synthesise carnitine cannot be extrapolated to any other subgroup of the general healthy population, for which the claim is intended.

Carnitine deficiency understood as clinical symptoms which can be corrected by carnitine administration has not been demonstrated in any other healthy population subgroup. In this context, the references submitted by the applicant on carnitine transporter deficiency syndromes do not provide evidence that dietary L-carnitine is required to maintain normal lipid metabolism in the target population for the claim (general healthy population); no evidence was provided that dietary carnitine could reverse the symptoms developed by the patient on long-term total parenteral nutrition and the supplementation studies with L-carnitine in healthy subjects do not provide information on whether dietary carnitine is required to maintain normal lipid metabolism (including normal fat oxidation), but rather on whether supplemental carnitine could modify the rate of fat oxidation under certain conditions. Therefore, the Panel considers that the evidence provided does not establish that dietary L-carnitine is required to maintain normal lipid metabolism in the target population for which the claim is intended.

On the basis of data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of L-carnitine and contribution to normal lipid metabolism in the target population.

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

Regulation (EC) No 1924/2006¹ 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 in 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).

1.2. Interpretation of the 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: L-carnitine and contribution to normal lipid metabolism.

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of L-carnitine, a positive assessment of its safety, nor a decision on whether L-carnitine 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.

2. Data and methodologies

2.1. Data

Information provided by the applicant

Food/constituent as stated by the applicant

According to the applicant, the food for which the health claim is made is L-carnitine. L-carnitine [(R)-(3-carboxy-2-hydroxypropyl) trimethylammonium hydroxide] is a zwitterionic quaternary ammonium compound generally present in many foods in highly varying quantities. A trivial name is levocarnitine. Only the L-isomer is biologically active. L-carnitine is present in biologic systems in both non-esterified (free) and esterified forms bound to either long-chain fatty acids (acylcarnitine) or to an acetyl group (acetylcarnitine). L-carnitine is essential for mammals to transport long-chain fatty acids into the mitochondria.

Health relationship as claimed by the applicant

According to the applicant, the claimed effect relates to: '(normal) lipid metabolism. L-carnitine is an endogenous substance in humans. It plays a fundamental biological role within lipid metabolism. Its function is that of an essential carrier for long-chain fatty acids from the cytosol through the inner mitochondrial membrane into the matrix, where beta-oxidation takes place. Therefore, L-carnitine is needed for (normal) lipid metabolism. L-carnitine is a conditionally essential nutrient. The claimed function in the human body is common knowledge. Therefore, outcome variables do not apply'.

¹ 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.

Mechanism by which the food/constituent could exert the claimed effect as proposed by the applicant

According to the applicant, L-carnitine is essential carrier for long-chain fatty acids across the mitochondrial membrane.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: 'L-carnitine contributes to normal lipid metabolism'. Equivalent alternatives are 'L-carnitine plays a role in lipid metabolism' or 'L-carnitine contributes to normal energy yielding metabolism'.

Specific conditions of use as proposed by the applicant

According to the applicant, the target population for the intended health claim is general population. The proposed daily dose of L-carnitine provided as pure L-carnitine or the equivalent amount of L-carnitine L-tartrate is 0.1–1 g per day via supplementation either in the form of food supplements or fortified foods such as protein shakes/powder, beverages and bars.

Data provided by the applicant

Health claim application on consumption of L-carnitine and normal lipid metabolism pursuant to Article 13.5 of Regulation 1924/2006, presented in a common and structured format as outlined in the Scientific and technical guidance for the preparation and presentation of applications for authorisation of health claims.²

As outlined in the General guidance for stakeholders on health claim applications,³ it is the responsibility of the applicant to provide the totality of the available evidence.

The application does not include a request for data propriety and confidentiality.

2.2. Methodologies

The general approach of the Dietetic Products, Nutrition and Allergies (NDA) Panel for the evaluation of health claim applications is outlined in the EFSA general guidance for stakeholders on health claim applications (EFSA NDA Panel, 2016).

The scientific requirements for health claims related to antioxidants, oxidative damage and cardiovascular health are outlined in a specific EFSA guidance (EFSA NDA Panel, 2011a).

3. Assessment

3.1. Characterisation of the food/constituent

The food proposed by the applicant as the subject of the health claim is L-carnitine.

Carnitine is a quaternary ammonium salt synthesised primarily in the liver and kidneys from amino acids, lysine and methionine. In living cells, carnitine is required for the transport of fatty acids from the cytosol into the mitochondria for beta-oxidation. L-carnitine is the form commonly used in food supplements. The content of L-carnitine in foods can be measured by established methods (EFSA NDA Panel, 2011b).

The Panel considers that the food/constituent which is the subject of the health claim, L-carnitine, is sufficiently characterised.

3.2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant is 'normal lipid metabolism'. The target population proposed by the applicant is the general population.

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

² EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), Turck D, Bresson J-L, Burlingame B, Dean T, Fairweather-Tait S, Heinonen M, Hirsch-Ernst KI, Mangelsdorf I, McArdle HJ, Naska A, Neuhäuser-Berthold M, Nowicka G, Pentieva K, Sanz Y, Sjödin A, Stern M, Tomé D, Van Loveren H, Vinceti M, Willatts P, Martin A, Strain JJ, Heng L, Valtuena Martinez S and Siani A, 2017. Scientific and technical guidance for the preparation and presentation of a health claim application (Revision 2). EFSA Journal 2017;15(1):4680, 31 pp. <https://doi.org/10.2903/j.efsa.2017.4680>.

³ EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2016. General scientific guidance for stakeholders on health claim applications. EFSA Journal 2016;14(1):4367, 38 pp. <https://doi.org/10.2903/j.efsa.2016.4367>

3.3. Scientific substantiation of the claimed effect

The EFSA NDA Panel has issued an opinion on a health claim related to L-carnitine and maintenance of normal blood Low-density lipoprotein (LDL)-cholesterol concentrations pursuant to Article 13(1) of Regulation (EC) No 1924/2006 with an unfavourable outcome (EFSA NDA Panel, 2011b). The unfavourable opinion was based on: a) the lack of a sustained effect of L-carnitine consumption on blood cholesterol concentrations in humans; b) the impossibility to extrapolate the effect observed in rats and rabbits to humans because of major differences in lipid metabolism between species and c) the lack of evidence provided for a mechanism by which L-carnitine could exert the claimed effect in humans. This claim was evaluated by the Panel as a claim NOT based on the essentiality of nutrients.

The applicant proposes that the claim submitted with this application is based on the essentiality of a nutrient. As stated in the general scientific guidance for stakeholders on health claim applications (EFSA NDA Panel, 2016), the scientific substantiation of claims based on the essentiality of a nutrient is determined by: i) the nutrient is required for normal human body function(s), i.e. it has an essential mechanistic role in a metabolic function and/or it has the ability to reverse clinical signs and symptoms of its deficiency; ii) the nutrient cannot be synthesised by the body or cannot be synthesised in amounts which are adequate to maintain normal body function(s) and iii) the nutrient must be obtained from a dietary source.

Pertinent publications were identified through a large collection of scientific publications compiled by the applicant since 1986, permanently updated through a weekly search alert set in PubMed including the key word carnitine, among others.

The Panel acknowledges that L-carnitine is needed for the transport of long-chain fatty acids across the mitochondrial membrane, and therefore for their use as energy substrate. The Panel notes, however, that the human body is able to synthesise L-carnitine from methionine and lysine, and that there is consensus that L-carnitine is not an essential nutrient (IoM, 1989). No dietary reference values have been set for L-carnitine.

The applicant claims that L-carnitine becomes conditionally indispensable under certain circumstances, such as in some genetic disorders such as carnitine transporter deficiency syndromes (Longo et al., 2006; Glenn and Gardner, 2007; Flanagan et al., 2010; Magoulas and El-Hattab, 2012), that a case of carnitine deficiency after long-term total parenteral nutrition (TPN) has been reported in the literature (Buchman et al., 1992) and that oral supplementation of L-carnitine increases fat oxidation in healthy subjects (Müller et al., 2002; Wutzke and Lorenz, 2004). The applicant also claims that some abnormalities related to lipid metabolism (e.g. lower fatty acid concentration, higher acetoacetate and β -hydroxybutyrate concentrations) were present in a group of infants receiving carnitine-free parenteral nutrition shortly after birth (Christensen et al., 1989), and that L-carnitine is mandatory in infant formula (Regulation (EU) No 609/2013).⁴

The Panel notes that L-carnitine is considered an indispensable nutrient for (both preterm and term) infants because of a temporarily insufficient synthesising capacity, and that this is the reason why a minimum L-carnitine content in infant formula has been established (EFSA NDA Panel, 2014). The Panel also notes, however, that this insufficient capacity to synthesise carnitine cannot be extrapolated to any other subgroup of the general healthy population, for which the claim is intended.

Carnitine deficiency, understood as clinical symptoms (rather than 'low' or 'abnormal' circulating concentrations of carnitine, fatty acids or their metabolites) which can be corrected by carnitine administration has not been demonstrated in any other healthy population subgroup (Rebouche, 1992). In this context, the references submitted by the applicant on carnitine transporter deficiency syndromes do not provide evidence that dietary L-carnitine is required to maintain normal lipid metabolism in the target population for the claim (general healthy population); no evidence was provided that dietary carnitine could reverse the symptoms developed by the patient on long-term TPN (Buchman et al., 1992); and the supplementation studies with L-carnitine in healthy subjects do not provide information on whether dietary carnitine is required to maintain normal lipid metabolism (including normal fat oxidation), but rather on whether supplemental carnitine could modify the rate of

⁴ Commission Regulation (EU) No 609/2013 of the European Parliament and of the Council of 12 June 2013 on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control and refeeding. Council Directive 92/52/EEC, Commission Directives 96/8/EC, 1999/21/EC, 2006/125/EC and 2006/141/EC, Directive 2009/39/EC of the European Parliament and of the Council and Commission Regulations (EC) No 41/2009 and (EC) No 953/2009, Text with EEA relevance. OJ L 181 29.6.2013 p. 35–56.

fat oxidation under certain conditions. Therefore, the Panel considers that the evidence provided does not establish that dietary L-carnitine is required to maintain normal lipid metabolism in the target population, for which the claim is intended.

The Panel concludes that a cause and effect relationship has not been established between the consumption of dietary L-carnitine and contribution to normal lipid metabolism in the target population.

4. Conclusions

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

- The food/constituent, L-carnitine, is sufficiently characterised.
- The claimed effect proposed by the applicant is 'normal lipid metabolism'. The target population proposed by the applicant is 'general population'. Contribution to normal lipid metabolism is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of L-carnitine and contribution to normal lipid metabolism.

Steps taken by EFSA

Health claim application on 'L-carnitine and normal lipid metabolism' pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0460_DE). Submitted by Lonza Ltd., Münchensteinerstrasse 38, 4002 Basel, Switzerland. The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence.

- 1) This application was received by EFSA on 13/7/2017.
- 2) The scientific evaluation procedure started on 2/8/2017.
- 3) On 6/9/2017, 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. The scientific evaluation was suspended on 22/9/2017 and was restarted on 6/10/2017, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
- 4) On 6/10/2017, EFSA received the applicant's reply (which was made available to EFSA in electronic format on 6/10/2017).
- 5) On 13/12/2017, the NDA Panel, having evaluated the data submitted, adopted by written procedure an opinion on the scientific substantiation of a health claim related to L-carnitine and normal lipid metabolism.

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Abbreviations

- LDL Low-density lipoprotein
NDA EFSA Panel on Dietetic Products, Nutrition and Allergies
TPN total parenteral nutrition