European Food Safety Authority

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SCIENTIFIC OPINION

Lycopene-whey complex (bioavailable lycopene) and risk of atherosclerotic plaques

Scientific substantiation of a health claim related to Lycopene-whey complex (bioavailable lycopene) and reduction of the risk of atherosclerotic plaques pursuant to Article 14 of Regulation (EC) No 1924/2006[1]

Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies

(Question No EFSA-Q-2008-703)

Adopted on 2 July 2009

PANEL MEMBERS

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SUMMARY

Following an application from Cambridge Theranostics Ltd. submitted pursuant to Article 14, of Regulation (EC) No 1924/2006 via the Competent Authority of United Kingdom, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to lycopene-whey complex (bioavailable lycopene) and reduction of the risk of atherosclerotic plaques.

The scope of the application was proposed to fall under a health claim referring to disease risk reduction.

The food constituent that is the subject of the health claim is a lycopene-whey complex (bioavailable lycopene). Lycopene-whey complex is prepared using a patented process by mixing tomato extract containing 10% lycopene with whey protein to form a granulated product. The amount of the active constituent, lycopene, is 2% in the final product. The lycopene-whey complex has been shown to have bioavailability similar to tomato paste in human subjects.

[1] For citation purposes: Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies on a request from Cambridge Theranostics Ltd. on the scientific substantiation of a health claim related to lycopene-whey complex (bioavailable lycopene). *The EFSA Journal* (2009) 1179, 1-10

The Panel considers that this substantiation applies to all lycopene sources of similar bioavailability. The Panel considers that the food constituent "lycopene" which is the subject of the health claim is sufficiently characterized.

The claimed effect is "prevents oxidative damage of plasma lipoproteins, which reduces the build up of arterial plaques and reduces the risk of heart disease, stroke and other clinical complications of atherosclerosis". The target population is adults.

The Panel considers that the evidence provided does not establish that the claimed effect, the prevention of oxidation of plasma lipoproteins, is beneficial to human health by reducing the risk of atherosclerotic diseases.

The applicant identified 80 publications as pertinent to the relationship between the consumption of the food/constituent and the claimed effect. Six of the studies were experimental intervention studies, 22 were observational studies, 44 were other human studies, and there were eight reviews.

In four of the six human intervention studies, *ex vivo* lipoprotein oxidisability or oxidised serum LDL were measured as the primary outcomes, endpoints which have not been established to be independent predictors of risk of atherosclerotic diseases. In addition the Panel notes various other limitations of the four studies. The Panel considers that the other two human intervention studies did not measure specific markers of oxidative damage of plasma lipoproteins and do not provide evidence for the claimed effect.

The 22 observational studies presented address the association between either dietary intake of tomato/lycopene or serum concentrations of lycopene and incident myocardial infarction, stroke or arterial plaque development assessed as intima-media thickness, incident new plaque or aortic sclerosis. The Panel considers that these studies do not establish a relationship between the intake of lycopene and the oxidation of plasma lipoproteins, or between the oxidation of plasma lipoproteins and the incidence/progression of atherosclerosis.

The 44 other human studies describe mechanistic effects of lycopene, tomato products, carotenoids, antioxidants in general, or bioavailability of lycopene. The Panel considers that the evidence provided does not establish that lycopene can reduce oxidative damage of plasma lipoproteins *in vivo*.

In weighing the evidence the Panel took into account the limitations of the intervention studies, i.e. the primary endpoints measured have not been established to be independent predictors of risk of atherosclerotic diseases, the higher doses used in some studies compared to those in the conditions of use proposed by the applicant, the small number of subjects, the short duration of studies and/or lack of controls in the study design, and the performance of some studies in patients for whom it was not established that the results can be extrapolated to the general population, as well as the limited evidence from observational and other human studies.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of lycopene and the claimed effect.

Key words: lycopene, lipoprotein oxidisability, atherosclerotic plaques, atherosclerosis, health claim.

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BACKGROUND

Regulation (EC) No 1924/2006[2] 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 that Regulation and are authorised in accordance with this Regulation and included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Articles 14 to 17 of that Regulation lay down provisions for the authorisation and subsequent inclusion of reduction of disease risk claims and claims referring to children's development and health in a Community list of permitted claims.

According to Article 15 of that Regulation, an application for authorisation shall be submitted by the applicant to the national competent authority of a Member State, who will make the application and any supplementary information supplied by the applicant available to European Food Safety Authority (EFSA).

Steps taken by EFSA:

- The application was received on 6/10/2008.
- The scope of the application was proposed to fall under a health claim referring to disease risk reduction.
- During the check for completeness[3] of the application, the applicant was requested to provide missing information on 13/11/2008.
- The applicant provided the missing information on 13/03/2009.
- The scientific evaluation procedure started on 15/03/2009.
- During the meeting on 2/07/2009, the NDA Panel, after having evaluated the overall data submitted, adopted an opinion on the scientific substantiation of a health claim related to lycopene-whey complex and the risk of atherosclerotic plaques.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16 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: lycopene-whey complex and "prevents oxidative damage of plasma lipoproteins, which reduces the build up of arterial plaques and reduces the risk of heart disease, stroke and other clinical complications of atherosclerosis".

[2] European Parliament and Council (2006). 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. Official Journal of the European Union OJ L 404, 30.12.2006. Corrigendum *OJ L 12, 18.1.2007, p. 3–18.*

[3] In accordance with EFSA "Scientific and Technical guidance for the Preparation and Presentation of the Application for Authorisation of a Health Claim"

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of lycopene-whey complex, a positive assessment of its safety, nor a decision on whether lycopene-whey complex 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 authorization procedure foreseen in Article 17 of Regulation (EC) No 1924/2006.

ACKNOWLEDGEMENTS

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1. Information provided by the applicant

Applicant's name and address: Cambridge Theranostics Limited, Babraham Research Campus, Babraham, Cambridge CB22 3AT, UK

The application includes proprietary data.

1.1. Food/constituent as stated by the applicant

Lycopene-whey complex (bioavailable lycopene) prepared by mixing tomato extract with whey protein.

1.2. Health relationship as claimed by the applicant

Atherosclerosis (clogging of the arteries) is caused by a build up of oxidatively damaged lipoproteins. Lycopene-whey complex prevents this oxidative damage of plasma lipoproteins, which reduces the build up of arterial plaques and thus reduces the risk of heart disease, stroke, and other clinical complications of atherosclerosis.

1.3. Wording of the health claim as proposed by the applicant

Lycopene-whey complex prevents oxidative damage of plasma lipoproteins, which reduces the build up of arterial plaques and reduces the risk of heart disease, stroke and other clinical complications of atherosclerosis.

1.4. Specific conditions of use as proposed by the applicant

Lycopene-whey complex is for all adults who wish to reduce their risk of atherosclerosis. Only those with intolerance of tomato or whey protein should not take it. It is suggested that 1-2 capsules, tablets, or a sachet of powder (containing a total of 6 – 16 mg lycopene) is taken per day.

2. Assessment

2.1. Characterisation of the food/constituent

The food constituent that is the subject of the health claim is a lycopene-whey complex (bioavailable lycopene). Lycopene-whey complex is prepared using a patented process by mixing tomato extract containing 10% lycopene with whey protein to form a granulated product. The manufacturing process is clearly described. The amount of the active constituent, lycopene, is 2% in the final product as demonstrated in batch to batch analyses (2.3-2.4%, n=10). Analytical specifications including content of lycopene, heavy metals, residual organic solvents, and microbes are given. The stability (up to 54 months) tests of the 2% lycopene-whey complex indicate no significant variation in lycopene content.

The lycopene-whey complex has been shown to have bioavailability similar to tomato paste in human subjects (Richelle et al., 2002, proprietary data as claimed by the applicant).

The Panel considers that this opinion applies to all lycopene sources of similar bioavailability

The Panel considers that the food constituent 'lycopene' which is the subject of the health claim is sufficiently characterised.

2.2. Relevance of the claimed effect to human health

The claimed effect is "prevents oxidative damage of plasma lipoproteins, which reduces the build up of arterial plaques and reduces the risk of heart disease, stroke and other clinical complications of atherosclerosis". The target population is adults.

Atherosclerosis, a main cause of cardiovascular disease, is a major cause of mortality and morbidity in the world. Atherosclerosis has a multifactorial aetiology and many potential risk factors have been identified (Mensink et al., 2003). Although oxidation of plasma lipoproteins has been proposed to play a role in atherogenesis, the evidence provided does not establish that plasma lipoprotein oxidation is an independent predictor of the development of atherosclerotic diseases.

The Panel considers that the evidence provided does not establish that the claimed effect, the prevention of oxidation of plasma lipoproteins, is beneficial to health by reducing the risk of atherosclerotic diseases.

2.3. Scientific substantiation of the claimed effect

The applicant performed a literature search using PubMed [MEDLINE] database with the following inclusion criteria: relationship of dietary input of tomato or lycopene or plasma, serum or lipid lycopene to lipoprotein oxidation and the risk of developing cardiovascular disease, coronary heart disease (CHD) or stroke, and exclusion criteria: no clinical end-point, other diseases, other products, other factors, post-event observations, *in vitro* biochemical analyses, non-human studies.

The applicant identified 80 publications as being pertinent to the health claim. Four of the studies were experimental human intervention studies with full randomization (Agarwal and Rao, 1998; Bose and Agrawal, 2007; Bub et al., 2000; Rao and Shen, 2002), two were non-controlled human unpublished studies (Dovgalevsky and Petyaev, 2007, 2008, both proprietary), 22 were observational studies, 44 were other human studies, and eight were reviews.

In four of the six human intervention studies provided (Agarwal and Rao, 1998, Bub et al., 2000 , Dovgalevsky and Petyaev, 2007, 2008) *ex vivo* lipoprotein oxidisability or oxidised serum LDL were measured as the primary outcomes, endpoints which have not been established to be independent predictors of risk of atherosclerotic diseases. In a randomized, cross-over study by Agarwal and Rao (1998), 19 healthy subjects (25-40 years) consumed either spaghetti sauce (39.2 mg lycopene), tomato juice (50.4 mg lycopene), or lycopene oleoresin from tomatoes (75.0 mg lycopene) for one week and in a short-term feeding study by Bub et al. (2000), 23 non-smoking men (27-40 years) consumed tomato juice (40 mg lycopene) for two weeks. In the two non-controlled prospective, open-label studies (Dovgalevsky and Petyaev, 2007, 2008) 2% lycopene-whey complex was given either as powder (6 or 16 mg lycopene) or as Ateronon® capsules (7 mg lycopene) for a duration of eight weeks to groups of

4-10 patients with diagnosed CHD (45-70 years). The evidence provided does not establish that the results observed in the CHD patients can be extrapolated to the general population.

The Panel notes the limitations of the four studies, i.e. use of *ex vivo* measurements of LDL oxidisability or oxidised serum LDL as primary outcome measures, endpoints which have not been established to be independent predictors of risk of atherosclerotic diseases, the doses used in some studies were higher than those in the conditions of use proposed by the applicant, the small number of subjects , the short duration and/or lack of controls in the study design and the performance of the two proprietary studies in CHD patients for whom it was not established that the results can be extrapolated to the general population.

The other two human intervention studies provided by the applicant (Bose and Agrawal, 2007; Rao and Shen, 2002) measured the effect of tomato products on oxidised lipids and/or protein in plasma but did not measure oxidised LDL or LDL oxidisability. The Panel considers that these studies do not provide evidence for the claimed effect (reduced oxidative damage of plasma lipoproteins).

The 22 observational studies presented address the association between either dietary intake of tomato/lycopene or serum concentrations of lycopene and incident myocardial infarction, stroke or arterial plaque development assessed as intima-media thickness, incident new plaque or aortic sclerosis. The Panel considers that these studies do not establish a relationship between the intake of lycopene and the oxidation of plasma lipoproteins, or between the oxidation of plasma lipoproteins and the incidence/progression of atherosclerosis.

The 44 other human studies describe mechanistic effects of lycopene, tomato products, carotenoids, antioxidants in general, or bioavailability of lycopene. The Panel considers that the evidence provided does not establish that lycopene can reduce oxidative damage of plasma lipoproteins *in vivo.*

In weighing the evidence the Panel took into account the limitations of the intervention studies, i.e. the primary endpoints measured have not been established to be independent predictors of risk of atherosclerotic diseases, the higher doses used in some studies compared to those in the conditions of use proposed by the applicant, the small number of subjects, the short duration of studies and/or lack of controls in the study design, and the performance of the two proprietary studies in CHD patients for whom it was not established that the results can be extrapolated to the general population, as well as the limited evidence in support of the claimed effect from observational and other human studies.

The Panel concludes that a cause and effect relationship has not been established between the consumption of lycopene and the claimed effect "prevents oxidative damage of plasma lipoproteins, which reduces the build up of arterial plaques and reduces the risk of heart disease, stroke and other clinical complications of atherosclerosis".

CONCLUSIONS

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

- The food constituent “lycopene” which is the subject of the claim is sufficiently characterised.

- The claimed effect is "prevents oxidative damage of plasma lipoproteins, which reduces the build up of arterial plaques and reduces the risk of heart disease, stroke and other clinical complications of atherosclerosis". The target population is adults. The Panel considers that the applicant has not provided any evidence that the prevention of oxidation of plasma lipoproteins is beneficial to human health by reducing the risk of atherosclerotic diseases.
- A cause and effect relationship has not been established between the consumption of lycopene and the claimed effect.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on lactolycopene and reduction the risk of atherosclerotic plaques pursuant to Article 14 of Regulation (EC) No 1924/2006 Claim serial No: 0222-UK Oct 2008 submitted by Cambridge Theranostics Limited.

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GLOSSARY / ABBREVIATIONS

CHD	Coronary hearth disease
LDL	Low density lipoprotein
LPS	Lipopolysaccharide
oxLDL	Oxidized LDL
TBARS	Thiobarbituric acid-reactive substances