

SCIENTIFIC OPINION

Danacol[®] and blood cholesterol

Scientific substantiation of a health claim related to a low fat fermented milk product (Danacol[®]) enriched with plant sterols/stanols and lowering/reducing blood cholesterol and reduced risk of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006¹

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

(Question No EFSA-Q-2008-779)

Adopted on 02 July 2009

This opinion, published on 19 August 2009, replaces the earlier version published on 4 August 2009².

PANEL MEMBERS*

Jean-Louis Bresson*, Albert Flynn*, Marina Heinonen, Karin Hulshof, Hannu Korhonen, Pagona Lagiou, Martinus Løvik, Rosangela Marchelli, Ambroise Martin*, Bevan Moseley, Hildegard Przyrembel, Seppo Salminen, Sean (J.J.) Strain*, Stephan Strobel, Inge Tetens, Henk van den Berg, Hendrik van Loveren and Hans Verhagen.

SUMMARY

Following an application from Danone France, submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of France, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to “phytosterols” and “lowering/reducing blood cholesterol and reducing the risk of coronary heart disease”.

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

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* Three members of the Panel did not participate in the discussion on the subject referred to above because of possible conflicts of interest.

² The version of 4 August 2009 did not indicate that Jean-Louis Bresson had been excluded from the discussion because of possible conflicts of interest. The version of 31 July 2009 replaced by the version of 4 August 2009 did not include panel experts which were excluded from the discussion because of possible conflicts of interest.

The food constituent that is subject of the proposed claim is a low fat fermented milk product (Danacol®) enriched with plant sterols/stanols (phytosterols). The active ingredients, the phytosterols esters, are of plant oil origin and are a mixture of β -sitosterol ≤ 80 %, campesterol ≤ 40 %, stigmasterol ≤ 30 %, β -sitostanol ≤ 15 %, campestanol ≤ 5 %, brassicasterol ≤ 3 % and other phytosterols ≤ 3 %. The phytosterols are esterified with fatty acids of vegetable origin. Data from published Danacol studies indicate a content of approximately 75 - 80 % β -sitosterol and 8.4 - 10 % campesterol. This profile is comparable to a mixture of phytosterols of a previous health claim application assessed by the European Food Safety Authority. The Panel considers that the phytosterols for which the health claim is proposed have been sufficiently characterised.

Elevated low-density lipoprotein (LDL) blood cholesterol is one recognised risk factor for coronary heart disease (CHD). CHD is an important cause of mortality and morbidity. Lowering LDL-cholesterol by dietary intervention has been shown to reduce the risk of coronary heart disease. The target population are adults with mildly raised LDL blood cholesterol concentration.

The Panel considers that the claimed effect of lowering LDL-cholesterol is beneficial to human health.

The application contains 23 publications, 19 controlled human studies, 1 uncontrolled human study, and 3 meta-analyses on the LDL-cholesterol lowering effect of phytosterols. In addition, the applicant provided 2 unpublished meta-analyses.

On the basis of the data presented, a biological significant LDL-cholesterol lowering effect can be achieved by a daily intake of 1.6 g phytosterols added to low fat fermented milk products. The size of the effect is comparable to that of plant sterols and plant stanols added to foods such as margarine-type spreads, mayonnaise, salad dressings, and dairy products such as milk, yoghurts and cheese, as discussed in the EFSA opinion on plant sterols/stanols and lowering/reducing blood LDL-cholesterol.

The Panel concludes that a cause and effect relationship has been established between the dietary intake of phytosterols and lowering of LDL-cholesterol.

The Panel considers that the following wording reflects the available scientific evidence: “Phytosterols have been shown to lower/reduce blood cholesterol. High blood cholesterol is a risk factor in the development of coronary heart disease”.

The Panel considers that phytosterols should be consumed only by people who need and want to lower their blood cholesterol and that patients on cholesterol-lowering medication should only consume the product under medical supervision.

Key words: Plant stanols, plant sterols, phytosterols, coronary heart disease, LDL, blood cholesterol

TABLE OF CONTENTS

Panel Members.....	1
Summary	1
Table of Contents	3
Background	4
Terms of reference	4
EFSA Disclaimer	4
Acknowledgements	5
1. Information provided by the applicant	6
1.1 Food/constituent as stated by the applicant	6
1.2 Health relationship as claimed by the applicant	6
1.3 Wording of the health claim as proposed by the applicant.....	6
1.4 Specific conditions of use as proposed by the applicant	6
1.5 Similar claims as proposed/authorized by other entities	6
2. Assessment	7
2.1 Characterisation of the food/constituent.....	7
2.2 Relevance of the claimed effect to human health	7
2.3 Scientific substantiation of the claimed effect	7
2.4 Panel's comments on the proposed wording	9
2.5 Conditions and restrictions of use	9
Conclusions and Recommendations	10
Documentation provided to EFSA	10
References	10

BACKGROUND

Regulation (EC) No 1924/2006³ 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 16/12/2008.
- The scope of the application was proposed to fall under a health claim referring to disease risk reduction including a request for the protection of proprietary data in accordance with Article 21 of Regulation (EC) No 1924/2006.
- Following the meeting of the Standing Committee on the Food Chain and Animal Health (SCFCAH) - General food law on 20 February 2009 when the Standing Committee adopted its decision on phytosterols and their cholesterol lowering effect, Member State France confirmed in a letter received by EFSA on 30/03/2009 that EFSA should conduct an evaluation of Danacol®.
- The scientific evaluation procedure started on 15/04/2008.
- During the meeting on 02/07/2009, the NDA Panel, after having evaluated the overall data submitted, adopted an opinion on the scientific substantiation of a health claim related to "Phytosterols" and "lowering/reducing blood cholesterol and reducing the risk of coronary heart disease".

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: a low fat fermented milk product (Danacol®) enriched with plant sterols/stanols and lowering/reducing blood cholesterol and reduced risk of (coronary) heart disease"

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of phytosterols, a positive assessment of its safety, nor a decision on whether

³ 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.

phytosterols are, or are 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 for use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation 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: Danone France - 150 bd Victor Hugo, 93589 Saint-Ouen Cedex.

The application includes a request for the protection of proprietary data in accordance with Article 21 of Regulation (EC) No 1924/2006.

The applicant claimed proprietary rights for the information provided in the dossier on specification, manufacturing process, stability information, bioavailability data, studies with Danacol® and two unpublished meta-analyses conducted by the applicant.

1.1 Food/constituent as stated by the applicant

Low fat fermented milk product (drink and spoonable product) (Danacol®) enriched with plant sterols/stanols (phytosterols).

1.2 Health relationship as claimed by the applicant

Danacol® containing phytosterols reduces LDL-cholesterol, a recognised risk factor of coronary heart disease.

1.3 Wording of the health claim as proposed by the applicant

Danacol® reduces LDL-cholesterol by 10 % in 3 weeks, and the reduction is maintained with daily consumption. High blood cholesterol is one of the main risk factors in the development of (coronary) heart disease.

1.4 Specific conditions of use as proposed by the applicant

The target population for the product and for the claim is the population subgroup with mildly raised blood cholesterol concentration and which needs to lower it.

The product should be consumed so as to provide 1.6 g phytosterols per day. The phytosterol content of Danacol® products can be either 1.6 g or 0.8 g per serving. As of the date of submission of this application, the existing products on the European market contain 1.6 g per serving (drinkable or spoonable), except in France, where the spoonable product contains 0.8 g per serving. In the latter case, the recommendation is therefore to consume two servings a day, to achieve 1.6 g of phytosterols. It is recommended that consumption of Danacol® should take into account intake of any other foods enriched with phytosterols.

To prevent a cholesterol increase, people should consume the product daily and should continue to consume the plant sterol-enriched product daily over time.

The product may not be appropriate for pregnant and breastfeeding women and children under the age of five years. Patients on cholesterol lowering medication should only consume the product under medical supervision.

1.5 Similar claims as proposed/authorized by other entities

The applicant provided approval letters which indicate that Brazil and the Joint Health Claim Initiative of the United Kingdom have approved cholesterol lowering claims on Danacol®.

2. Assessment

2.1 Characterisation of the food/constituent

Danacol® products are marketed as drinkable and spoonable yogurts. 100 g (= 1 serving size) of the drinkable yogurt contains 0.6 g fat and 1.6 g phytosterols. The spoonable version contains 0.3 g fat/ 100 g. One serving size (125 g) in the European market contains 1.6 g phytosterols with the exception of France where it contains 0.8 g phytosterols.

The active ingredients, phytosterols esters, are of plant oil origin and are a mixture of β -sitosterol ≤ 80 %, campesterol ≤ 40 %, stigmasterol ≤ 30 %, β -sitostanol ≤ 15 %, campestanol ≤ 5 %, brassicasterol ≤ 3 % and other phytosterols ≤ 3 %. The phytosterols are esterified with fatty acids of vegetable origin. Data from published Danacol studies indicate a content of approximately 75 – 80 % β -sitosterol and 8.4 – 10 % campesterol. The Panel considers that the claimed effect is attributed to phytosterols added to a low fat yogurt. Throughout this opinion, “phytosterols” refers to a mixture of plant sterol and stanol esters which is the subject of this application, and the quantities of phytosterols are expressed as the equivalent weights of free (i.e. un-esterified) phytosterols.

The Panel considers that the phytosterols, subject to this application, have been sufficiently characterised.

2.2 Relevance of the claimed effect to human health

The claimed effect is “ reduces LDL-cholesterol, a recognised risk factor of coronary heart disease”. The target population are adults with mildly raised LDL blood cholesterol concentration.

Coronary heart disease (CHD) is a leading cause of mortality and morbidity in European populations with over 1.9 million deaths in the European Union and over 4.35 million deaths in Europe each year (Pedersen *et al.*, 2005). Elevated blood cholesterol is an important modifiable risk factor in the development of CHD (WHO, 2002b).

It has been shown that blood cholesterol can be decreased by drugs and by dietary and lifestyle changes (Denke, 2005; Gordon, 2000; Katan, *et al.*, 2003; Law, 2000; Ornish *et al.*, 1998; van Horn *et al.*, 2008).

The Panel considers that lowering LDL-cholesterol is beneficial to human health by decreasing the risk of coronary heart disease.

2.3 Scientific substantiation of the claimed effect

The review of the human data made by the applicant was considered as comprehensive. Pertinent data have been identified and included in the application.

The application contains 23 publications including 19 controlled intervention studies, 1 uncontrolled intervention study, and 3 meta-analyses on the LDL-cholesterol lowering effect. In addition, the applicant provided 2 unpublished meta-analyses.

In a published meta-analysis of 14 trials, Law (2000) concluded that 2 g plant sterols or plant stanols added to margarine resulted in an average LDL-cholesterol reduction of 14 % or 0.54 mmol/L (95% CI: 0.46 to 0.63 mmol/L). One of the study included in the Law (2000) meta-analysis, was a double-blind, placebo-controlled randomised trial over 3.5 weeks, where mean placebo adjusted LDL cholesterol reduction was 0.26 mmol/L (95% CI: 0.15 to 0.36 mmol/L) in 80 subjects receiving 1.6 g plant sterols/day corresponding to a reduction of

8.5 % when considering the baseline LDL-cholesterol levels of the subjects (Hendriks et al., 1999).

A meta-analysis of 41 trials by Katan et al., 2003 showed that an intake of 1.5 – 1.9 g/day and of 2 – 2.4 g/day of phytosterols added to different foods reduced the LDL-cholesterol levels by 8.5 % (95% CI: 7.0 – 10.1) and 8.9 % (95% CI: 7.4 – 10.5), respectively. In this meta-analysis it appeared that the LDL lowering effect of a dietary intervention with phytosterols tapered off at intakes of about 2 g/d or more, and that there was little additional effect at doses higher than 2.5 g/d.

Chen et al. (2005) included 23 studies in their meta-analysis with a mean dose of 2 g phytosterols most often added to margarine. The mean placebo adjusted reduction of LDL-cholesterol levels was 8.7 % (treatment group: 11 % versus placebo 2.3 %).

The individual intervention studies provided by the applicant, which are not covered in the meta analyses mentioned above, are reviewed in more recent meta analyses by AbuMweis et al., 2008 and Demonty et al., 2009 and covered in the general EFSA opinion on plant sterols and plant stanols (EFSA, 2009).

The applicant also provided an unpublished meta-analysis of 29 publications reporting on 43 controlled interventions (Ashwell, 2004). The meta-analysis included interventions with doses in the range from 0.45 g to 9 g phytosterols per day. In most of the interventions the daily intake was between 1.5 and 3.2 g/day. This meta-analysis revealed an average 8 % reduction of the blood LDL-cholesterol levels by phytosterols added to various food matrices (mainly vegetable oils, fat spreads and dairy products with different fat contents).

The application also contains a meta-analysis (Danacol meta-analysis, 2008) of 3 randomised controlled studies comprising 2 trials with a drinkable low fat fermented milk product enriched with 1.6 g phytosterols (Mannarino et al, 2008; Plana et al., 2007) and one trial with a spoonable low fat fermented milk product enriched with 1.6 g phytosterols (Hansel et al., 2007).

The study by Mannarino et al., 2008, a multicentre (7 centers), randomised, stratified by centre and by statin treatment, double-blind, placebo-controlled trial with 116 adult hypercholesterolaemic subjects (20 - 75 years of age), evaluated the effect of a daily consumption of 100 mL of a low fat ferment milk product enriched with 1.6 g phytosterols, compared to a control product without phytosterols. The product was consumed together with a main meal (lunch or dinner). According to the study synopsis provided by the applicant the LDL-cholesterol lowering after 3 and 6 weeks of intervention, was 7.91 % (95%CI: 5.25-13.63) and 9.44% (95%CI: 3.90 - 11.92) .

In the study by Plana et al., (2007) 84 adult hypercholesterolaemic subjects (18 - 75 years of age) were recruited in a 6-centre, randomised, double-blind, placebo-controlled trial, and ingested 1 x 100 mL of a low fat fermented milk drink enriched with 1.6 g phytosterols per day after lunch . After 3 and 6 weeks of intervention, the placebo-adjusted relative LDL-cholesterol reductions were 12.2 % and 10.6 % when compared to baseline values.

The study by Hansel et al., (2007) a multicentre (5 centers), randomised, stratified by statin treatment, double-blind, placebo-controlled trial with 194 adult hypercholesterolaemic patients (18-75 years of age), evaluated the effect of daily two servings of a 125 g spoonable low fat fermented milk product enriched with each 0.8 g phytosterols consumed with the same meal. Three weeks and 6 weeks after treatment, a significant 9.5 % and 7.8 % placebo-adjusted relative LDL-cholesterol reduction was observed when compared to baseline values.

The relative reduction of LDL-cholesterol after 6 weeks, the primary endpoint of the meta-analysis of these three studies with 393 subjects, was 8.75 % (95%CI: 11.06, 6.45). The relative reduction of LDL-cholesterol after 3 weeks, a secondary endpoint of this study, was 9.49 % (95%CI: 11.76, 7.23). The results of this Danacol-analysis are in the range of the results seen in the published meta-analyses.

In addition to the 3 multicentre randomised, double-blind, placebo-controlled trials, the applicant provided a single-blinded, randomised trial (Rudkowska et al., 2008). 30 hypercholesterolaemic subjects aged 40 - 80 years received in a cross-over design of three 30-day phases, one serving of a low fat fermented milk product enriched with 1.6 phytosterols or a control product, consumed either with the dinner, or 2 hours prior to the dinner. Four weeks of wash-out periods were in between the 3 interventions phases. Twenty-six subjects completed the study. The baseline-adjusted blood LDL-cholesterol lowering effect after 30 days of intervention, was 4.2 % in the group consuming Danacol with the dinner and 8.69 % when consumed 2 hours prior supper, when compared to the placebo group. The Panel considers that the small number of subjects limits the value of this study as a source for the quantification of the effect size and does not permit to draw conclusions on a relationship between timing of the consumption and the size of the effect.

On the basis of the data presented, the Panel considers that a biological significant LDL-cholesterol lowering effect can be achieved by a daily intake of 1.6 g phytosterols added to low fat fermented milk products. The size of the effect is comparable to that of plant sterols and plant stanols added to foods, such as margarine-type spreads, mayonnaise, salad dressings, and dairy products such as milk, yoghurts and cheese, as discussed in the EFSA opinion on plant sterols/stanols and lowering/reducing blood LDL-cholesterol (EFSA, 2009). In that Opinion the available information on the dose-response relationship of phytosterols and their LDL-cholesterol-lowering effect, the time needed to obtain the claimed effect, the sustainability of the effect, and the relevance of food matrices and other food characteristics were reviewed.

The Panel concludes that a cause and effect relationship has been established between the dietary intake of phytosterols and lowering of LDL-cholesterol.

2.4 Panel's comments on the proposed wording

Taking into account the scientific evidence presented, the Panel considers that the following wording reflects the scientific evidence:

“Phytosterols” have been shown to lower/reduce blood cholesterol. High blood cholesterol is a risk factor in the development of coronary heart disease”.

2.5 Conditions and restrictions of use

The Panel recommends that phytosterols should be consumed only by people who need and want to lower their blood cholesterol.

With respect to the specified conditions of use, it is suggested that the labelling provisions outlined in Commission Regulation (EC) No 608/2004 shall continue to apply for products making the proposed reduction of disease risk claim.

The scientific justification of the claim is related to a daily intake of phytosterol esters equivalent to 1.6 g of phytosterols added to low fat fermented milk product.

Phytosterols may not be nutritionally appropriate for pregnant and breastfeeding women and children under the age of five years. Patients on cholesterol lowering medication should only consume products with added phytosterols under medical supervision.

Relevant studies performed under free living conditions showed the feasibility of consuming 1.6 g phytosterols. The Panel considers that the amount of phytosterols needed to lower blood LDL-cholesterol and the pattern of consumption can reasonably be achieved as part of a balanced diet.

CONCLUSIONS AND RECOMMENDATIONS

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

- The phytosterols, subject to this health claim, have been sufficiently characterised.
- The claimed effect is “ reduces LDL-cholesterol, a recognised risk factor of coronary heart disease”. The target population are adults with mildly raised LDL blood cholesterol levels. Lowering LDL-cholesterol is beneficial to human health by decreasing the risk of coronary heart.
- A biological significant LDL-cholesterol lowering effect can be achieved by a daily intake of 1.6 g phytosterols added to low fat fermented products. The size of the effect is comparable to that of plant sterols and plant stanols added to foods, such as margarine-type spreads, mayonnaise, salad dressings, and dairy products such as milk, yoghurts and cheese, as discussed in the EFSA opinion on plant sterols/stanols and lowering/reducing blood LDL-cholesterol.
- A cause and effect relationship has been established between the consumption of phytosterols and lowering of LDL-cholesterol.
- The recommended amount of phytosterols required to lower blood LDL-cholesterol and patterns of consumption can reasonably be achieved as part of a balanced diet.
- The Panel recommends that phytosterols should be only consumed by people who need and want to lower their blood cholesterol.
- The following wording reflects the available scientific evidence: “Phytosterols have been shown to lower/reduce blood cholesterol. High blood cholesterol is a risk factor in the development of coronary heart disease”.
- With respect to the specified conditions of use, it is suggested that the labelling provisions outlined in Commission Regulation (EC) No 608/2004 shall continue to apply for products bearing the proposed reduction of disease risk claim.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on a low fat fermented milk product (Danacol®) enriched with plant sterols/stanols (phytosterols) and blood cholesterol pursuant to Article 14 of regulation (EC) No 1924/2006 (Claim serial No: 0228_FR). December 2008. Submitted by Danone France.

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