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SCIENTIFIC OPINION

Plant Stanols and Plant Sterols and Blood LDL-Cholesterol

Scientific Opinion of the Panel on Dietetic Products Nutrition and Allergies on a request from the European Commission and a similar request from France in relation to the authorization procedure for health claims on plant stanols and plant sterols and lowering/reducing blood LDL-cholesterol pursuant to Article 14 of Regulation (EC) No 1924/2006[1]

Opinion of the Panel on Dietetic Products, Nutrition and Allergies

(Question No EFSA-Q-2009-00530 and EFSA-Q-2009-00718)

Adopted on 30 June 2009

PANEL MEMBERS

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SUMMARY

Following a request from the European Commission and a similar request from France, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver a scientific advice in relation to the authorisation procedure for health claims on plant stanols and plant sterols and lowering/reducing blood cholesterol pursuant to Article 14 of Regulation (EC) No 1924/2006.

The quantities of plant sterols/plant stanols in this opinion are expressed as equivalent weights of free (unesterified) stanols and sterols.

Over 80 randomised, controlled trials have investigated the effect of plant sterols/plant stanols added to a wide range of food formats on blood concentrations of LDL-cholesterol. A number of meta-analyses on these trial has shown that plant sterols/plant stanols lower LDL-cholesterol in a dose-dependent manner with the effect appearing to taper off at daily intakes greater that about 2g. The efficacy for lowering LDL-cholesterol is similar for plant sterols and plant stanols.

[1] For citation purposes: Scientific Opinion of the Panel on Dietetic Products Nutrition and Allergies on a request from the European Commission and a similar request from France in relation to the authorisation procedure for health claims on plant sterols/stanols and lowering/reducing blood LDL-cholesterol pursuant to Article 14 of Regulation (EC) No 1924/2006. *The EFSA Journal* (2009) 1175, 1-9.

The Panel notes that 1.5 - 1.9 g and 2.0 - 2.4 g plant sterols/plant stanols per day was observed to lower blood LDL-cholesterol by an average of 8.5 % and 8.9 %, respectively. The Panel concludes that for an intake of 1.5 - 2.4 g/d an average reduction of between 7 and 10.5 % can be expected. The Panel considers that such a reduction is of biological significance in terms of reduced risk of coronary heart disease.

The Panel concludes that the blood LDL cholesterol lowering effect is usually established within the first 2 - 3 weeks and can be sustained by a continued consumption of plant sterols/stanols. This effect has been shown up to 85 weeks.

The Panel concludes that while plant sterols/stanols added to foods such as margarine-type spreads, mayonnaise, salad dressings, and dairy products such as milk, yoghurts and cheese have been shown consistently to lower blood LDL-cholesterol, the efficacy of plant sterols/stanols added to other food formats is less well established.

Key words: Plant stanols, plant sterols, phytosterols, coronary heart disease, LDL cholesterol, novel food ingredient(s).

TABLE OF CONTENTS

BACKGROUND AS PROVIDED BY THE EUROPEAN COMMISSION

In the context of the procedure for the authorisation of health claims under Regulation (EC) No 1924/2006[2], the Standing Committee of the Food Chain and Animal discussed and voted at its meeting 20 February 2009 on the first batch of health claims applications to be either authorised or rejected.

To this end, the Committee discussed the desirability to indicate a quantitative effect in health claims (amount and time frame of a reduction, for example) taking into account such requests by stakeholders in the case of the sterol/stanol lowering effect of blood cholesterol. The Committee agreed that there is a need for scientific advice from EFSA to ensure that such health claims are authorised in a way which will not mislead the consumer, and that conditions of use are set in a coherent way. Such advice should also take into account that claims quantifying the effect may be used on products with different food matrixes.

TERMS OF REFERENCE AS PROVIDED BY EUROPEAN COMMISSION

Therefore, EFSA should in particular consider and provide advice on the extent to which:

- The range of daily intake of plant sterols/plant stanols and the corresponding biologically significant LDL-cholesterol lowering effect expressed in percentage which can be reasonably expected.
- The reference to the time needed to obtain the claimed effect expressed in weeks and to the sustainability of the claimed effect.
- The food matrix to which plant sterols/plant stanols are added and other food characteristics that possibly determine the size of effect.

This opinion also covers a similar request by France on plant sterols/plant stanols in relation to the matrix impact on the cholesterol reduction and especially the matrix influence on the magnitude of the cholesterol lowering effect (letter received on 30 March 2009).

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[2] OJ L 404 30.12.2006 p. 9–25 [corrigendum: OJ L 12 18.01.2007 p. 3–18].

ASSESSMENT

1. Introduction

In the context of the procedure for the authorisation of health claims under Regulation (EC) No 1924/2006, EFSA has issued its opinions on applications for plant sterols (EFSA, 2008a) and plant stanols (EFSA, 2008b) pursuant to Article 14 of Regulation (EC) No 1924/2006. The present assessment provides further quantitative and qualitative information supporting risk managers in the implementation of regulatory decisions.

The quantities of phytosterols in this opinion are expressed as equivalent weights of free (unesterified) stanols and sterols.

2. The range of daily intake of plant sterols and plant stanols and the corresponding biologically significant LDL-cholesterol lowering effect expressed in percentage which can be reasonably expected.

In 2008, the NDA Panel concluded that a clinically significant LDL-cholesterol lowering effect of about 9 % could be achieved by a daily intake of 2 - 2.4 g of phytosterols (added as free or esterified sterols) in an appropriate food (e.g. plant sterols added to fat-based foods and low-fat foods such as milk and yoghurt) (EFSA, 2008a). This conclusion was based on two meta-analyses of trials of the effect on LDL-cholesterol of plant sterols and plant stanols added to foods (Katan et al., 2003; Demonty et al., 2009). In its opinion on plant stanols, the NDA Panel stated that a clinically significant LDL-cholesterol lowering effect of about 10 % can be achieved by a daily intake of 2 g of plant stanols (as stanol esters) in an appropriate food (e.g. fat-based foods and low-fat foods such as yoghurt), preferably with meals (EFSA, 2008b). This was based on an unpublished meta-analysis comprising 30 randomised, double-blind placebo controlled trials of the effect on LDL-cholesterol of plant stanol esters added to foods (mainly margarine type spreads but also including yoghurt, mayonnaise, gel capsules, butter, low fat cheese, milk, muesli, “ready-made low fat meals”, and pasta).

In these two previous EFSA opinions on plant sterols and stanols, the Panel also considered that the source of the sterols (vegetable or tall oil), the actual ratio between the most abundant sitosterol and campesterol and the source of fatty acids (butter or vegetable oil) do not have a relevant impact on the size of the blood LDL-cholesterol lowering effect (EFSA, 2008a,b). The efficacy for lowering LDL-cholesterol is similar for plant sterols and stanols (Katan et al., 2003; Demonty et al., 2009).

A recently published meta-analysis of 84 randomised control trials has investigated the effect of plant sterols/stanols at daily intakes from 0.45 to 9 g added to a number of different food formats (including fat-based food or low-fat food such as milk and yoghurt) on blood LDL-cholesterol concentrations (Demonty et al., 2009). The absolute placebo-adjusted pooled LDL-cholesterol lowering effect was -0.34 mmol/L (95%CI: -0.31, -0.36). This lowering effect corresponded with a relative LDL-cholesterol change of -8.8 % (95%CI: -8.31, -9.35) given that the pooled overall LDL-cholesterol concentration at baseline was 3.86 mmol/L (95 % CI: 3.77, 3.98). The mean intake in the studies analysed was 2.15 g/day.

In another recent meta-analysis of 59 trials where plant sterols/stanols had been added to various food formats (including fat spreads, mayonnaise and salad dressing, milk and yoghurt) the absolute LDL-cholesterol lowering effect was -0.31 mmol/L (95%CI: -0.27, -0.35) compared to the control (AbuMweis et al., 2008). This study provided the ranges but

not a mean of LDL-cholesterol at baseline and no figures on the relative (%) LDL-cholesterol reduction.

The results of the two recent meta-analyses are in agreement with the outcome of an earlier meta-analysis by Katan et al. (2003) of 41 trials showing that an intake of 1.5 - 1.9 g/day and of 2 - 2.4 g/day of plant sterols/stanols added to different foods (mainly margarine, but also mayonnaise, olive oil or butter) reduced LDL-cholesterol by 8.5 % (95%CI: 7.0, 10.1) and 8.9 % (95%CI: 7.4, 10.5), respectively (Table 1).

Table 1: **Mean Percentage Reductions in LDL-cholesterol according to the dose (Katan et al., 2003)**

Dose of sterol and stanol (g/d)	No. of trial arms	Reduction in LDL-cholesterol % (95% CI)
0.7 - 1.1	8	6.7 (4.9 - 8.6)
1.5 - 1.9	13	8.5 (7.0 - 10.1)
2.0 - 2.4	14	8.9 (7.4 - 10.5)
≥ 2.5	21	11.3 (10.2 - 12.3)

Also a meta-analysis of 23 studies with a mean dose of 2 g plant sterols/stanols which in most of the studies was added to margarine provided very similar results. The placebo adjusted reduction of LDL-cholesterol was 8.7 % (Chen at al., 2005). This decrease corresponded to an absolute placebo-adjusted LDL-cholesterol lowering effect of approximately -0.35 mmol/L.

In an earlier meta-analysis of 14 trials, Law (2000) concluded that 2 g plant sterols/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). The smaller number of trials in this meta-analysis by Law (2000) could have influenced the results.

The meta-analyses demonstrated the lowering of LDL-cholesterol in a dose-dependent manner with the effect appearing to taper off at daily intakes greater that about 2g of plant sterols/stanols.

The Panel considers that values on the mean relative LDL-cholesterol lowering effects of plant sterols/stanols (Table 1) which resulted from the meta-analysis of Katan et al. (2003), and which was confirmed by more recent meta-analyses, are representative of available clinical studies. The trials included data from a large number of clinical studies with different study protocols, different exposures (dose, food characteristics, time and frequency of plant sterols/stanols consumption) and different subject characteristics (baseline LDL-cholesterol, age, sex, lifestyle, background diet and co-medication with statins). The available evidence suggests intake once per day without a meal may be less effective than division of the daily dose into several doses and/or intake of those doses with the main meal.

The Panel notes that 1.5 - 1.9 g and 2.0 - 2.4 g plant sterols/plant stanols per day was observed to lower blood LDL-cholesterol by an average of 8.5 % and 8.9 %, respectively. The Panel concludes that for an intake of 1.5 - 2.4 g/d an average reduction of between 7 and 10.5 % can be expected. The Panel considers that such a reduction is of biological significance in terms of reduced risk of coronary heart disease.

3. Reference to the time needed to obtain the claimed effect expressed in weeks and to the sustainablility of the claimed effect.

The effect of plant sterols/stanols on LDL-cholesterol is usually established within the first 2-3 weeks of intervention and remains stable over the following study weeks (Miettinen et al., 1995; Hallikainen and Uusitupa, 1999). Lowering of LDL-cholesterol has been shown to be sustained with continued consumption of the plant sterols/stanols for up to 52- 85 weeks (Hendriks et al., 2003; Miettinen et al., 1995; De Jong et al., 2008). LDL-cholesterol returns to baseline within a few weeks after consumption of plant sterols/stanols ceases (Christiansen et al., 2001; Miettinen et al., 1995).

The Panel concludes that the blood LDL cholesterol lowering effect is usually established within the first 2 - 3 weeks and can be sustained by a continued consumption of plant sterols/stanols. This effect has been shown up to 85 weeks.

4. The food matrix to which plant sterols/plant stanols are added and other food characteristics that possibly determine the size of effect

The average LDL-cholesterol lowering effects of plant sterols/stanols added to fat spreads, mayonnaise, salad dressings and dairy products, such as milk, yoghurts including low-fat yoghurts and cheese, were consistent and of similar magnitude among published studies and meta-analyses (AbuMweis et al., 2008; Chen et al., 2005; Demonty et al., 2009; Katan et al., 2003; Law, 2000).

The efficacy of plant sterols/stanols added to other food formats such as soft gel capsules and tablets, cereals, bread, pasta, orange juice, and other food formats is not well established (Lagström et al., 2006; Seppo et al., 2007; Theuwissen and Mensink, 2007; Woodgate et al., 2006). In a head-to-head study the LDL-cholesterol lowering effect of plant sterol-enriched milk was almost three times that of enriched bread and cereals (Clifton et al., 2004). In the meta-analysis by AbuMweis et al. (2008) reduction of LDL-cholesterol was significantly greater with plant sterols/stanols enriched fat spreads (0.33 mmol/L, 95%CI: 0.28, 0.38; n = 38), mayonnaise and salad dressing (0.32 mmol/L, 95%CI: 0.25, 0.40; n = 6), milk and yoghurt (0.34 mmol/L, 95%CI: 0.28, 0.40; n = 7) than with plant sterols/stanols enriched foods such as croissants and muffins, non-fat beverages, cereal bars, and chocolate (0.20 mmol/L, 95%CI: 0.11, 0.28; n = 11).

While it has been suggested that formulation of food products with added plant sterols/stanols may be an important determinant of efficacy for LDL-cholesterol lowering, there is insufficient information regarding the formulation of these products to confirm this (AbuMweis et al., 2008).

The Panel concludes that while plant sterols/stanols added to foods such as margarine-type spreads, mayonnaise, salad dressings, and dairy products such as milk, yoghurts including low-fat yoghurts and cheese have been shown consistently to lower blood LDL-cholesterol levels, the efficacy of plant sterols/stanols added to other food formats is less well established.

CONCLUSIONS

The Panel notes that 1.5 - 1.9 g and 2.0 - 2.4 g plant sterols/plant stanols per day was observed to lower blood LDL-cholesterol by an average of 8.5 % and 8.9 %, respectively. The Panel concludes that for an intake of 1.5 - 2.4 g/d an average reduction of between 7 and 10.5

% can be expected. The Panel considers that such a reduction is of biological significance in terms of reduced risk of coronary heart disease.

The Panel concludes that the blood LDL cholesterol lowering effect is usually established within the first 2 - 3 weeks and can be sustained by a continued consumption of plant sterols/stanols. This effect has been shown up to 85 weeks.

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