



EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of a health claim related to 3 g/day plant sterols/stanols and lowering blood LDL-cholesterol and reduced risk of (coronary) heart disease pursuant to Article 19 of Regulation (EC) No 1924/2006.

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SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to 3 g/day plant sterols/stanols and lowering blood LDL-cholesterol and reduced risk of (coronary) heart disease pursuant to Article 19 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 Unilever PLC and Unilever NV, submitted pursuant to Article 19 of Regulation (EC) No 1924/2006 via the Competent Authority of the United Kingdom, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of an application to modify the conditions of use of an authorised Article 14 claim related to 1.5 - 3.0 g plant sterols/stanols per day and lowering blood LDL-cholesterol by 7 - 12 % and reduced risk of (coronary) heart disease. The applicant has further requested that the minimum duration to obtain the effect be one to two weeks. The applicant provided a published systematic review and meta-analysis that evaluated the comparative efficacy of plant sterols and plant stanols for lowering blood LDL-cholesterol in healthy and hypercholesterolaemic subjects and an unpublished meta-analysis on 27 randomised controlled human studies on the LDL-lowering efficacy at a dose range between 2.6 and 3.4 g per day. On the basis of the data presented, the Panel concludes that plant sterols and stanol esters at daily intakes ranging from 1.5 to 3.0 g plant sterols/stanols in matrices approved by Regulation (EC) No 376/2010 (yellow fat spreads, dairy products, mayonnaise and salad dressings) have a similar efficacy on blood LDL-cholesterol lowering, that plant sterols and stanol esters at a daily intake of 3 g (range 2.6 g to 3.4 g) plant sterols/stanols in matrices approved by Regulation (EC) No 376/2010 lower LDL-cholesterol by 11.3 % (95 % CI: 10.0 - 12.5), and that the minimum duration required to achieve the maximum effect of plant sterols and stanols on LDL-cholesterol lowering is two to three weeks.

¹ On request from the Competent Authority of the United Kingdom following an application by Unilever PLC, Question No EFSA-Q-2011-01241, adopted on 26 April 2012.

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KEY WORDS

Plant stanols, plant sterols, phytosterols, coronary heart disease, LDL-cholesterol

SUMMARY

Following an application from Unilever PLC, submitted pursuant to Article 19 of Regulation (EC) No 1924/2006 via the Competent Authority of the United Kingdom, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of an application to modify the conditions of use of an Article 14 claim related to plant sterols/stanols and lowering blood LDL-cholesterol authorised by Regulation (EC) No 376/2010 amending Regulation (EC) No 983/2009 and Regulation (EC) No 384/2010. Specifically, the applicant has requested an extension of the conditions of use, i.e. the intake of 1.5 - 3.0 g/d of plant sterols/stanols leads to an LDL-cholesterol lowering effect of 7 – 12 % within one to two weeks. The application included a request for the protection of proprietary data.

The applicant provided a published systematic review and meta-analysis that evaluated the comparative efficacy of plant sterols and plant stanols for lowering blood LDL-cholesterol in healthy and hypercholesterolaemic subjects. Trials were included in the analysis if they were randomised controlled trials directly comparing plant sterols versus plant stanols in healthy or hypercholesterolemic subjects and reported efficacy data suitable for calculation of the change from baseline. Both parallel and cross-over trials were eligible for inclusion. Based on data from 14 studies with 531 subjects, plant sterols and plant stanols at intakes ranging from 1.5 to 3.0 g/d in matrices approved by Regulation (EC) No 376/2010 (yellow fat spreads, dairy products, mayonnaise and salad dressings) were statistically not significantly different in lowering total cholesterol and LDL-cholesterol. In one additional study not included in this meta-analysis no statistically significant differences in LDL-cholesterol lowering efficacy were found between plant sterols and stanols consumed in margarine at an intake of 2.5 g per day over 85 weeks.

Related to the size of the effect, the applicant provided an unpublished meta-analysis on 27 randomised controlled human studies on the LDL-lowering efficacy of ≥ 2.6 to ≤ 3.4 g plant sterols or plant stanols per day in matrices approved by the European Commission. In this analysis the relative pooled LDL-cholesterol lowering effect was 11.3 % (95 % CI: 10.0 - 12.5). The Panel notes some limitations of the applicant's meta-analysis that contribute to uncertainty of the estimate of the LDL-cholesterol lowering effect, e.g. the study quality not being taken into account, limitations in the description of the random effects model applied by the applicant, and the estimation of relative net changes of LDL-cholesterol levels and variance parameters which were not reported in most of the original publications.

The applicant claimed that the minimum duration required for efficacy was one to two weeks. In three of seven treatment arms, in which the earliest LDL-cholesterol measure was made after one week, the maximum LDL-cholesterol lowering effect was achieved already after one week of intervention, while in four other treatment arms LDL-cholesterol levels continued to decrease until treatment week two, three or four of the intervention. In seven out of seventeen treatment arms in which the earliest LDL-cholesterol measurement was made after two weeks of the intervention the maximum LDL-cholesterol lowering effect was attained after two weeks of intervention, in another six treatment arms most of the reduction was already achieved after two weeks, while in four studies it took longer than two weeks before the maximum reduction was reached. The Panel considers that the minimum duration required to achieve the maximum effect of plant sterols and stanols on LDL-cholesterol lowering is two to three weeks.

The Panel considers that plant sterols and stanol esters at daily intakes ranging from 1.5 to 3.0 g sterols/stanols in matrices approved by Regulation (EC) No 376/2010 (yellow fat spreads, dairy products, mayonnaise and salad dressings) have a similar efficacy on lowering blood LDL-cholesterol.

The Panel concludes that plant sterols and stanol esters at a daily intake of 3 g (range 2.6 - 3.4 g) sterols/stanols in matrices approved by the Regulation (EC) No 376/2010 (yellow fat spreads, dairy products, mayonnaise and salad dressings) lower LDL-cholesterol by 11.3 % (95% CI: 10.0 – 12.5).

The minimum duration required to achieve the maximum effect of plant sterols and stanols on LDL-cholesterol lowering is two to three weeks.

The Panel could have reached these conclusions without considering the unpublished meta-analysis claimed as proprietary by the applicant.

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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. Article 19 of this Regulation lays down provisions for the authorisation for modification, suspension and revocation of permitted health claims.

STEPS TAKEN BY EFSA

- The application was received on 15/12/2011.
- The scope of the application was proposed to fall under a health claim referring to disease risk reduction.
- The scientific evaluation procedure started on 10/01/2012.
- On 18-20/01/2012, 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 23/01/2012 in compliance with Art. 16(1) of Regulation (EC) No 1924/2006.
- On 01/02/2012, EFSA received the requested information as submitted by the applicant and the clock was restarted.
- During its meeting on 25-27/04/2012, the NDA Panel, after having evaluated the overall data submitted, adopted an opinion on the scientific substantiation of a health claim related to 3 g plant sterols/stanols and lowering blood LDL-cholesterol by 12 % and reduced risk of (coronary) heart disease.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 19 of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of an application to modify the conditions of use of an authorised Article 14 claim related to plant sterols/stanols and lowering blood LDL-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 plant sterols/stanols, a positive assessment of its safety, nor a decision on whether plant sterols/stanols 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 of 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.

⁴ 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.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address:

Unilever PLC: Port Sunlight, Wirral, Merseyside, CH62 4ZD, UK

Unilever NV: Weena 455, Rotterdam, 3013 AL, NL

The application indicates confidential and proprietary data. The applicant claims confidentiality and proprietary rights for an unpublished meta-analysis which has been conducted on published studies.

Food/constituent as stated by the applicant

Plant sterols (present as free sterols or sterol esters) as defined in Commission Decisions on authorizing the placing on the market of products with added plant sterols (2000/500/EC, 2004/333-336/EC, 2004/845/EC, 2006/58-59/EC) and plant stanol esters [as defined in the Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies related to the scientific substantiation of a health claim on plant stanol esters and lower/reduced blood cholesterol and reduced risk of (coronary) heart disease (EFSA, 2008a)]. In the context of this dossier, the term “phytosterols” is used as a generic term encompassing both the term plant sterols and plant stanols.

Health relationship as claimed by the applicant

The disease risk reduction claim regarding the LDL-cholesterol lowering effect of plant sterols/stanols, which is the subject of the proposed amendment on the conditions of use has received a positive opinion from the European Food Safety Authority (EFSA, 2008a, 2008b, 2009). Consequently, the European Commission authorised this claim to be used in consumer communications as laid down in Regulation (EC) No 983/2009 amended by Regulation (EC) No 376/2010 and Regulation (EC) No 384/2010. More specific regarding the dose-response relationship, EFSA published that plant sterol/stanol intake of 1.5 - 2.4 g/d and blood LDL-cholesterol lowering of 7 - 10.5 % in 2 – 3 weeks has been scientifically proven (EFSA, 2009), which is reflected in the EU authorisation decision in Regulations (EC) No 384/2010 and Regulations (EC) No 376/2010. New evidence has shown that an additional effect of up to 12 % is achieved with higher daily plant sterol/stanol intakes of up to 3 g/d. In addition, there is evidence that the minimum duration needed for plant sterols/stanols to exert a significant LDL-cholesterol lowering effect is 1 to 2 weeks. As such, the purpose of this dossier is to provide substantiation for an extension of the conditions of use: the intake of 1.5 - 3.0 g/d of plant sterols/stanols leads to an LDL-cholesterol lowering effect of 7 – 12 % within 1 - 2 weeks. It is well established that elevated blood LDL-cholesterol is independently associated with an increased risk for coronary heart disease (CHD) and reduction in LDL-cholesterol is of importance and of benefit to individuals in the population with moderately elevated blood cholesterol concentrations.

Wording of the health claim as proposed by the applicant

“Plant sterols and plant stanol esters have been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease”.

Specific conditions of use as proposed by the applicant

The target population are people of the general population who need and want to lower their blood LDL-cholesterol concentrations.

Consumers should be informed that the beneficial effect is obtained with a daily intake of 1.5 - 3.0 g plant sterols/stanols. Reference to the magnitude of the effect may only be made for foods within the

following categories: yellow fat spreads, dairy products, mayonnaise and salad dressings. When referring to the magnitude of the effect, the entire range '7 to 12 %' and the duration to obtain the effect 'in 1 to 2 weeks' must be communicated to the consumer.

The daily intake of 1.5 - 3.0 g of added plants sterols/stanols is attained through the use of either one portion containing a maximum of 3 g or three portions containing a maximum of 1 g per portion.

As specified in Regulation (EC) No 608/2004: "There shall be an easily visible and legible statement that the product may not be nutritionally appropriate for pregnant and breastfeeding women and children under the age of five years".

As specified in Regulation (EC) No 608/2004. "There shall be a statement that the consumption of more than 3 g per day of added plant sterols/plant stanols should be avoided"

As specified in Regulation (EC) No 608/2004: "There shall be a statement that patients on cholesterol lowering medication should only consume the product under medical supervision".

As specified in Regulation (EC) No 608/2004: "Advice shall be included that the product should be used as part of a balanced and varied diet, including regular consumption of fruit and vegetables to help maintain carotenoid levels.

ASSESSMENT

1. INTRODUCTION

The applicant has proposed to change the conditions of use for claims made on food products with added plant sterols and plant stanols as authorized by Regulation (EC) No 376/2010 amending Regulation (EC) 983/2009 and Regulation (EC) No 384/2010. The authorised claim is: 'Plant sterols and plant stanol esters have been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease.' The conditions of use of the claim are: 'Information to the consumer that the beneficial effect is obtained with a daily intake of 1.5 – 2.4 g plant sterols/stanols. Reference to the magnitude of the effect may only be made for foods within the following categories: yellow fat spreads, dairy products, mayonnaise and salad dressings. When referring to the magnitude of the effect, the entire range '7 to 10 %' and the duration to obtain the effect 'in 2 to 3 weeks' must be communicated to the consumer'.

Specifically, the applicant has requested an extension of the conditions of use, i.e. the intake of 1.5 – 3.0 g per day of plant sterols/stanols leads to an LDL-cholesterol lowering effect of 7 – 12 % within 1 - 2 weeks.

The Panel recalls the conclusions from its earlier opinion on plant sterols/stanols and lowering LDL-cholesterol (EFSA, 2009) that (i) the efficacy for lowering LDL-cholesterol is similar for plant sterols and plant stanols, that (ii) 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, and that for an intake of 1.5 - 2.4 g/d an average reduction of between 7 and 10.5 % can be expected, that (iii) 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, and that (iv) 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.

This opinion focuses on the efficacy of 3.0 g/d of plant sterols/stanols on LDL-cholesterol lowering and on the minimum duration for the effect to occur.

Throughout this opinion, quantities of sterols and stanol esters are expressed as the equivalent weights of free [i.e. un-esterified] sterols and stanols.

2. SIMILARITY OF BLOOD LDL-CHOLESTEROL LOWERING EFFECTS OF PLANT STEROLS AND PLANT STANOLS

The applicant provided a published systematic review and meta-analysis that evaluated the comparative efficacy of plant sterols and plant stanols for lowering blood LDL-cholesterol in healthy and hypercholesterolemic subjects (Talati et al., 2010). Trials were included in the analysis if they were randomised controlled trials directly comparing plant sterols versus plant stanols in healthy or hypercholesterolemic subjects and reported efficacy data suitable for calculation of the change from baseline. Both parallel and cross-over trials were eligible for inclusion. The weighted mean difference of the change from baseline with the 95 % confidence interval was calculated as the difference between the means in the plant sterol and plant stanol groups using a random-effects model. Based on data from 14 studies with 531 subjects, plant sterols and plant stanols at intakes ranging from 1.5 to 3.0 g/d in matrices approved by Regulation (EC) No 376/2010 (yellow fat spreads, dairy products, mayonnaise and salad dressings) were statistically not significantly different in lowering total cholesterol (difference: -1.11 mg/dL; 95 % CI: -4.12 to 1.90; $p = 0.47$) and LDL-cholesterol (difference: -0.35 mg/dL; 95 % CI: -2.98 to 2.28; $p = 0.79$). Four studies included in this meta-analysis used intakes higher than 2 g/d (but not exceeding 3 g/d) and showed comparable effects in lowering total and LDL-cholesterol for plant sterols and stanols without evidence for a difference in the efficacy between sterols and stanols (de Jong et al. 2008a; Nestel et al. 2001; Noakes et al. 2002; Weststrate et al. 1998).

In another study (de Jong et al., 2008b), not included by Talati et al. (2010), the long-term efficacy of plant sterols and stanols was investigated in a double-blind, randomized, placebo-controlled parallel trial comparing a margarine enriched with 2.5 g/d plant sterols or 2.5 g/d plant stanols versus a control margarine over 85 weeks with in total 54 subjects. No statistically significant differences in LDL-cholesterol lowering efficacy were found between plant sterols and stanols at 45 weeks (11.6 % and 8.7 % for plant sterols and stanols, respectively) and at the end of the intervention period at 85 weeks (8.7 % and 13.1 % for plant sterols and stanols, respectively).

The Panel considers that the evidence from randomised controlled human intervention studies which directly compared the efficacy of plant sterols and stanol esters at daily intakes ranging from 1.5 to 3.0 g sterols/stanols in matrices approved by Regulation (EC) No 376/2010 shows that plant sterols and stanols at intakes up to 3 g per day have a similar efficacy on lowering blood LDL-cholesterol.

3. BLOOD LDL-CHOLESTEROL LOWERING EFFECT OF A DAILY INTAKE OF 3 G PLANT STEROLS/STANOLS

In order to find pertinent studies for inclusion into a meta-analysis to study the effect size, the applicant relied on the systematic searches performed by the authors of two recent meta-analyses (Demonty et al., 2009; Musa-Veloso et al., 2011) who used almost identical search strategies. Demonty et al. (2009) searched 5 databases (Medline, Cab Abstracts, Biological Abstracts, Web of Science, and the Cochrane Library) through July 2007. Keywords related to plant sterols and stanols (phytosterols), sitosterol, sitostanol, campesterol, campestanol, stigmasterol, brassicasterol, blood lipids, cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides. Musa-Veloso et al. (2011) searched 16 databases (Medline, Cab Abstracts, Allied & Complementary Medicine, Mantis, Pascal, Foodline: Science, Global Health, Biosis Previews, Elsevier Biobase, National Technical Information Service, Gale Group Health & Wellness Database, Embase, New England Journal of Medicine, Adis

Clinical Trials Insight, Web of Science, and the Cochrane Library) through November 2010, and used identical search terms to those described by Demonty et al. (2009). Both searches were limited to human studies. There was no restriction on publication date or language.

An additional search was performed by the applicant using 9 databases (Medline, Embase, Biosis, Cab Abstracts, FROSTI, Food Science & Technology Abstracts, Chemical Abstracts, Pascal, Agricola) from September 2010 through September 2011 using similar selection criteria as for the 2 recent meta-analyses (Demonty et al. 2009; Musa-Veloso et al. 2011). The inclusion criteria were: randomized controlled trial within human adults (parallel-arm or cross-over trials); treatment with “usual phytosterols”, where “usual phytosterols” was defined as 4-desmethylsterols and/or 4-desmethylstanols extracted from vegetables or plant oils such as soybean oil, rapeseed oil and tall oil; blood lipids as primary or secondary outcomes; and absence of a co-intervention from which consumption of phytosterol-enriched foods or supplements could not be isolated. The exclusion criteria were: not a randomized controlled trial; relevant blood lipid data missing; phytosterols consumed for less than 2 weeks; control group did not receive a placebo; ferulated phytosterols such as rice bran oil and shea nut oil sterols were used; colectomised patients were part of the study; and dose of phytosterols > 3.8 g per day. On request by EFSA, the applicant limited the dose range for studies pertinent to this claim to ≥ 2.6 to ≤ 3.4 g phytosterols per day.

In total, 29 (19 stanol and 10 sterol) treatment arms were identified which studied doses of ≥ 2.6 to ≤ 3.4 g plant sterols or stanols per day without limitation with regard to the food format (unpublished meta-analysis, Unilever, 2011). The food formats used were margarine or spreads in 24 studies, yoghurts in two studies, and mayonnaise, ground beef and muffin/croissant in one study each. The latter two trials (with ground beef and muffin/croissant as food matrix) were excluded when only studies were considered which used food formats specified in Regulation (EC) No 376/2010. With this restriction the applicant's selection resulted in 19 stanol (11 parallel/8 cross-over trials) and 8 sterol (3 parallel/5 cross-over trials) arms. The main outcome variable was the relative net change in LDL-cholesterol. When the outcome variable was measured at various time points during the intervention, the value corresponding to, or closest to, the 4-week time point was taken for the analysis. When relative net changes were reported, these values were collected. For studies in which relative net changes were not reported, they were calculated from the absolute changes. A pooled estimate of the relative LDL-cholesterol lowering effect of phytosterols was calculated using a random effects model according to the methods described by DerSimonian and Laird (1986) in order to take into account the large variation in LDL-cholesterol lowering effects observed between studies. Several studies did not report the relative (%) net change and most of the studies did not report variance parameters for the relative change. For the weighting of the studies the applicant used the number of subjects. For cross-over studies, the weight was defined as the total number of subjects included, whilst for the parallel studies, the weight was defined as half of the total number of subjects included. The pooled estimates and accompanying 95 % CIs were determined using a mixed statistical procedure for analyses of variances (SAS version 9.2). In this analysis among 27 treatment arms which used the matrices margarine and other spreads, dressing and yoghurt as specified in the Commission Regulation, the relative pooled LDL-cholesterol lowering effect was 11.3 % (95 % CI: 10.0 - 12.5).

The Panel notes some limitations of the applicant's meta-analysis that contribute to uncertainty of the estimate of the LDL-cholesterol lowering effect. Study quality was not taken into account on the basis that from the meta-analysis of Demonty et al. (2009) with 141 treatment arms it was concluded that study quality did not influence the dose-response for plant sterols and stanols. The Panel considers that this conclusion cannot be extrapolated to a small subset of studies included in the unpublished meta-analysis by the applicant. The Panel also notes the limitations in the description of the random effects model applied by the applicant. Uncertainties derive also from the estimation of relative (%) net changes of LDL-cholesterol levels and variance parameters which were not reported in most of the original publications.

The Panel notes that the results of this unpublished meta-analysis provided by the applicant are comparable to the results of the published meta-analysis by Katan et al. (2003) which showed a pooled mean reduction of LDL-cholesterol levels of 11.3 % (95 % CI: 10.2 - 12.3) for ≥ 2.5 g phytosterols consumed daily. The meta-analysis by Katan et al. (2003) comprised 21 treatment arms (13 stanol arms, 8 sterol arms; average dose 3.0 g) from five studies with doses between 2.5 and 2.9 g, 13 studies with doses between 3.0 and 3.4 g, and two studies with 4.0 and 4.2 g phytosterols, respectively).

The Panel considers that the evidence from randomised controlled human intervention studies of plant sterols and stanol esters at a daily intake of 3 g (range 2.6 - 3.4 g) plant sterols/stanols in matrices approved by Regulation (EC) No 376/2010 shows an average pooled LDL-cholesterol reduction of 11.3 % (95% CI: 10.0 – 12.5).

The Panel could have reached this conclusion without considering the unpublished meta-analysis claimed as proprietary by the applicant.

4. MINIMUM DURATION FOR EFFECT OF PLANT STEROLS/STANOLS

The applicant claims that the minimum duration required for efficacy was one to two weeks. In three (Mensink et al., 2002; plant stanols; Noakes et al., 2005, plant sterol and plant stanol arm) of seven treatment arms, in which the earliest LDL-cholesterol measurement was made after one week, the maximum LDL-cholesterol lowering effect was achieved already after one week of intervention. In the four other treatment arms LDL-cholesterol levels continued to decrease in week two (Jones et al., 2000, plant stanol arm), week three (Jones et al., 2000, plant sterol arm; Mussner et al., 2002, plant sterols) and week four (Goldberg et al., 2006, plant stanols) of the intervention. The Panel considers that the maximum LDL-cholesterol reduction is not generally attained after one week of intervention with plant sterols and stanols.

In seven (Blair et al., 2000; Gonzales et al., 2007; Homma et al., 2003, treatment arms 1 and 2; Maki et al., 2001, treatment arm 1; Niittynen et al., 2007; Nguyen et al., 1999, treatment arm 1) out of 17 treatment arms in which the earliest LDL-cholesterol measurement was made after two weeks of the intervention, the maximum LDL-cholesterol lowering effect was already attained after 2 weeks of the intervention; in another six (Hallikainen and Uusitupa, 1999, treatment arms 1 and 2; Maki et al., 2001, treatment arm 2; Nguyen et al., 1999, treatment arms 2 and 3; Seki et al., 2003a) of these 17 treatment arms most of the reduction was already achieved after two weeks. In the four remaining studies (Matvienko et al., 2002; Deveraj et al., 2004; Saito et al., 2006; Seki et al., 2003b) it took longer than two weeks before the maximum reduction was reached.

The Panel notes that in most of the studies blood LDL-cholesterol was measured for the first time only after two or three weeks of intervention, when the full effect has usually been established. The Panel considers that there is insufficient evidence to conclude that the maximum effect is generally achieved already after one week, and refers to its previous opinion from 2009 when it concluded that the blood LDL-cholesterol lowering effect is usually established within the first two to three weeks of consumption of stanols/sterols (EFSA, 2009).

The Panel considers that the minimum duration required to achieve the maximum effect of plant sterols and stanol esters on LDL-cholesterol lowering is two to three weeks.

CONCLUSIONS

Plant sterols and stanol esters at daily intakes ranging from 1.5 to 3.0 g sterols/stanols in matrices approved by Regulation (EC) No 376/2010 (yellow fat spreads, dairy products, mayonnaise and salad dressings) have a similar efficacy on lowering blood LDL-cholesterol.

Plant sterols and stanol esters at a daily intake of 3 g (range 2.6 - 3.4 g) sterols/stanols in matrices approved by the Regulation (EC) No 376/2010 (yellow fat spreads, dairy products, mayonnaise and salad dressings) lower LDL-cholesterol by 11.3 % (95% CI: 10.0 – 12.5).

The minimum duration required to achieve the maximum effect of plant sterols and stanol esters on LDL-cholesterol lowering is two to three weeks.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on plant sterols and stanols and blood cholesterol pursuant to Article 19 of Regulation (EC) No 1924/2006 (Claim serial No: 0316_UK). November 2011. Submitted by Unilever PLC (UK) and Unilever NV (NL).

REFERENCES

- Blair SN, Capuzzi DM, Gottlieb SO, Nguyen T, Morgan JM, Cater NB (2000). Incremental reduction of serum total cholesterol and low-density lipoprotein cholesterol with the addition of plant stanol ester-containing spread to statin therapy. *Am J Cardiol* 86(1): 46-52.
- Commission of the European Communities, 2004. Commission Regulation (EC) No 608/2004 of 31 March 2004 concerning the labelling of foods and food ingredients with added phytosterols, phytosterol esters, phytstanols and/or phytostanol esters. *Off. J. Eur. Union* 47, 44-45. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do*uri=OJ:L:2004:097:0044:0045:EN:PDF.
- Commission of the European Communities. 983/2009 of 21 October 2009 on the authorisation and refusal of authorisation of certain health claims made on food and referring to the reduction of disease risk and to children's development and health (Text with EEA relevance) [L277]. *Off J Eur Communities* 52, 3-12. Available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:277:0003:0012:EN:PDF>.
- Commission. Commission Regulation (EU) No 376/2010 of 3 May 2010 amending Regulation (EC) No 983/2009 on the authorisation and refusal of authorisation of certain health claims made on food and referring to the reduction of disease risk and to children's development and health (Text with EEA relevance) [L111]. *Off J Eur Communities* 53, 3-4. Available at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:111:0003:0004:EN:PDF>.
- De Jong A, Plat J, Bast A, Godschalk RWL, Basu S, Mensink RP (2008a). Effects of plant sterol and stanol ester consumption on lipid metabolism antioxidant status, and markers of oxidative stress, endothelial function, and low-grade inflammation in patients on current statin treatment. *Eur J Clin Nutr.* 2008;62:263-273.
- De Jong A, Plat J, Lutjohann D, Mensink RP (2008b). Effects of long-term plant sterol or stanol ester consumption on lipid and lipoprotein metabolism in subjects on statin treatment. *Br J Nutr* 100(5): 937-941.
- Demonty, I.; Ras, R.T.; van der Knaap, H.C.; Duchateau, G.S.; Meijer, L.; Zock P.L.; Geleijnse, J.M. and Trautwein, E.A., 2009. Continuous dose-response relationship of the LDL-cholesterol-lowering effect of phytosterol intake [plus supplemental data] *J. Nutr.* 139, 271-284.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clin Trials.* 1986;7:177-188.

- Devaraj S, Jialal I, Vega-Lopez S (2004). Plant sterol-fortified orange juice effectively lowers cholesterol levels in mildly hypercholesterolemic healthy individuals. *Arterioscler Thromb Vasc Biol* 24(3): e25-28.
- EFSA (European Food Safety Authority), 2008a. Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies on a request from McNeil Nutritionals Ltd. related to the scientific substantiation of a health claim on plant stanol esters and lower/reduced blood cholesterol and reduced risk of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006. *The EFSA Journal* (2008) 825, 1-13.
- EFSA (European Food Safety Authority), 2008b. Scientific Opinion of the Panel on Dietetic Products Nutrition and Allergies on a request from Unilever PLC/NV on Plant Sterols and lower/reduced blood cholesterol and reduced the risk of (coronary) heart disease (EFSA-Q-2008-085). *The EFSA Journal* (2008) 781, 1-15.
- EFSA (European Food Safety Authority), 2009. 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.
- Goldberg AC, Ostlund RE, Jr., Bateman JH, Schimmoeller L, McPherson TB, Spilburg CA (2006). Effect of plant stanol tablets on low-density lipoprotein cholesterol lowering in patients on statin drugs. *Am J Cardiol* 97(3): 376-379.
- Goncalves S, Vasco Maria, A, Silva-Herdade, AS, Martins e Silva, J, Saldanha, C. (2007). Milk enriched with phytosterols reduces plasma cholesterol levels in healthy and hypercholesterolemic subjects. *Nutrition Research* 27: 200-205.
- Hallikainen, M.A. and Uusitupa, M.I.J., 1999. Effects of 2 low-fat stanol ester-containing margarines on serum cholesterol concentrations as part of a low-fat diet in hypercholesterolemic subjects. *Am. J. Clin. Nutr.* 69, 403-410.
- Homma Y, Ikeda I, Ishikawa T, Tateno M, Sugano M, Nakamura H (2003). Decrease in plasma low-density lipoprotein cholesterol, apolipoprotein B, cholesteryl ester transfer protein, and oxidized low-density lipoprotein by plant stanol ester-containing spread: a randomized, placebo-controlled trial. *Nutrition* 19(4): 369-374.
- Jones PJ, Raeni-Sarjaz M, Ntanos FY, Vanstone CA, Feng JY, Parsons WE (2000). Modulation of plasma lipid levels and cholesterol kinetics by phytosterol versus phytostanol esters. *J Lipid Res* 41(5): 697-705.
- Katan MB, Grundy SM, Jones P, Law M, Miettinen T, Paoletti R, 2003. Stresa Workshop Participants, 2003. Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. *Mayo Clin. Proc.* 78, 965-978.
- Maki KC, Davidson MH, Umporowicz DM, Schaefer EJ, Dicklin MR, Ingram KA, et al. (2001). Lipid responses to plant-sterol-enriched reduced-fat spreads incorporated into a National Cholesterol Education Program Step I diet. *Am J Clin Nutr* 74(1): 33-43.
- Matvienko OA, Lewis DS, Swanson M, Arndt B, Rainwater DL, Stewart J, et al. (2002). A single daily dose of soybean phytosterols in ground beef decreases serum total cholesterol and LDL cholesterol in young, mildly hypercholesterolemic men. *Am J Clin Nutr* 76(1): 57-64.
- Mensink RP, Ebbing S, Lindhout M, Plat J, van Heugten MM (2002). Effects of plant stanol esters supplied in low-fat yoghurt on serum lipids and lipoproteins, non-cholesterol sterols and fat soluble antioxidant concentrations. *Atherosclerosis* 160(1): 205-213.
- Musa-Veloso, K.; Poon, T.H.; Elliot, J.A. and Chung, C., 2011. A comparison of the LDL-cholesterol lowering efficacy of plant stanols and plant sterols over a continuous dose range: Results of a

- meta-analysis of randomized, placebo-controlled trials. Prostaglandins, Leukotrienes and Essential Fatty Acids [advance electronic publication, Feb. 21, 2011].
- Mussner MJ, Parhofer KG, Von Bergmann K, Schwandt P, Broedl U, Otto C (2002). Effects of phytosterols ester-enriched margarine on plasma lipoproteins in mild to moderate hypercholesterolemia are related to basal cholesterol and fat intake. *Metabolism* 51(2): 189-194.
- Nestel P, Cehun M, Pomeroy S, Abbey M, Weldon G (2001). Cholesterol-lowering effects of plant sterol esters and non-esterified stanols in margarine, butter and low-fat foods. *Eur J Clin Nutr* 55(12): 1084-1090.
- Nguyen TT, Dale LC, von Bergmann K, Croghan IT (1999). Cholesterol-lowering effect of stanol ester in a US population of mildly hypercholesterolemic men and women: a randomized controlled trial. *Mayo Clin Proc* 74(12): 1198-1206.
- Niittynen L, Jauhiainen, TA, Poussa, TA, Korpela, R. (2007). Effects of yoghurt enriched with free plant sterols on the levels of serum lipids and plant sterols in moderately hypercholesterolaemic subjects on a high-fat diet. *Int J Food Sci Nutr* 1: 1-11.
- Noakes M, Clifton P, Ntanos F, Shrapnel W, Record I, McInerney J (2002). An increase in dietary carotenoids when consuming plant sterols or stanols is effective in maintaining plasma carotenoid concentrations. *Am J Clin Nutr* 75(1): 79-86.
- Noakes M, Clifton PM, Doornbos AM, Trautwein EA (2005). Plant sterol ester-enriched milk and yoghurt effectively reduce serum cholesterol in modestly hypercholesterolemic subjects. *Eur J Nutr* 44(4): 214-222.
- Saito S, Takeshita M, Tomonobu K, Kudo N, Shiiba D, Hase T, et al. (2006). Dose-dependent cholesterol-lowering effect of a mayonnaise-type product with a main component of diacylglycerol-containing plant sterol esters. *Nutrition* 22(2): 174-178.
- Seki S, Abe, T., Hidaka, I., Kojima, K., Yoshino, H., Aoyama, T., Okazaki, M., Kondo, K. (2003a). Vegetable Oil Enriched with Phytosterol Ester and the Degree of Serum Cholesterol Lowering Effect in Healthy Subjects. *J. Oleo Sci.* 52(6): 285-294.
- Seki S, Hidaka I, Kojima K, Yoshino H, Aoyama T, Okazaki M, et al. (2003b). Effects of phytosterol ester enriched vegetable oil on plasma lipoproteins in healthy men. *Asia Pac J Clin Nutr* 12(3): 282-291.
- Talati R, Sobieraj DM, Makanji SS, Phung OJ, Coleman CI (2010). The comparative efficacy of plant sterols and stanols on serum lipids: a systematic review and meta-analysis. *J Am Diet Assoc* 2010; 110(5): 719-726.
- Unilever (2011). Health claim application on plant sterols and stanols and blood cholesterol pursuant to Article 19 of Regulation (EC) No 1924/2006 (Claim serial No: 0316_UK). November 2011. Submitted by Unilever Unilever PLC (UK) and Unilever NV (NL).
- Weststrate JA, Meijer GW (1998). Plant sterol-enriched margarines and reduction of plasma total- and LDL-cholesterol concentrations in normocholesterolaemic and mildly hypercholesterolaemic subjects. *Eur J Clin Nutr* 52(5): 334-343.

GLOSSARY / ABBREVIATIONS

CHD Coronary heart disease

LDL Low density lipoproteins