

**Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies
on a request from the Commission related to two scientific publications
concerning aspects of serum levels of phytosterols**

(Request N° EFSA-Q-2004-178)

(adopted on 21 April 2005)

SUMMARY

The European Commission has referred two scientific publications on aspects of elevated plant sterol consumption to the European Food Safety Authority for its consideration and judgement as to whether the findings require an updating of the 2002 opinion of the Scientific Committee on Food (SCF) “General view of the Scientific Committee on Food on the long-term effects of the intake of elevated levels of phytosterols from multiple dietary sources, with particular attention to the effects on β -carotene”. This review considered that the efficacy of both plant sterols and plant stanols in reducing serum cholesterol levels was similar.

One paper (Miettinen *et al.*, 2000) concerns the combined intake of plant stanols and lipid-lowering medication (simvastatin) and the finding that the statin reduces the level of serum cholesterol by inhibition of synthesis from cholesterol precursors but does not affect absorption of cholesterol from the diet. Absorption is reduced by elevated levels of plant stanols in the diet and the authors recommend combination therapy of statins and foods containing elevated levels of plant stanols for patients having high levels of cholesterol absorption. This is consistent with two studies reported in the SCF review and the conclusion that phytosterol esters can be used safely to provide an “additional” cholesterol-lowering effect in hypercholesterolaemic patients.

The second paper (Sudhop *et al.*, 2002) considered the hypothesis that elevated serum levels of plant sterols might be a risk factor for coronary heart disease on the basis that patients having the autosomal recessive disease sitosterolaemia (or phytosterolaemia) and absorbing high levels of plant sterols from a normal diet develop premature atherosclerosis. The results of this study were anticipated in the conclusions of the SCF review that while the studies available provided no evidence of adverse effects associated with a small increase of plasma phytosterols, more information on possible long-term exposure to higher intakes of plant sterols was needed.

The Panel concludes that the principles raised by these publications have been dealt with adequately in the SCF review and that it is unnecessary at the present time to update the advice or to modify the conclusions.

KEY WORDS

Phytosterols, cholesterol, phytosterolaemia, lipid-lowering medication, coronary heart disease.

BACKGROUND

On 26 September 2002, the SCF adopted its opinion “General view of the Scientific Committee on Food on the long-term effects of the intake of elevated levels of phytosterols from multiple dietary sources, with particular attention to the effects on β -carotene”.

In 2000 and 2004, under Regulation (EC) N° 258/97, the Commission authorised the use of phytosterols and phytosterol esters to be used in a number of foods and food ingredients. Furthermore by Commission Regulation (EC) N° 608/2004 of 31st March 2004 concerning the labelling of foods and food ingredients with added phytosterols, phytosterol esters, phytostanols and/or phytostanol esters consumers receive the information that intake of more than 3 g per day of additional phytosterols should be avoided. Consumers also have to be informed that a food or food ingredient contains additional phytosterols and that patients taking cholesterol-lowering medication should consume food and food ingredients with additional phytosterols under medical supervision.

On 21st April 2004, the German authorities informed the Commission of two scientific reports that might be of concern with respect to the safe use of phytosterols in foods and food ingredients. As this additional information might possibly have an impact on the safety of foods and food ingredients with added phytosterols and because of Community interest in this matter, the European Commission has decided to seek the opinion of the European Food Safety Authority.

TERMS OF REFERENCE

In accordance with Article 29 (1) (a) of Regulation N° 178/2002 the European Commission requests the European Food Safety Authority to issue a scientific opinion on the addition of phytosterols and phytosterol esters to foods and food ingredients.

The Authority is asked to consider the request by Germany, in particular the scientific reports:

1. (Preliminary report) Serum plant sterols as a potential risk factor for coronary heart disease, T. Sudhop *et al.*, *Metabolism*, Vol 51, No 12 (December) 2002, pp 1519-1521;
2. Noncholesterol sterols and cholesterol lowering by long-term Simvastatin treatment in coronary patients, T.A. Miettinen *et al.*, *Arterioscler Thromb Vasc Biol.*, May 2000, pp 1340-1346.

The Authority is asked to consider whether there is a need to update the abovementioned SCF opinion or whether the conclusions of that opinion stay.

ASSESSMENT

The scientific reports

The contents of the two scientific reports supplied by the German authorities and referenced in the Terms of Reference can be described as follows:

1. Miettinen TA, Strandberg TE and Gylling H (2000). Noncholesterol sterols and cholesterol lowering by long-term Simvastatin treatment in coronary patients. *Arterioscler Thromb Vasc Biol* 20: 1340-1346

Human serum contains small amounts of the precursors of cholesterol synthesis including cholestenol, desmosterol and lathosterol and the whole precursor sterol group is positively related to cholesterol synthesis. In addition there are other non-cholesterol sterols in serum the most prominent of which are cholestanol and plant sterols (campesterol, sitosterol and avenasterol). The overall level of serum cholesterol is a function of both synthesis and absorption. Coronary patients in the Scandinavian Simvastatin Survival Study with low baseline ratios of serum cholestanol and plant sterols to cholesterol (indicating low cholesterol absorption) but not those with high ratios (high absorption) experienced reduced recurrences of coronary events during simvastatin treatments.

In this study, serum cholesterol, its precursor sterols (reflecting cholesterol synthesis), plant sterols (campesterol and sitosterol) and cholestanol (reflecting cholesterol absorption) were measured before and during a 5-year period of placebo treatments (n=433) and simvastatin treatment (n=434) in patients to determine whether changes in cholesterol synthesis and serum levels were related to cholesterol absorption. The serum cholesterol level was unchanged, the ratios of cholesterol precursor sterols to cholesterol were decreased and the ratios of plant sterols to cholesterol were increased in relation to increasing baseline ratios of cholestanol quartiles. The latter predicted 5-year ratios and simvastatin-induced reductions of the precursor sterols, with the lowering of the ratios (cholesterol synthesis reduction) being almost twice that in the lowest versus the highest quartile. The ratios of plant sterols, especially campesterol, to cholesterol were markedly increased during simvastatin treatment, mostly in subjects with the highest baseline cholestanol quartiles. Simvastatin reduced serum cholesterol more (p=0.003) in the lowest versus the highest cholestanol quartile during the 5-year treatment period.

The authors concluded that baseline cholesterol metabolism, measured by serum non-cholesterol sterols, predicts the effectiveness of simvastatin in reducing cholesterol synthesis and serum levels of cholesterol. The statin reduces the synthesis of cholesterol markedly more effectively in subjects with high rather than low baseline synthesis. Thus subjects with high cholesterol absorption and low synthesis may need a combined approach to their therapy, for which the authors suggest the use of plant stanols instead of plant sterols for this small subgroup.

2. Sudhop T, Gottwald BM and von Bergmann K (2002). Serum plant sterols as a potential risk factor for coronary heart disease (a preliminary report). *Metabolism* 51: 1519-1521

The two common plant sterols, campesterol and sitosterol, are structurally related to cholesterol. Their presence in diet is almost equal to that of cholesterol but their absorption rate is markedly lower. When foods having an elevated level of plant sterols are consumed they lower significantly the blood concentration of cholesterol by inhibiting intestinal absorption of cholesterol and thus reduce one of the risk factors for coronary heart disease (CHD). However patients having the inherited disease of phytosterolaemia have markedly increased plasma concentrations of plant sterols as a result of hyperabsorption and these have

been implicated as a risk factor for premature atherosclerosis. The question raised by the authors was whether elevated plasma levels of the plant sterols campesterol and sitosterol could be risk factors for CHD in non-phytosterolaemia subjects. They therefore examined the role of plant sterols in patients admitted for elective artery coronary bypass graft. Serum concentrations of campesterol and sitosterol were analysed in 42 men and 11 women who had not received lipid-lowering treatment previously. Twenty six patients reported a positive family history in their first-degree relatives (parents and siblings) for CHD. Lipid profile and other risk factors were comparable in both groups. Patients with a positive family history for CHD had significantly higher plasma levels of campesterol (0.50 ± 0.17 vs. 0.38 ± 0.16 mg/dL), sitosterol (0.40 ± 0.11 vs. 0.31 ± 0.11 mg/dL; $p=0.004$) and their ratios to cholesterol. The authors concluded that these results support the hypothesis that plant sterols might be an additional risk factor for CHD but that more studies are warranted to confirm these preliminary results.

The general view of the Scientific Committee on Food (September 2002)

The above document did not refer to either of the above publications but does consider the principles raised by them.

In section 3.2: Phytosterol esters when used in conjunction with cholesterol-lowering drugs, it addresses the issues raised in the publication by Miettinen *et al.* (2000). It refers to two studies (Neil *et al.*, 2001; Nigon *et al.*, 2001) in which patients with hypercholesterolaemia being treated with statins or fibrates were given plant sterols in vegetable fat spreads. Serum cholesterol levels were significantly reduced whether the patients were on lipid-lowering drugs or not. The conclusions from both studies were that phytosterol esters can be used safely to provide an “additional” cholesterol-lowering effect in hypercholesterolaemic patients in general. For a small subgroup of patients the use of plant stanols was recommended. The general view of the SCF considered the efficacy of plant stanol esters *versus* plant sterol esters and concluded that their cholesterol-lowering effects are quite similar, but there is a small difference in their absorption with stanols being absorbed to a lesser degree (section 3.1: “The blood Tc- and LDLc-lowering effect of sterols and stanols is quite similar, although the hydrogenated sterol esters may be somehow more efficient in reducing the intestinal absorption of cholesterol”).

In the SCF opinion, it is also stated that patients taking cholesterol-lowering medication are advised that they should consume foods containing elevated levels of plant sterols only under medical supervision.

In section 4.2 the SCF stated that “In general, it is assumed that increasing the length of the side-chain of cholesterol decreases the absorbability of the resulting sterol, and that hydrogenation of the nucleus double-bond of a sterol causes a decrease of absorbability, as demonstrated for cholesterol/cholestanol and sitosterol/sitostanol pairs”.

The main thesis of the study by Sudhop *et al.* (2002) is that since excessive absorption of plant sterols in the diet by patients with the inherited disease phytosterolaemia has been implicated as a risk factor for premature atherosclerosis that increased serum levels of plant sterols might be a risk factor for CHD. Such an increase might result from long-term intakes of elevated levels of plant sterols in the diet. This issue is addressed in section 7: Concluding remarks. “The absorption of plant sterols is much lower than that of cholesterol. However consumption of phytosterols leads to small but dose-related increase of their plasma

concentrations in short-term studies. Very high plasma levels of phytosterols in individuals with an autosomal recessive disease, sitosterolaemia, lead to severe and premature atherosclerosis. While the studies available provide no evidence of adverse effects associated with a small increase of plasma phytosterols, more information on possible effects of long-term exposure to higher intakes of plant sterols is needed". This remains the position and future studies will need to consider the level of total and LDL cholesterol as a risk factor for CHD and their reduction by elevated levels of plant sterols in the diet against the hypothesised risk factor of elevated levels of serum plant sterols.

CONCLUSION

The Panel has considered the results and conclusions of the two publications referred to it by the Commission. The Panel's opinion is that the principles raised by these publications have been dealt with adequately in the "General view of the Scientific Committee on Food on the long-term effects of the intake of elevated levels of phytosterols from multiple dietary sources, with particular attention to the effects on β -carotene" and that it is unnecessary at the present time to update the advice or to modify the conclusions.

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