

## **Addition of plant sterols and stanols to food: assessment of a new study from the Netherlands**

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Plant sterols and stanols are added to foods such as margarine, milk and bread, because of their cholesterol-lowering effect. Most foods with such additives are novel foods which must accordingly be assessed and approved in terms of their potential health risks.

Plant sterols are found in low quantities in all fatty plant-based foods such as oils, nuts, seeds and cereals. For humans, they are not essential and are hardly used in the human metabolism. Plant stanols are hydrolysed plant sterols which are not naturally present in plant-based foods.

The Federal Institute for Risk Assessment (BfR) below assesses a study from the Netherlands which provides valuable information on the unwanted effects of plant sterols on human retinal microvessels. Retinal vessels analysis is increasingly used for early diagnosis of cardiovascular risks. The findings of the study indicate that intake of plant sterols may entail cardiovascular risks for healthy persons who consume foods containing plant sterols in relatively large quantities and over a long period of time. Due to the amount of data available, the extent of this potential risk cannot currently be quantified.

The BfR has already pointed out in earlier opinions that foods to which plant sterols or stanols are added are largely consumed by persons who do not have increased cholesterol levels as well as by children. The European Food Safety Agency currently recommends that daily consumption of plant sterols and stanols be limited to three grams.

In view of the results of the Dutch study, the BfR is of the opinion that the use of plant sterols as a food additive should be reassessed at the European level.

### **1 Subject of the Assessment**

The study "Effects of long-term plant sterol and stanol consumption on the retinal vasculature: A randomized controlled trial in statin users" by Kelly, Plat, Mensink and Berendschot was published in the magazine *Atherosclerosis* 214 (2011) 225–230. Results from this study indicate that the consumption of foods containing plant sterols has unwanted effects on human retinal microvessels. The BfR has evaluated the relevance of the described effects on behalf of the Federal Ministry of Food, Agriculture and Consumer Protection (BMELV).

### **2 Findings**

Focusing on persons taking statin medication while at the same time eating margarine containing phytosterols or phytostanols, the study "*Effects of long term plant sterol and stanol consumption on the retinal vasculature: A randomized controlled trial in statin users*" found a significant correlation between the campesterol concentration in the blood plasma and the thickness of veins in the retina after 85 weeks. This correlation was independent of the simultaneous reduction of the LDL cholesterol level. An increase in the diameter of the retinal vessels is being discussed as an early risk marker for cardiovascular disease.

This means that findings from experiments on humans are available for the first time ever which may indicate the independent atherogenic potential of slightly elevated plasma

phytosterol concentrations. However, the extent to which the consumption of phytosterol margarine in test persons actually influences the risk of developing cardiovascular disease cannot be assessed. Based on the findings of this study, it nevertheless seems possible that there is an increased atherogenic risk, especially for persons who regularly eat foods with plant sterol additives and who cannot expect any advantage from lowering the cholesterol level.

The study “*Consumption of plant sterols in Belgium: consumption patterns of plant sterol-enriched foods in Flanders Belgium*” by Sioen and colleagues, published in the *British Journal of Nutrition* (2011), 105, 911–918, reports that of the Flemish population, 21% of pre-school children and 28% of adults eat foods containing phytosterol. In that particular survey, more than half of the adult consumers who knew what their cholesterol level was stated that they had no elevated cholesterol level.

Despite its local nature, the Belgium consumption study nevertheless confirms that foods with phytosterol addition are largely eaten by healthy persons including children with normal cholesterol levels. In view of the experimental and epidemiological indications that phytosterols have a potentially harmful effect on vessels, the BfR holds that there is currently insufficient evidence of the safety of such foods for healthy persons, especially children.

The BfR therefore recommends that the Federal Ministry of Food, Agriculture and Consumer Protection (BMELV) contact the EU Commission, so that the latter commissions the European Food Safety Authority (EFSA) to conduct a new assessment of phytosterols as food fortifier. Furthermore, the BfR recommends that suitable management measures be taken to ensure that the consumption of such foods is restricted to people with increased cholesterol levels and that healthy individuals, especially children, do not eat foods with phytosterol addition on a regular basis.

### 3 Statement of Reasons

The study “Effects of long term plant sterol and stanol consumption on the retinal vasculature: A randomized controlled trial in statin users” touches on the question to what extent plant sterols must be construed as an independent risk factor for the genesis of cardiovascular disease. On this question, the BfR had already made the following statements in 2004:

- a) There are indications but no conclusive chain of evidence to support the hypothesis that phytosterols can contribute to the genesis of coronary heart disease even in slightly elevated plasma concentrations.
- b) The hypothesis results from
  - the correlation between early coronary incidents with very high phytosterol levels in the plasma of phytosterolaemics and
  - the observation that early coronary incidents in coronary heart disease test persons correlate with familiar hypercholesterolaemia with plasma phytosterol concentrations in the upper segment of normal distribution.

In its opinion from 21 April 2005, the NDA panel of the EFSA (Panel on Dietetic Products, Nutrition and Allergies) commented that this issue had been done sufficient justice in the existing safety assessments of phytosterols as part of the novel food applications (EFSA, 2005).

Since then, however, several studies have been published which reported a positive correlation between the phytosterol concentration in the plasma and the incidence of cardiovascular disease (coronary heart disease) (Assmann et al., 2006; Rajaratnam et al., 2000 and Thiery et al., 2006). Nevertheless, epidemiological studies with opposite results have also appeared (BfR, 2008). In addition, the study "*Genetic Regulation of Serum Phytosterol Levels and Risk of Coronary Artery Disease*" by D. Teupser and J. Thiery from the University of Leipzig with contributions from 42 other authors from both national and international institutions appeared in August 2010 in "*Circulation: Cardiovascular Genetics*", a magazine published by the *American Heart Association*. This study reported on the identification of certain genetic polymorphisms which were concordant and associated in a statistically significant way with the serum level of plant sterols and with the incidence of cardiovascular disease. The fact that two of the identified polymorphisms concern a gene of the sterol transport protein ABCG5/8 can be seen as an indication of a possible causal link. The congenital functional loss of this transport protein is known as the cause for the congenital metabolic disorder phytosterolaemia which is characterised by very high phytosterol plasma concentrations and a high risk of premature heart attack (Sudhop and Bergemann, 2004).

Based on a population of test persons taking statin medication (18 to 65 years of age), the study "*Effects of long term plant sterol and stanol consumption on the retinal vasculature: A randomized controlled trial in statin users*" investigated the influence of phytosterols and phytostanols on human retinal vessels. The retinal vessels form part of microcirculation and are accessible by non-invasive optical methods, meaning that the vessel diameter can be measured with optoelectronic methods such as eye fundus photography with electronic image interpretation. Although cardiovascular disease (coronary heart disease) essentially denotes diseases of the large vessels, some studies have shown a significant correlation between the diameter of the retinal vessels (especially the veins) as well as the quotient of the artery and vein diameter (A/V quotient) and established cardiovascular parameters including deadly heart attacks (Wong et al., 2002, Ikram et al., 2004; Wang et al., 2002 and McGeechan et al., 2008). Retinal vessels analysis is therefore increasingly used for early diagnosis of cardiovascular risks.

The test persons examined by means of eye fundus photography neither had elevated blood pressure nor increased blood sugar levels. However, in order to lower their cholesterol level, they had been treated with statin-type cholesterol synthesis inhibitors for some time past. In the study, they were additionally given half-fat margarine for 85 weeks. This margarine either contained 2,5 g **phytosterols** (eleven test persons), 2.5 g **Phytostanols** (eight subjects) or no added plant sterols or stanols (11 test persons) per daily intake (30 g). Apart from eye fundus photography, the test person's plasma concentrations for various sterol compounds before and after the intervention were also measured.

All test persons who were given margarines with **phytosterols** or **phytostanols** showed a significant reduction of the LDL cholesterol level by approximately 10% compared to the control group. At the same time, cholesterol synthesis was, despite statin medication, significantly higher in both groups than it was in the control group. For 11 of the test persons who received **phytosterol** margarine, the plasma concentrations for **campesterol** and  **$\beta$  sitosterol** (in relation to cholesterol) rose by 110 % and 44 % respectively, whereas both concentrations were reduced by 14.3 and 6.8 % respectively in test persons who received **phytostanols**. The basal plasma concentrations of **campestanol** and **sitostanol** were about 100 times lower for the test persons in all groups than then basal **phytosterol** concentrations. Although, for the test persons who took **phytostanols** for 85 weeks, the **campestanol** and

sitostanol plasma concentrations rose ten-fold and six-fold respectively, they still remained lower overall than the initial phytosterol concentrations in all groups.

In the eye fundus photographs of all test persons which were taken before and after the intervention, the diameters of four retinal arteries and four retinal veins were measured for each subject. In addition, the difference between the post-intervention values and the initial values was determined. In direct comparison to the intervention groups, no statistically significant changes in the vessel diameter were found. However, a trend towards an increase of the vein diameter and towards a decrease of the A/V quotient was observed in the phytosterol group compared to the two other groups. In addition, the evaluation of the vein diameter in dependence of the phytosterol level across all individuals in two statistical regression models showed a significant positive correlation of the vein diameter with the campesterol concentration (in relation to cholesterol) in the blood plasma.

The authors interpret the results of the study as an indication of a possible detrimental effect of phytosterols on vessels which a) exists independently of any reduction of the cholesterol level and b) would have to be verified by additional studies.

This study for the first time presents findings based on experiments with humans which show that a food-based increase of the plant sterol plasma level has a detrimental influence on the risk parameter for coronary heart diseases independently of the reduction of the LDL cholesterol level. Although the analysis of the microvessels of the retina for an early recognition of cardiovascular risks has not been fully established, this method is already widely used in medical research / practice. This study does not permit any statement yet on the question whether the consumption of plant sterols does indeed increase the risk of a heart attack in test persons affected by changes in the retinal vessels or whether, due to the reduction of the cholesterol level, a positive net effect is to be expected. Here it is necessary to wait for the results of studies which investigate the influence of the consumption of foods containing phytosterols on clinical endpoints.

In addition, it cannot be excluded that the vessels of the examined subjects were already affected by their underlying disease. For this reason, it would have to be investigated whether healthy persons also react to a food-based increase of the plasma phytosterol concentrations with changes in the diameter of the retinal microvessels.

Overall, even this study does not furnish sufficient data to allow a final assessment of the atherogenic potential of slightly increased phytosterol plasma concentrations. However, within the context of the totality of studies suggesting independent atherogenic potential of phytosterols, this study provides further indications of the existence of such a risk. Especially for healthy persons who start consuming such foods on a regular basis as children an increased atherogenic risk seems possible.

For Germany it was found that 3.5 % of the users of foods containing phytosterols are underage children who were not known to have elevated cholesterol levels (Niemann et al., 2007). In Belgium, a recent food consumption study established that 21 % of pre-school children in a Flemish region also eat foods containing phytosterols and that for 58 % of adult consumers of such foods who know what their cholesterol level is, that level was not elevated (Sioen, et al., 2011). These figures show that the mandatory labelling of foods containing added plant sterols is not a sufficient measure to ensure that the consumption of such foods is restricted to people with elevated cholesterol levels.

#### 4 Framework of Action / Measures

The BfR suggests that the EFSA is commissioned to carry out a reassessment of phytosterols added to foods. Furthermore, the BfR recommends that suitable management measures be taken to ensure that the consumption of such foods is restricted to people with increased cholesterol levels and that healthy individuals, especially children, do not eat foods with phytosterol addition on a regular basis.

## 5 References

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