



Summary of evidence

Phytosterol/Stanol enriched foods

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It is based on a previous Heart Foundation nutrition policy paper, *Plant sterols and stanols. A position statement from the National Heart Foundation of Australia's Nutrition and Metabolism Advisory Committee* (2003), prepared by Dr Manny Noakes.

This summary of evidence was developed through a review and consultation process. A working group consisting of the following members guided the development:

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- Professor David Sullivan (Clinical Lipidologist, Royal Prince Alfred Hospital)
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Expert comments on this summary of evidence were received from Dr Andrew Boyden (Medical Affairs Manager, Heart Foundation).

This paper was approved by the National Cardiovascular Health Advisory Committee.

Important findings

The Heart Foundation's findings below are based on the scientific literature discussed in this statement.

Evidence	Level of evidence
Phytosterols lower LDL-cholesterol in people with normocholesterolemia, hypercholesterolaemia and diabetes.	I
For people with increased risk of CVD, consuming phytosterol/stanol enriched foods provides an additional option for risk reduction through lowering the level of cholesterol.	II
A daily intake of approximately 2 g of phytosterol/stanol enriched margarine reduces LDL-C levels by approximately 10%, but has little effect on HDL cholesterol (HDL-C) or triglycerides.	I
A daily intake of approximately 2.5 g of phytosterol enriched breakfast cereal, reduced fat yoghurt, reduced fat milk or bread reduces LDL-C levels by approximately 5 to 15%.	II
Consuming phytosterol/stanol enriched foods at levels higher than 2–3 g per day provides no additional benefits to lowering LDL-C.	I
Daily consumption frequency does not influence the cholesterol-lowering efficacy of phytosterol/stanols.	II
Phytosterol/stanol enriched foods have an additive effect in lowering LDL-C when combined with statins.	II
There are no reported adverse effects from daily consumption of phytosterol/stanol enriched foods, although long-term safety information is not available.	II
When consuming phytosterol/stanol enriched foods, blood carotenoids are reduced. An additional serving of high-carotenoid fruit and vegetables is effective in maintaining blood carotenoid concentrations.	II
People with the rare inherited metabolic disease homozygous sitosterolaemia have high blood phytosterol levels and premature atherosclerosis. Restricted intake of phytosterols is recommended for these people.	II

Background information

Phytosterols (or plant sterols) are an essential component of cell membranes and are produced by plants but not the human body. Stanols are saturated sterols; they have no double bond in the sterol ring, and are much less abundant.

Phytosterols and stanols are found in wood pulp, leaves, nuts, vegetable oils, seeds, cereals and some other plants. The chief source of commercially available phytosterols is deodorised distillate from soybean oil or palm oil, or tall (pine) oil.

The major phytosterol is sitosterol (approximately 80%). Others present in the diet include campesterol and stigmasterol, and trace amounts of sitostanol.

Phytosterols and stanols are similar in structure to cholesterol. The difference is the presence of a methyl or ethyl group in their side chains. This difference means that, in comparison to cholesterol, phytosterols and stanols are not absorbed, or are minimally absorbed.

Daily phytosterol consumption is estimated to be between 160 to 400 mg in various populations.¹

1. Mechanism for lowering cholesterol levels

Evidence	Level of evidence
Phytosterols lower LDL-cholesterol in people with normocholesterolemia, hypercholesterolemia and diabetes.	I

Studies indicate that incorporating phytosterol/stanols into the diet may be an effective method of lowering total and LDL-C levels.

It has been found that the serum LDL-C-lowering effect of phytosterol/stanol originates from reduced intestinal cholesterol absorption.² In the past it was hypothesised that phytosterols were incorporated into the mixed micelles in the intestinal tract more readily than cholesterol, therefore displacing cholesterol from mixed micelles and resulting in reduced intestinal cholesterol absorption. However, recent findings suggest that there is an additional process in which phytosterol/stanols actively influence cellular cholesterol metabolism within intestinal enterocytes.²

Additionally, in response to the reduced supply of exogenous cholesterol, receptor mediated lipoprotein cholesterol uptake is probably enhanced.² The discovery of transporters in the intestinal mucosa cells and hepatocytes has given new insights into the regulation of the intestinal absorption of sterols.³

The physiologically active forms are most likely the free, unesterified phytosterol/stanols. This is because steryl and stanyl esters are thought to be rapidly hydrolysed by intestinal enzymes, yielding the physiologically active free sterols and stanols.⁴ Moreau and colleagues⁵ have suggested that free sterols and stanols are effective in lowering LDL-C, as long as they are formulated and delivered in a

'bioavailable' physical state. This implies that efficacy may need to be assessed for each phytosterol formulation in the context of the form of delivery.

The cholesterol-lowering effect of phytosterol/stanol esters has been well documented.^{6,7} A systematic review studying the efficacy of phytosterols has shown that in people with normocholesterolemia, hypercholesterolemia and diabetes (n=3609), 2.4 g/day of phytosterols enriched foods can significantly lower LDL-C by 9.9%.⁸ The cholesterol-lowering effect of phytosterols has also been demonstrated in postmenopausal women with CHD.⁹

2. Cardiovascular disease

Evidence	Level of evidence
For people with increased risk of CVD, consuming phytosterol/stanol enriched foods provide an additional option for risk reduction through lowering the level of cholesterol.	II

There is considerable evidence that dietary saturated (and trans) fatty acids lead to increases in blood levels of LDL-C (hypercholesterolaemia), and ultimately to atherosclerosis. Hypercholesterolaemia represents a significant risk for CVD.

Phytosterol/stanol enriched spreads are used for the treatment of hypercholesterolaemia and in the long-term may assist in the reduction of CVD risk. The cholesterol-lowering effect has been observed in long-term (52 weeks) studies^{10,11} as well as in short-term trials with people with mild hypercholesterolemia.

The first line of treatment for hypercholesterolemia is dietary management, in particular, the reduction of saturated fat intake to lower LDL-C concentrations. The effect of phytosterol/stanols on blood lipids has been shown to be additive to that of fatty acid manipulation.

In statin studies, approximately one year of effective LDL-C reduction is required for demonstrating a lowering of CHD risk.¹² As the cholesterol-lowering effect of phytosterol/stanol enriched foods is about half that of statins, studies would need to continue for many years and be of sufficient statistical power.

Although long-term cholesterol-lowering studies, needed for actual prevention of CVD, are lacking for phytosterols/stanols, a 2003 review has estimated that the risk reduction of CVD over the first five years of consumption of free or esterified phytosterol/stanols to be 12% to 20%, and for life-time consumption 20%.¹³

The higher the absorption of cholesterol, the higher are the phytosterol contents in serum, resulting in the higher content of phytosterols in atherosclerotic plaque.¹⁴ Several studies have concluded that statin treatment is associated with an increase in phytosterol absorption and also arterial plaque.^{14,15} In contrast, no association was found between elevated levels of phytosterols and atherosclerosis in mice that were genetically modified to have elevated levels of plasma phytosterols, and in middle-aged men and women.¹⁶ However, the role of dietary phytosterols in the development of atherosclerotic plaque is not known and warrants further research.

3. Nutritional information

Australian regulations

Food Standards Australia and New Zealand (FSANZ) have regulations around phytosterol but not stanol esters.

In 2000, FSANZ approved the use of phytosterol esters in table spreads and margarines at 13.7% (w/w).¹⁷ In 2006, approval was given for phytosterol esters derived from vegetable oils to be added into breakfast cereals and low fat milk and yoghurt and, phytosterols derived from tall oils as ingredients in low fat milk.¹⁸ The allowed range is 0.8 g to 1.0 g phytosterols from either vegetable oil or tall oil per serve of food (e.g. 250 mL low fat milk, one 200 g tub of yoghurt, 45 g of cereal).

Historical perspective

At un-supplemented intake levels, phytosterol/stanols have only modest effects on cholesterol absorption. However, for about 40 years it has been recognised that higher levels of consumption can interfere with cholesterol absorption and result in decreased serum cholesterol levels.

Studies on the efficacy of phytosterols date back to the 1950s and dose-response studies for unesterified phytosterols were conducted in the 1970s by Lees et al.¹⁹

In 1993, Becker et al²⁰ showed 6 g/day of sitosterols lowered LDL-C by 20%, and by 33% with 1.5 g/day of sitostanol in children with familial hypercholesterolemia. It was thought that stanols were more effective and safer than sterols, but the negative outcome of a study by Denke et al²¹ led to the recognition that the lipid solubility of free stanols was very limited. This was overcome by esterifying them with fatty acids; the resultant stanol esters being freely soluble in fat spread.²² Short-term studies suggest that equivalent amounts of phytosterol/stanol esters are similarly effective in lowering LDL-C.²²

Recently the interest in unesterified phytosterols has been revived, with several studies demonstrating efficacy of microcrystalline and lecithin solubilised forms²³⁻²⁵ and efficacy in low fat foods.²⁶

Enriched foods

Evidence	Level of evidence
A daily intake of approximately 2 g of phytosterol/stanol enriched margarine reduces LDL-C levels by approximately 10%, but has little effect on HDL-C or triglycerides.	I
A daily intake of approximately 2.5 g of phytosterols enriched breakfast cereal, reduced fat yoghurt, reduced fat milk or bread reduces LDL-C levels by approximately 5 to 15%.	II
Consuming phytosterol/stanol enriched foods at levels higher than 2–3 g per day provides no additional benefits to lowering LDL-C.	I

In recent times, the esterification of sterols and stanols has allowed for their incorporation into dietary fats, in particular table spreads, margarine and mayonnaise.

A systematic review of 14 randomised controlled trials (RCT)⁶ concluded that 2 g per day of phytosterol/stanols enriched margarine reduced serum concentrations of LDL-C by an average of 0.54mmol/l in people aged 50–59 (14%), 0.43mmol/l in people aged 40–49 (9%), and 0.33mmol/l in people aged 30–39 (11%). The dose–response relationship between phytosterol/sterol enriched foods and LDL-C is continuous up to a dose of about 2 g per day. At higher doses no further reduction in LDL-C is apparent.

One of the included trials by Maki and colleagues²⁷ investigated the effects of phytosterol enriched margarines in subjects with hypercholesterolemia in the context of a diet low in total and saturated fat. In this study, intakes of 1.1 g and 2.2 g/day of phytosterols were associated with LDL-C falls of 7.6% and 8.1% respectively. The systematic review found little change in serum HDL-C or triglyceride.

A randomised, double-blind crossover study of children with familial hypercholesterolaemia found a daily intake of 1.6 g phytosterol (PS) enriched spread significantly decreased plasma LDL-C by 10.2% during the PS intervention.²⁸

In addition to studies with margarine, efficacy has also been demonstrated for phytosterols in a variety of low fat foods, such as breakfast cereal, yoghurt, milk and bread as discussed below.

Clifton and colleagues²⁹ measured the relative effects of phytosterol enriched (2.6 g/day phytosterol esters) foods. Subjects with moderately elevated plasma total cholesterol were randomly allocated to treatment or control. The study concluded that serum total and LDL-C were significantly lowered when added to: milk (8.7% and 15.9%), and yoghurt (5.6% and 8.6%). Bread and breakfast cereal reduced serum LDL-C levels by approximately 6.5% and 5.4% respectively. In other studies, people with hypercholesterolaemia who consumed phytosterol enriched milk (2 g/day) showed a significant decrease in total cholesterol of 9.62% and LDL-C by 12.2% after 15 days.³⁰ Similarly, in a controlled trial in which 2.4 g sterol esters were incorporated within low fat cereal, bread and margarine, the average reduction in LDL-C was 13.6%.³¹

When bread, breakfast cereal and margarine were enriched with a higher level of phytosterols (6.6 g/day phytosterols esters) and consumed every day for 12 weeks, results showed a decrease in carotenoids and an increase in plasma phytosterol with no additional LDL-C lowering.³² Carotenoid levels were partially restored to baseline when five pieces of fruit and vegetables (including one carotenoid-rich) were consumed each day. When a phytosterol enriched milk (2 g/day) was combined with a phytosterol enriched margarine (2 g/day), no additional cholesterol-lowering benefits were observed above consuming the phytosterol enriched milk alone.³³

A phytosterol enriched reduced calorie orange juice (1 g/240 mL) consumed twice a day with meals was found to be effective in reducing total plasma cholesterol (7.2%) and plasma LDL-C (12.4%), and could be incorporated into the dietary portion of therapeutic lifestyle changes.³⁴ In contrast, Jones and colleagues³⁵ found no effect on plasma lipid levels when phytosterols (1.8 g/day) were incorporated into a non-fat or low-fat beverage.

At present there are no published studies on the efficacy of phytosterols taken as a direct supplement, although such products are available outside Australia.

Consumption frequency and occasion

Evidence	Level of evidence
Daily consumption frequency does not influence the cholesterol-lowering efficacy of phytosterol/stanols.	II

Studies have shown that daily consumption frequency does not influence the cholesterol-lowering efficacy of phytosterol/stanols.² It was found that consumption of 2.5 g phytosterol esters at one meal resulted in a similar LDL-C reduction as compared with consumption of the same amount of phytosterol divided over three meals.³⁶ Other studies have confirmed that no relation is evident between the consumption frequency of phytosterol/stanol esters and the reduction in LDL-C.^{6,37}

A 3.0 g phytosterol enriched yoghurt drink substantially decreased LDL-C when taken with a meal compared with being consumed without a meal.³⁸

4. Interaction with statin treatment

Evidence	Level of evidence
Phytosterol/stanol enriched foods have an additive effect in lowering LDL-C when combined with statins.	II

Simons³⁹ evaluated the effect of 4 g of phytosterol enriched margarine given with or without 400 ug cerivastatin and concluded that phytosterols have an additive effect to statin therapy in lowering LDL-C, with a further 8% reduction that is equivalent to doubling the dose of a statin. Several randomised controlled trials have demonstrated that phytosterol/stanol esters are an effective adjunct to cholesterol-lowering statins, reducing LDL-C from 7% to 15.6%.³⁹⁻⁴⁴ In a study of postmenopausal women with CHD, the effect of simvastatin was additive to the effect of phytosterol enriched margarine.⁹

5. Safety

Evidence	Level of evidence
There are no reported adverse effects from daily consumption of phytosterol/stanol enriched foods, although long-term safety information is not available.	II
When consuming phytosterol/stanol enriched foods, blood carotenoids are reduced. An additional serving of high-carotenoid fruit and vegetables is effective in maintaining blood carotenoid concentrations.	II
Individuals with the rare inherited metabolic disease homozygous sitosterolaemia have high blood phytosterol levels and premature atherosclerosis.	II

On the basis of the limited number of studies undertaken to date, there is nothing to suggest that the consumption of either phytosterol or sterol esters is unsafe. This

conclusion is based on studies in which the stanol/sterol has been consumed for up to 12 months. Studies of longer-term consumption have not been performed in significant numbers of people. Although plasma sitosterol concentrations have been associated with increased coronary events,⁴⁵ this report does not relate to the effect of randomised dietary interventions.

Phytosterols are poorly absorbed by the majority of the population.^{46,47} About 4 to 10% of dietary sitosterol, stigmasterol and campesterol and less than 1% of sitostanol is absorbed from the intestine.⁴⁶ Most of the ingested phytosterols pass through the gut and are excreted⁴⁶ or re-secreted after absorption. Phytosterols that are absorbed and not re-secreted from the gut are rapidly and efficiently excreted through the bile.⁴⁷ Some patients with abnormal ABCG5/8 transporter function have diminished excretion of phytosterols. This can result in high plasma levels of phytosterols in response to dietary exposure.⁴⁸ The long-term effects of these levels are not known.

Studies indicate the toxicity of phytosterols is very low. In animal studies, intakes as high as 4.1 g of phytosterols per kilogram of body weight per day were observed to have no adverse effect.⁴⁹ The effects of phytosterols on reproductive parameters have now been investigated in depth. Contradicting earlier findings, studies using highly purified phytosterols have indicated no oestrogenic activity.⁵⁰ No effect on reproductive performance of high doses of phytosterols was observed in a two-generation study in rats.⁵¹

Hendriks and colleagues⁵² reported no significant effects of 3 g/day of phytosterols on levels of alkaline phosphatase, alanine transaminase, aspartate transaminase or gamma-glutamyl transaminase. Similar results have been observed in other studies.^{24,32} Coagulation and fibrinolytic factors appear unaffected. Plat and Mensink⁵³ reported no significant effects of 2.8 g/day of stanols on fibrinogen levels, factor VII activity, plasminogen activator inhibitor type-1 activity and tissue plasminogen activator levels. Ayesh et al.⁵⁴ reported no adverse effects of phytosterols on gastrointestinal parameters, including faecal short chain fatty acids, faecal microflora or faecal bacterial enzyme activity. Sterol-ester consumption also does not result in increased concentration of faecal bile acids or sterol metabolites.⁵⁵

Red blood cells incorporate phytosterols into their membrane. A study to assess the effect on statin-treated patients by de Jong⁵⁶ concluded that phytosterol/sterol ester consumption did not change the osmotic fragility of erythrocytes.

Effect on lowering carotenoids and other nutrients

The consumption of phytostanol esters (2.6 g/day) has been reported to lower serum alpha-tocopherol.⁵⁷ Most of the tocopherols are carried in LDL-C, which is reduced by phytostanol esters. It is important to note that the ratio of alpha-tocopherol to cholesterol was not changed. A lower ratio implies a deficiency of tocopherol beyond the lowering expected for reduction of LDL-C concentration.

Several studies indicate serum levels of some carotenoids, notably beta-carotene, are reduced by the ingestion of phytosterol/stanols.^{27,52,53,58–60} This is important because prospective⁶¹ and several cross-sectional studies have shown an inverse association between dietary or plasma carotenoids and type 2 diabetes or related metabolic indices. In contrast, a recent study has found no prospective association between baseline plasma carotenoids and the risk of type 2 diabetes in middle-aged and older women.⁶²

Very recently it was shown that, when consuming phytosterol (2.3 g/day) or stanol (2.5 g/day) enriched spreads, a moderate increase of dietary carotenoids (an additional daily serving of high-carotenoid vegetables or fruits) is effective in maintaining blood carotenoid concentrations.⁶⁰ In a study extending for one year,⁶³ consumption of 1.6 g phytosterol enriched spread did not result in a lower lipid adjusted carotenoid concentration. However, carotenoid concentrations changed over time. Phytosterol intake reduced lipid adjusted alpha- and beta-carotene concentrations by only 15 to 25% after one year, relative to control whereas lipid-adjusted fat-soluble vitamin concentrations remained unchanged. In the same study, further extensive safety examination of the long-term effects of phytosterol consumption showed no effects on red blood cell deformability, hormone levels in males (free and total testosterone) and females (luteinizing hormone, follicle stimulating hormone, beta-estradiol and progesterone), or all clinical chemical and haematological parameters measured. There was also no difference in adverse events reported between subjects consuming control spread and subjects consuming phytosterol enriched spread. In conclusion, consumption of 1.6 g phytosterol esters for one year was associated with a significant 6% fall in LDL-C without apparent adverse effects. A study to compare the effects of phytosterol esters and plant-free sterols on beta-carotene and alpha-tocopherol found that phytosterol esters reduced the bioavailability more than did plant free sterols.⁶⁴

Sitosterolaemia

A very small proportion of the population (approximately one in 6 million) suffer from a rare inherited metabolic disease called homozygous sitosterolaemia, which results in xanthomatosis and premature atherosclerosis. These people have high serum levels of sitosterol and other phytosterols due to a high rate of intestinal absorption and reduced biliary removal of phytosterols by the liver.⁶⁵ Restricted intake of phytosterols is recommended for these individuals. Heterozygotes for phytosterolaemia appear to respond normally to ingested phytosterols.⁶⁶ Patients with sitosterolaemia have been observed to develop premature and severe coronary artery atherothrombotic disease.^{65,67} However, as discussed, studies of large populations have shown no association between plasma phytosterol levels and CVD.

NHMRC levels of evidence for clinical interventions⁶⁸

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test and post-test.

References

1. Ostlund R Jr. Phytosterols in human nutrition. *Annu Rev Nutr* 2002; 22, 533–549.
2. Plat J, Mensink R. Plant Stanol and Sterol Esters in the Control of Blood Cholesterol Levels: Mechanism and Safety Aspects. *Am J Cardiol* 2005; 96: 15–22.
3. von Bergmann K, Sudhop T, Lutjohann D. Cholesterol and plant sterol absorption: recent insights. *Am J Cardiol* 2005; Jul 4; 96: 10D–14D.
4. Miettinen T, Vuoristo M, Nissinen M et al. Serum, biliary and faecal cholesterol and plant sterols in colectomized patients before and during consumption of stanol ester margarine. *Am J Clin Nutr* 2000; 71: 1095–1102.
5. Moreau R, Whitaker B, Hicks K. Phytosterols, phytostanols, and their conjugates in foods: structural diversity, quantitative analysis, and health-promoting uses. *Prog Lipid Res* 2002; Nov; 41: 457.
6. Law M. Plant sterol and stanol margarines and health. *BMJ* 2000; Mar 25; 320: 861–4.
7. Plat J, Kerckhoffs D, Mensink R: Therapeutic potential of plant sterols and stanols. *Curr Opin Lipidol* 2000; 11: 571–76.
8. Normen L, Holmes D, Frohlich J. Plant sterols and their role in combined use with statins for lipid lowering. *Curr Opin Investig Drugs* 2005; Mar; 6: 307–16.
9. Gylling H, Radhakrishnan R, Miettinen T. Reduction of serum cholesterol in postmenopausal women with previous myocardial infarction and cholesterol malabsorption induced by dietary sitostanol ester margarine: women and dietary sitostanol. *Circulation* 1997; 96: 4226–31.
10. Miettinen T, Puska P, Gylling H et al. Reduction of serum cholesterol with sitostanol-ester margarine in a mildly hypercholesterolemic population. *N Engl J Med* 1995; 333: 1308–12.
11. Brink E, Hendriks H. Long-term follow-up study on the use of a spread enriched with plant sterols, TNO report, V 99.869, Nutrition and Food Research Institute, 2000.
12. Miettinen T, Gylling H. Plant stanol and sterol esters in prevention of cardiovascular diseases. *Ann Med* 2004; 36: 126–34.
13. Katan M, Grundy S, Jones P et al. Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. *Mayo Clin Proc* 2003; Aug; 78: 965–78.
14. Miettinen T, Railo M, Lepantalo M et al. Plant sterols in serum and in atherosclerotic plaques of patients undergoing carotid endarterectomy. *J Am Coll Cardiol* 2005; Jun 7; 45: 1794–801.
15. Miettinen TA, Gylling H. Effect of Statins on Noncholesterol Sterol Levels: Implications for Use of Plant Stanols and Sterols. *Am J Cardiol* 2005; 96: 40–46.
16. Wilund K, Yu L, Xu F et al. No association between plasma levels of plant sterols and atherosclerosis in mice and men. *Arterioscler Thromb Vasc Biol* 2004; Dec; 24: 2326–32.
17. Food Standards Australia and New Zealand. Application A410: Phytosterol esters derived from vegetable oils. Canberra. Food Standards Australia and New Zealand, 2000.
18. Food Standards Australia and New Zealand. Second Review Report. Application A433: Phytosterol esters derived from vegetable oils in breakfast cereals. Application A434: Phytosterol esters derived from vegetable oils in low fat milk and yoghurt. Application A508: Phytosterol esters derived from tall oils as ingredients in low fat milk. Canberra, Food Standards Australia and New Zealand, 2006.

19. Lees A, Mok H, Lees R. Plant sterols as cholesterol-lowering agents: clinical trials in patients with hypercholesterolemia and studies of sterol balance. *Atherosclerosis* 1977; Nov; 28: 325–38.
20. Becker M, Staab D, von Bergmann K: Treatment of severe familial hypercholesterolemia in childhood with sitosterol and sitostanol. *J Pediatr* 1993; Feb; 122: 292–6.
21. Denke M. Lack of efficacy of low-dose sitostanol therapy as an adjunct to a cholesterol-lowering diet in men with moderate hypercholesterolemia. *Am J Clin Nutr* 1995; Feb; 61: 392–6.
22. Thompson GR, Grundy SM. History and Development of Plant Sterol and Stanol Esters for Cholesterol-Lowering Purposes. *Am J Cardiol* 2005; 96: 3–9.
23. Gremaud G, Dalan E, Pigué C et al. Effects of non-esterified stanols in a liquid emulsion on cholesterol absorption and synthesis in hypercholesterolemic men. *Eur J Nutr* 2002; Apr; 41: 54–60.
24. Christiansen L, Lahteenmaki P, Mannelin M et al. Cholesterol lowering effect of spreads enriched with microcrystalline plant sterols in hypercholesterolaemic subjects. *Eur J Nutr* 2001; 40: 66–73.
25. Vanstone C, Raeini-Sarjaz M, Parsons W et al. Unesterified plant sterols and stanols lower LDL-cholesterol concentrations equivalently in hypercholesterolemic persons. *Am J Clin Nutr* 2002; Dec; 76: 1272–8.
26. Tikkanen M, Hogstrom P, Tuomilehto J et al. Effect of a diet based on low-fat foods enriched with nonesterified plant sterols and mineral nutrients on serum cholesterol. *Am J Cardiol* 2001; Nov 5; 88: 1157–62.
27. Maki K, Davidson M, Umporowicz D et al. Lipid responses to plant-sterol-enriched reduced-fat spreads incorporated into a National Cholesterol Education Program Step I diet. *Am J Clin Nutr* 2001; 74: 33–43.
28. Amundsen A, Ose L, Nenseter M et al. Plant sterol ester-enriched spread lowers plasma total and LDL cholesterol in children with familial hypercholesterolemia. *Am J Clin Nutr* 2002; Aug; 76: 338–44.
29. Clifton P, Noakes M, Sullivan D et al. Cholesterol-lowering effects of plant sterol esters differ in milk, yoghurt, bread and cereal. *Eur J Clin Nutr* 2004; Mar; 58: 503–9.
30. Goncalves S, Maria A, Silva A et al. Phytosterols in milk as a depressor of plasma cholesterol levels: experimental evidence with hypercholesterolemic Portuguese subjects. *Clin Hemorheol Microcirc* 2006; 35: 251–5.
31. Nestel P, Cehun M, Pomeroy S et al. Cholesterol-lowering effects of plant sterol esters and non-esterified stanols in margarine, butter and low-fat foods. *Eur J Clin Nutr* 2001; Dec; 55: 1084–90.
32. Clifton P, Noakes M, Ross D et al. High dietary intake of phytosterol esters decreases carotenoids and increases plasma plant sterol levels with no additional cholesterol lowering. *J Lipid Res* 2004; Aug; 45: 1493–9.
33. Noakes M, Clifton P, Doornbos A et al. Plant sterol ester-enriched milk and yoghurt effectively reduce serum cholesterol in modestly hypercholesterolemic subjects. *Eur J Nutr* 2005; Jun; 44: 214–22.
34. Devaraj S, Jialal I, Vega-Lopez S. Plant sterol-fortified orange juice effectively lowers cholesterol levels in mildly hypercholesterolemic healthy individuals. *Arterioscler Thromb Vasc Biol* 2004; Mar; 24: e25–8.
35. Jones P, Vanstone C, Raeini-Sarjaz M et al. Phytosterols in low- and nonfat beverages as part of a controlled diet fail to lower plasma lipid levels. *J Lipid Res* 2003; Sep; 44: 1713–9.

36. Plat J, van Onselen E, van Heugten M et al. Effects on serum lipids, lipoproteins and fat soluble antioxidant concentrations of consumption frequency of margarines and shortenings enriched with plant stanol esters. *Eur J Clin Nutr* 2000; Sep; 54: 671–7.
37. Matvienko O, Lewis D, Swanson M et al. 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* 2002; Jul; 76: 57–64.
38. Doornbos A, Meynen E, Duchateau G et al. Intake occasion affects the serum cholesterol lowering of a plant sterol-enriched single-dose yoghurt drink in mildly hypercholesterolaemic subjects. *Eur J Clin Nutr* 2006; Mar; 60: 325–33.
39. Simons L. Additive effect of plant sterol-ester margarine and cerivastatin in lowering low-density lipoprotein cholesterol in primary hypercholesterolemia. *Am J Cardiol* 2002; Oct 1; 90: 737–40.
40. Blair S, Capuzzi D, Gottlieb S et al. 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* 2000; Jul 1; 86: 46–52.
41. Neil H, Meijer G, Roe L. Randomised controlled trial of use by hypercholesterolaemic patients of a vegetable oil sterol-enriched fat spread. *Atherosclerosis* 2001; Jun; 156: 329–37.
42. O'Neill F, Brynes A, Mandeno R et al. Comparison of the effects of dietary plant sterol and stanol esters on lipid metabolism. *Nutr Metab Cardiovasc Dis* 2004; Jun; 14: 133–42.
43. Cabezas M, de Vries J, Van Oostrom A et al. Effects of a stanol-enriched diet on plasma cholesterol and triglycerides in patients treated with statins. *J Am Diet Assoc* 2006; Oct; 106: 1564–9.
44. Gylling H, Miettinen T. Effects of inhibiting cholesterol absorption and synthesis on cholesterol and lipoprotein metabolism in hypercholesterolaemic non-insulin dependent diabetic men. *J Lipid Res* 1996; 37: 1776–85.
45. Assmann G, Cullen P, Erbey J et al. Plasma sitosterol elevations are associated with an increased incidence of coronary events in men: results of a nested case-control analysis of the Prospective Cardiovascular Munster (PROCAM) study. *Nutr Metab Cardiovasc Dis* 2006; Jan; 16: 13–21.
46. Heinemann T, Axtmann G, von Bergmann K. Comparison of intestinal absorption of cholesterol with different plant sterols in man. *Eur J Clin Invest* 1993; Dec; 23(12): 827–31: 827–31.
47. Salen G, Ahrens E, Grundy S: Metabolism of beta-sitosterol in man. *J Clin Invest* 1970; 49: 952–67.
48. Kwiterovich P, Chen S, Virgil D et al. Response of obligate heterozygotes for phytosterolemia to a low-fat diet and to a plant sterol ester dietary challenge. *J Lipid Res* 2003; Jun; 44: 1143–55.
49. Hepburn P, Horner S, Smith M. Safety evaluation of phytosterol-esters. Part 2. Sub-chronic 90-day oral toxicity study on phytosterol-esters - a novel functional food. *Food Chem Toxicol* 1999; 37: 521–32.
50. Baker V, Hepburn P, Kennedy S et al. Safety evaluation of phytosterol-esters. Part 1. Assessment of oestrogenicity using a combination of in vivo and in vitro methods. *Food Chem Toxicol* 1999; 37: 13–22.
51. Waalkens-Berendsen D, Wolterbeek A, Wijnands M et al. Safety evaluation of phytosterol-esters. Part 3. Two generation reproductive study with phytosterol-esters in rats – a novel functional food. *Food Chem Toxicol* 1999; 37: 683–96.
52. Hendriks H, Weststrate J, van Vliet T et al. Spreads enriched with three different levels of vegetable oil sterols and the degree of cholesterol lowering in normocholesterolaemic and mildly hypercholesterolaemic subjects. *Eur J Clin Nutr* 1999; 53: 319–27.

53. Plat J, Mensink R. Vegetable oil based versus wood based stanol ester mixtures: effects on serum lipids and hemostatic factors in non-hypercholesterolaemic subjects. *Atherosclerosis* 2000; Jan; 148: 101–112.
54. Ayesch R, Weststrate J, Drewitt P et al. Safety evaluation of phytosterol esters. Part 5. Faecal short-chain fatty acid and microflora content, faecal bacterial enzyme activity and serum female sex hormones in healthy normolipidaemic volunteers consuming a controlled diet either with or without a phytosterol ester-enriched margarine. *Food Chem Toxicol* 1999; 37: 1127–38.
55. Weststrate J, Ayesch R, Bauer-Plank C et al. Safety evaluation of phytosterol-esters. Part 4. Faecal concentrations of bile acids and neutral sterols in healthy normolipidaemic volunteers consuming a controlled diet either with or without a phytosterol-ester enriched margarine. *Food Chem Toxicol* 1999; 37: 1063–71.
56. de Jong A, Plat J, Mensink R. Plant sterol or stanol consumption does not affect erythrocyte osmotic fragility in patients on statin treatment. *Eur J Clin Nutr* 2006; Aug; 60: 985–90.
57. Gylling H, Puska P, Vartiainen E et al. Retinol, vitamin D, carotenes and alpha-tocopherol in serum of a moderately hypercholesterolemic population consuming sitostanol ester margarine. *Atherosclerosis* 1999; Aug; 145: 279–85.
58. Weststrate J, Meijer G: Plant sterol-enriched margarines and reduction of plasma total- and LDL-cholesterol concentrations in normocholesterolaemic and mildly hypercholesterolaemic subjects. *Eur J Clin Nutr* 1998; 52: 334–43.
59. Davidson M, Maki K, Umporowicz D et al. Safety and tolerability of esterified phytosterols administered in reduced-fat spread and salad dressing to healthy adult men and women. *J Am Coll Nutr* 2001; 20: 307–19.
60. Noakes M, Clifton P, Ntanos F et al. An increase in dietary carotenoids is effective in preventing the reduction in plasma carotenoid concentrations from plant sterol-enriched margarines. *Am J Clin Nutr* 2002; 75: 79–86.
61. Montonen J, Knekt P, Jarvinen R et al. Dietary antioxidant intake and risk of type 2 diabetes. *Diabetes Care* 2004; Feb; 27: 362–6.
62. Wang L, Liu S, Pradhan A et al. Plasma lycopene, other carotenoids, and the risk of type 2 diabetes in women. *Am J Epidemiol* 2006; Sep 15; 164: 576–85.
63. Hendriks H, Brink E, Meijer G et al. Safety of long-term consumption of plant sterol esters-enriched spread. *Eur J Clin Nutr* 2003; May; 57: 681–92.
64. Richelle M, Enslin M, Hager C et al. Both free and esterified plant sterols reduce cholesterol absorption and the bioavailability of beta-carotene and alpha-tocopherol in normocholesterolemic humans. *Am J Clin Nutr* 2004; Jul; 80: 171–7.
65. Salen G, Kwiterovich PJ, Shefer S et al. Increased plasma cholestanol and 5 α -saturated plant sterol derivatives in subjects with sitosterolemia and xanthomatosis. *J Lipid Res* 1985; 26: 203–9.
66. Stalenhoef A, Hectors M, Demecker P. Effect of plant sterol-enriched margarine on plasma lipids and sterols in subjects heterozygous for phytosterolaemia. *J Intern Med* 2001; 249: 163–6.
67. Sudhop T, von Bergmann K. Sitosterolemia – a rare disease. Are elevated plant sterols an additional risk factor? *Z Kardiol* 2004; Dec; 93: 921–8.
68. National Health and Medical Research Council: A guide to the development, implementation and evaluation of clinical practice guidelines. Canberra, National Health and Medical Research Council, 1999.



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****Update of evidence – 2017**

Based on the [review of current evidence by Foods Standards Australia New Zealand \(FSANZ\)](#) on phytosterol/stanol enriched foods, the following findings/statements in this 2009 summary of evidence are no longer relevant or applicable:

- Page 8 – 3. Nutritional information

“The allowed range is 0.8 g to 1.0 g phytosterols from either vegetable oil or tall oil per serve of food (e.g. 250 mL low fat milk, one 200 g tub of yoghurt, 45 g of cereal).”

- Page 10 – 5. Safety

“When consuming phytosterol/stanol enriched foods, blood carotenoids are reduced. An additional serving of high-carotenoid fruit and vegetables is effective in maintaining blood carotenoid concentrations”.

- Page 11,12 – Effect on lowering carotenoids and other nutrients

“The consumption of phytostanol esters (2.6 g/day) has been reported to lower serum alpha-tocopherol.⁵⁷ Most of the tocopherols are carried in LDL-C, which is reduced by phytostanol esters. It is important to note that the ratio of alpha-tocopherol to cholesterol was not changed. A lower ratio implies a deficiency of tocopherol beyond the lowering expected for reduction of LDL-C concentration.

Several studies indicate serum levels of some carotenoids, notably beta-carotene, are reduced by the ingestion of phytosterol/stanols.^{27,52,53,58–60} This is important because prospective⁶¹ and several cross-sectional studies have shown an inverse association between dietary or plasma carotenoids and type 2 diabetes or related metabolic indices. In contrast, a recent study has found no prospective association between baseline plasma carotenoids and the risk of type 2 diabetes in middle-aged and older women.⁶²

Very recently it was shown that, when consuming phytosterol (2.3 g/day) or stanol (2.5 g/day) enriched spreads, a moderate increase of dietary carotenoids (an additional daily serving of high-carotenoid vegetables or fruits) is effective in maintaining blood carotenoid concentrations.⁶⁰ In a study extending for one year,⁶³ consumption of 1.6 g phytosterol enriched spread did not result in a lower lipid adjusted carotenoid concentration. However, carotenoid concentrations changed over time. Phytosterol intake reduced lipid adjusted alpha- and beta-carotene concentrations by only 15 to 25% after one year, relative to control whereas lipid-adjusted fat-soluble vitamin concentrations remained unchanged. In the same study, further extensive safety examination of the long-term effects of phytosterol consumption showed no effects on red blood cell deformability, hormone levels in males (free and total testosterone) and females (luteinizing hormone, follicle stimulating hormone, beta-estradiol and progesterone), or all clinical chemical and haematological parameters measured. There was also no difference in adverse events reported between subjects consuming control spread and subjects consuming phytosterol enriched spread. In conclusion, consumption of 1.6 g phytosterol esters for one year was associated with a significant 6% fall in LDL-C without apparent adverse effects. A study to compare the effects of phytosterol esters and plant-free sterols on beta-carotene and alpha-tocopherol found that phytosterol esters reduced the bioavailability more than did plant free sterols.⁶⁴”

This information is current as of August 2017.