Foods fortified with plant sterols and stanols

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Background document to the advisory report:
Dutch dietary guidelines for people with atherosclerotic cardiovascular disease
No. 2023/01e, The Hague, February 7, 2023

Health Council of the Netherlands

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1 Introduction

This background document belongs to the advisory report *Dutch dietary guidelines for people with atherosclerotic cardiovascular disease* (ASCVD).[1] A description of the methodology for the search, selection and evaluation of the literature regarding the relationship between consumption of foods fortified with plant sterols and/or stanols and health outcomes in people with and without ASCVD is presented in this document. Furthermore, a description of the scientific evidence on this topic in people with and without ASCVD and the conclusions that have been drawn by the council's Committee on Nutrition are given. Safety aspects related to consumption of these foods are also addressed.

1.1 Definition and intake of plant sterols and stanols

Plant sterols and stanols, also known as phytosterols, are naturally present in foods of plant origin. Plant sterols and stanols have a chemical structure comparable to that of cholesterol. Plant stanols are saturated plant sterols (these do not have double bonds in the sterol ring structure). Plant sterols or stanols esterified to fatty acids or other organic acids are named plant sterol or stanol esters. In this document, the Committee uses the terms plant sterols and plant stanols for both esterified and non-esterified forms.

There exist many types of plant sterols and stanols. The most abundant naturally occurring plant sterols are sitosterol, campesterol, and stigmasterol. The most abundant naturally occurring plant stanols are sitostanol and campestanol. Plant stanols are much less abundant in nature than sterols.

In Western populations, the intake of naturally occurring plant sterols and stanols with the general diet is approximately 200 to 400 mg per day, and up to 600 mg in vegetarians. Higher intakes can be achieved via the consumption of foods fortified with plant sterols and/or stanols. In particular, margarines fortified with plant sterols or stanols are marketed in many countries, including the Netherlands.[2-4]

1.2 Recommendation on plant sterols and/or stanols in the Netherlands

There currently is no Health Council recommendation regarding the consumption of plant sterols and/or stanols. Regarding the use of nutrient supplements, the *Dutch dietary guidelines 2015* state that nutrient supplements are not needed, except for specific groups for which supplementation applies.[5] For instance, vitamin D supplements are recommended for various groups of people, such as 0 to 4-year-olds, women aged 50 and over, and everyone aged 70 and over.[6]

The European Food and Safety Authority (EFSA) approved a health claim of disease risk reduction for plant sterols and stanols, which was authorised by the European Commission (EC). The health claim sounds as follows: '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'. In 2009, the conditions for use linked to the claim were intakes of 1.5 to 2.4 g of plant sterols/stanols per day, incorporated in yellow fat spreads, dairy products, mayonnaise or salad dressings. In 2012, EFSA gave a positive opinion regarding health effects of higher intakes of plant sterols and stanols, applicable to daily intakes of 1.5 to 3 g plant sterols/stanols, which led to amended conditions for use.[7-9]

2 Methodology

Foods fortified with plant sterols and/or stanols are targeted at people who wish to reduce their LDL cholesterol levels. Since people with ASCVD (the target group of the current advisory report, further explained below) often have elevated LDL cholesterol levels and lipid management is one of the pillars of cardiovascular risk management[10,11], the Committee aimed to evaluate the health effects of foods fortified with plant sterols and/or stanols on health outcomes in people with ASCVD. The majority of studies on the health effects of plant sterols and/or stanols is performed in people without established ASCVD, but with elevated cholesterol levels. Only a few studies were specifically performed in people with established ASCVD.[2,3,12,13] Since this topic was not previously evaluated for the *Dutch dietary guidelines 2015*, the Committee additionally evaluated the evidence on this topic in people without ASCVD but with (often) elevated LDL cholesterol levels.

2.1 Question

The Committee aimed to answer the following question: What is the relationship (effect or association) of consumption of foods fortified with plant sterols and/or stanols with health outcomes in people with and without ASCVD?

2.2 Target group

The target group of the current advisory report is people with ASCVD. The Committee defines this group as people with clinically established coronary heart disease (CHD, consisting of acute coronary syndromes [myocardial infarction and unstable angina], stable angina and revascularisation procedures such as percutaneous coronary intervention [PCI] and coronary artery bypass grafting [CABG]), peripheral arterial disease (PAD) or cerebrovascular disease (consisting of stroke and transient ischemic attack). In the target population, atherosclerosis in the coronary arteries, aorta, iliac and femoral arteries, and cerebral arteries is the main underlying pathological process. Groups with a high risk (but no manifestation) of ASCVD, such as people with hypertension or elevated LDL cholesterol levels, fall outside this definition. Also, the target group of this advice does not include people with heart failure (except when those people also suffer from ASCVD). A detailed description of the target group of this advisory report is provided in the background document *Methodology for the evaluation of the evidence*.[14]

As explained above, the Committee also evaluated studies performed in people without established ASCVD, but with (mostly) elevated cholesterol levels.

2.3 Nutritional topics

In the current background document, the Committee focusses on the health effects of foods fortified with plant sterols and/or stanols. In particular (but not solely) fat-based

foods fortified with plant sterols or stanols, including yellow fat spreads and dairy products, have been the topics of scientific investigations.
Studies into natural consumption of plant sterols and/or stanols via the general diet were not evaluated by the Committee since intakes reached by natural diet are much lower than via fortified foods. The effects of natural consumption of plant sterols and/or stanols are therefore not representative for effects of foods fortified with plant sterols and/or stanols.

2.4 Health outcomes

The Committee selected the following health outcomes for this advisory report (further explained in the background document *Methodology for the evaluation of the evidence*[14]):

- short-term surrogate outcomes:
  - body weight
  - systolic blood pressure
  - low-density lipoprotein (LDL) cholesterol
  - estimated glomerular filtration rate (eGFR)
  - glycated haemoglobin (HbA1c) and fasting blood glucose
- long-term health outcomes:
  - all-cause mortality
  - morbidity and/or mortality from total CVD, CHD, stroke (cerebrovascular disease), heart failure, atrial fibrillation, type 2 diabetes, chronic obstructive pulmonary diseases (COPD), total cancer, breast cancer, colorectal cancer, lung cancer, dementia, depression
  - subtypes of CHD, such as myocardial infarction, angina pectoris and revascularisation procedures (i.e., coronary artery bypass surgery and percutaneous coronary intervention)

2.5 Selection and evaluation of the literature and drawing conclusions

2.5.1 People without ASCVD and with elevated LDL cholesterol

The Committee made use of reports on the efficacy and safety of foods fortified with plant sterols and/or stanols that were published by EFSA and the European Commission Scientific Committee on Food (SCF).[8,9,15-17] These reports were drawn up to support the evaluation of EU requested health claims and conditions of use (explained in paragraph 1.2). EFSA's scientific opinion on the efficacy was based on systematic reviews (SRs) with meta-analyses (MAs) of RCTs on the effects of foods fortified with plant sterols and/or stanols on LDL cholesterol.[8,9] This approach is in line with that used by the Committee, and therefore the Committee deemed the reports on efficacy useful for its evaluation. The MAs referred to in EFSA's reports were looked up by the Committee to gain further details on methodological aspects where needed. A

more recent MA (published in 2014)[3], that was not (entirely) included in EFSA's evaluation was additionally included in the Committee's evaluation but gave, according to the Committee's opinion, no reasons for adaptations of the conclusions drawn by EFSA.

Safety and other considerations

The Committee was not composed in such a way that it could evaluate safety of foods fortified with plant sterols and/or stanols. Therefore, the Committee relied on the judgements and scientific opinions of the SCF and EFSA regarding the safety aspects.[15,16,17]

In addition, for the purpose of interpretation of studies on plasma plant sterols in relation to CVD risk, and Mendelian randomisation (MR) studies on this topic in particular, dr. S. Burgess, medical statistician and expert on MR studies at Cambridge University (United Kingdom) and Prof. J. Plat, professor in physiology of nutrition with special attention for sterol metabolism at Maastricht University, were consulted by the Committee.

2.5.2 People with ASCVD

The Committee specifically searched for studies into the relationship of consumption of foods fortified with plant sterols and/or stanols with health outcomes performed in people with ASCVD, using a similar approach as for the other nutritional topics of the current advisory report. A detailed description of the approach used by the Committee for selecting and evaluating the scientific literature is provided in the background document *Methodology for the evaluation of the evidence*.[14] In short, the Committee aimed to base its evaluation of scientific literature on systematic reviews (SRs), including meta-analyses (MAs) and pooled analyses, of randomised controlled trials (RCTs) and/or prospective cohort studies examining the relationship of foods fortified with plant sterols and/or stanols with the above-listed health outcomes in people with ASCVD. To identify such publications, the Committee searched PubMed and Scopus in February 2022. The search strategy is presented in Annex A. The Committee did not find SRs, MAs or pooled analyses of RCTs and/or prospective cohort studies in people with ASCVD. Next, the Committee searched for reports of individual RCTs and/or prospective cohort studies in March 2022 and found 2 RCTs performed in people with ASCVD that were suitable for its evaluation.[4,18] These RCTs focussed on LDL cholesterol as outcome. The search strategy and specification of the study selection are presented in Annex A.

No studies on long term effects on or associations with cardiovascular diseases (or other chronic disease outcomes) of foods fortified in plant sterols and/or stanols were found, nor in people with and without ASCVD.

2.5.3 Drawing conclusions

A detailed description of the approach used for drawing conclusions is provided in the background document *Methodology for the evaluation of the evidence*.[14] In short, the Committee drew conclusions on (the certainty of) the evidence regarding the associations of consumption of foods fortified with plant sterols and/or stanols with risk of health outcomes in people with (prior) ASCVD, based on the number of studies, number of participants and number of cases that contributed to the evaluation. Also, it took the quality of the studies, in particular the risk of bias, and the heterogeneity between studies into account. The risk of bias of RCTs was judged based on what was reported in the selected MA reports. For individual RCTs not included in MAs, it was judged by the Committee using the revised Cochrane Collaboration's tool RoB 2.[19] This was done when 3 or more individual RCTs were included in the Committee's evaluation. The Committee used the decision tree (presented in the background document *Methodology for the evaluation of the evidence*[14]) as a tool to support consistency in drawing conclusions.

3 Effects of foods fortified with plant sterols and/or stanols

In this chapter, the Committee describes the scientific evidence for effects of foods fortified with plant sterols and/or stanols on LDL cholesterol in people with and without ASCVD.

3.1 People without ASCVD and with elevated LDL cholesterol

Conclusion:
Intervention studies show that consumption of foods fortified with 1.5 to 3 g/d plant sterols and/or stanols reduces LDL cholesterol levels with 7 to 11% in two to three weeks in people without ASCVD, and often with elevated LDL cholesterol.

Explanation:
The Committee drew the above given conclusion on efficacy based on reports with scientific opinions from the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA; 2009 and 2012).[8,9] The main findings from these reports are described below. In addition, the main MAs that contributed to the opinions of the EFSA Panels are described.

In 2009, the EFSA NDA Panel concluded that it has been scientifically proven that a daily plant sterol/stanol intake of 1.5 to 2.4 g lowers LDL cholesterol with 7.0 to 10.5% in 2 to 3 weeks. The panel gave a positive opinion on a health claim based on these findings. The panel noted that 1.5 to 1.9 g/d and 2.0 to 2.4 g/d plant sterols/stanols was observed to lower blood LDL cholesterol by an average of 8.5% and 8.9%, respectively.[8] These quantifications were obtained from a MA of Katan et al. (2003).[2] The MA of Katan et al. (2003) included 41 RCTs with 58 treatment arms and 41 placebo arms. Stanols or sterols at daily doses ranging between 0.7 to 4.0 g were added to fat-based foods (mainly margarine, and in a few RCTs to mayonnaise, olive oil, or butter). The stanols and sterols were mainly esterified. Many of the study participants were selected because of their elevated cholesterol levels. The average LDL cholesterol level in the placebo group was 3.55 mmol/L in people aged 45-54 years, and 4.17 mmol/L in people aged 55-64 years. The mean effect observed by Katan et al. was 10.1% (95%CI: 8.9, 11.3) LDL cholesterol reduction in 27 RCTs testing stanols at a mean dose of 2.5 g/d, and 9.7% (95%CI: 8.5, 10.8) LDL cholesterol reduction in 21 RCTs testing sterols at a mean dose of 2.3 g/d. The effect on LDL cholesterol reduction became stronger with increasing dose, and tended to flatten from intakes of 2 g/d. The authors observed little additional effect at doses higher than 2.5

g/d. The mean effect for ≥2.5 g plant sterols/stanols per day was 11.3% (95%CI: 10.2, 12.3). There was no statistically significant heterogeneity between studies. The effects on LDL cholesterol were established within a few weeks. The absolute (but not relative) LDL cholesterol reduction increased with age. The authors noted this may be due to the higher LDL cholesterol levels at higher age.
Katan et al. noted the observed effects were independent of background diet and were present in groups of people taking cholesterol-lowering drugs. Also, Katan et al. noted that adding plant sterols or stanols appeared somewhat more effective than doubling the statin dose. However, these observations were based on data of a few RCTs.
No judgement about the quality of the included studies and on the likelihood of publication bias was given by the authors. The first author of the paper disclaimed to have received grants from Unilever Research Laboratory for research on the effects of sterols on lipoproteins. Another author disclaimed to have received grants from the McNeil Corporation for research in stanols. Two authors disclaimed to have contributed to or to hold a patent or shares related to plant stanols. Another author reported to hold a patent of which the content was not reported.

The NDA Panel concluded that the findings of Katan et al. were confirmed in more recent MAs that included over 80 RCTs. The largest and most recent SR and MA referred to in EFSA's evaluation, was of Demonty et al. (2009).[12] This MA included 84 RCTs, 141 trial arms and 6805 participants. Most participants were from Europe or North America and were healthy or hypercholesteraemic. The pooled overall LDL cholesterol level at baseline was 3.86 mmol/L (95%CI: 3.77, 3.98). The mean plant sterol/stanol dose was 2.15 (95%CI 0.45, 9.00) g/d, provided in fat-based foods and foods with lower fat content, such as dairy products. Study durations ranged from 21 to 182 days.
The authors found a continuous dose-response relationship of plant sterol/stanol intake with LDL cholesterol. The pooled LDL cholesterol lowering effect was -0.34 mmol/L (95%CI: -0.31, -0.36) or 8.8% (95%CI: -8.31, -9.35) for a mean daily plant sterol/stanol dose of 2.15 g. The LDL cholesterol-lowering dose-response curve had a plateau at intakes of approximately 3 g/d, corresponding to an LDL cholesterol lowering effect of 10.7%. Between-trial heterogeneity as assessed by the Q-statistic was statistically significant for both the absolute and relative changes in LDL cholesterol. This may, among others, be due to differences in baseline LDL cholesterol and food formats provided. People with higher baseline LDL cholesterol levels had greater absolute LDL-reductions, and a larger effect was found with solid foods than liquid foods at high (>2 g/d) doses of plant sterols/stanols. There was a tendency towards a slightly lower efficacy of single versus multiple daily intakes of plant sterols/stanols. No differences in effect were found between sterols and stanols.
RCT quality was assessed using a custom designed tool adapted from the Delphi Consensus[20], and the method by Chalmers et al.[21] The authors judged the overall study quality as good for 68 strata and low for the remaining 73 strata. The overall

quality of the RCTs, the compliance, and the randomisation method did not significantly affect either the absolute or the relative dose-response curve. There were no subgroup analyses by study quality presented. Moreover, based on visual inspection of funnel plots and a probability plot of the ranked changes in LDL cholesterol, the authors concluded there were no indications for publication bias. Most of the authors of the MA (including the first and last author) were employed at Unilever R&D, the Netherlands, or worked on this study during an internship at Unilever R&D, the Netherlands.

The NDA Panel concluded that the findings of Katan et al. are representative of available RCTs. The panel noted that the RCTs included data from a large number of RCTs with different study protocols, different exposures (dose, food characteristics, time and frequency of plant sterols/stanols consumption) and different subject characteristics (baseline LDL cholesterol, age, sex, lifestyle, background diet and co-medication with statins). The panel also noted that the available evidence suggests intake once per day without a meal may be less effective than division of the daily dose into several doses and/or intake of those doses with the main meal.

In 2012, the NDA Panel of EFSA gave a positive opinion on the substantiation of a health claim on the effects of 3 g/d plant sterols/stanols in matrices approved by the EC (yellow fat spreads, dairy products, mayonnaise and salad dressings) on LDL cholesterol. The panel concluded it has been scientifically proven that such a dose reduces LDL cholesterol with 11.3% (95%CI 10.0, 12.5) in 2 to 3 weeks.[9] This was based on an unpublished MA of 27 treatment arms, of which 19 on stanols (11 parallel; 8 cross-over RCTs) and 8 on sterols (3 parallel; 5 cross-over RCTs) that specifically examined doses of ≥2.6 to ≤3.4 g plant sterols or stanols per day. The food formats were mainly margarine or spreads. The MA was performed by the applicant of the claim (Unilever), and on the request of EFSA only results of studies that examined doses between ≥2.6 to ≤3.4 g plant sterols or stanols per day were presented. For the selection of the studies for this MA, the applicant relied on the systematic literature searches of Demonty et al.[12] (described above) and of Musa-Veloso et al.[13] (2011), and additionally searched for more recent studies using the same search strategy. A brief description of the MA of Musa-Veloso et al. is given below*. Based on the 27 treatment arms, the relative pooled effect on LDL cholesterol lowering was 11.3% (95%CI: 10.0, 12.5). The EFSA panel noted several limitations in the applicants MA that contributed to the uncertainty of the reported estimate. First, study quality was not taken into account based on the observation of Demonty et al. that overall study quality, randomisation methods and subject compliance did not impact on the results. However, the panel considered this conclusion cannot be extrapolated to a small subset of studies in the MA of the applicant. Second, the panel noted limitations in the description of the random effects model, and noted uncertainties derived from the estimation of the relative (%) changes of LDL cholesterol concentrations and variance parameters which were not reported in most of the original RCT reports.

The full MA (including a broader range of doses) was published in 2014[3], and briefly described below**.

The NDA Panel noted it could have reached its conclusion without considering the unpublished MA of the applicant. The results provided by the applicant were very similar to the results of the MA of Katan et al. Katan et al. showed a pooled mean reduction of LDL cholesterol levels of 11.3% (95%CI: 10.2, 12.3) for ≥2.5 g plant sterols/stanols per day. The majority of RCTs (n=13) included in this evaluation were of doses between 3.0 and 3.5 g/d, followed by RCTs with doses between 2.5 and 2.9 g/d (n=5).

Moreover, the NDA Panel (2012) concluded[9], based on a SR and MA of Talati et al.[22] (2010) that included 14 parallel and cross-over RCTs with 531 healthy and hypercholesteraemic subjects, and one additional RCT of de Jong et al.[23] (2008) in 54 subjects, that the efficacy of plant sterols and stanols at daily intakes ranging from 1.5 to 3.0 g/d in food matrices approved by the EC have a similar efficacy on lowering blood LDL cholesterol.

*The MA of Musa-Veloso et al.[13] included a total 182 strata from 113 publications and 1 unpublished report and observed maximum LDL cholesterol reductions with plant sterols/stanols of 12.1%, with greater maximum reduction for sterols (16.4%) than stanols (8.3%). Musa-Veloso et al. did not take study quality into account based on the observation of Demonty et al. that overall study quality, randomisation methods and subject compliance did not impact on the results. The authors were affiliated with a consultancy firm specialised in the areas of regulatory affairs, food safety, and human and animal nutrition. The authors reported to have no conflicts of interest.

**In 2014, the MA of Ras et al.[3] was published. The study built forward on the MAs of Musa-Veloso et al. and Demonty et al. This MA included 124 studies (201 strata). In line with EFSA's conclusions, the authors reported a gradual reduction of LDL cholesterol with increasing doses of plant sterols/stanols up to intakes of approximately 3 g/d. At intakes of 3 g/d, the average LDL cholesterol reduction was 12%. There were comparable dose-response relationships between plant sterols (129 strata) and stanols (59 strata). Tests for heterogeneity and publication bias were not performed, and neither was the quality of the studies assessed. The first and last author of the paper declared to be employed at Unilever, which marketed food products enriched with plant sterols at that time.[3]

3.2 People with ASCVD

Conclusion:
There is too little research to draw a conclusion on the effects of consumption of foods fortified with plant sterols and/or stanols on LDL cholesterol levels in people with ASCVD.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion: There are two, small-scale individual RCTs in people with ASCVD that addressed the effects of plant sterols or stanols on LDL cholesterol. Two studies provide too little evidence to draw a conclusion. Below the two RCTs are described.

The cross-over RCT of Gylling et al. (1997)[4] included 22 postmenopausal women with CHD. A myocardial infarction, angioplasty or CABG operation had occurred at least 3 months before inclusion in the study. These women did not use estrogen therapy, and neither used lipid lowering agents. The average baseline LDL cholesterol level was 3.85 ± 0.17 mmol/L. The effect of 3 g/d plant stanols (sitostanol ester) in rapeseed oil margarine (intervention) compared to rapeseed oil margarine without sitostanol (control) was tested on LDL cholesterol levels, each for 7 weeks. At the end of the intervention period, there was a greater reduction in LDL cholesterol levels in the intervention than control group, with a 15% reduction in the intervention group and 8% reduction in the control group (P-value for difference between groups <0.05).
In a second group of 10 postmenopausal women using simvastatin treatment for over 1 year, the rapeseed oil margarine with sitostanol was given for 12 weeks. Their LDL cholesterol levels were reduced with 16% during the intervention. However, there was no comparison made with the rapeseed oil margarine without sitostanol.

The RCT of Gomes et al. (2017)[18] examined the effect of 2 g/d plant sterols in a vegetable spread on LDL cholesterol. The study included 41 people with CHD and LDL cholesterol >70 mg/dL (1.81 mmol/L) who were undergoing statin treatment. The participants were randomly assigned into four groups: control group (n=10), ezetimibe group (n=10), plant sterol group (n=11), and ezetimibe plus plant sterol group (n=10). Initial baseline LDL cholesterol levels were 2.52 ± 0.80 mmol/L in the control group and 2.47 ± 0.72 mmol/L in the plant sterol group. The LDL cholesterol levels in the plant sterol group decreased on average with 17% after the intervention period of 6 weeks. In the control group, the LDL cholesterol levels increased with 9%. In the plant sterol plus ezetimibe group it decreased with 27% and in the ezetimibe group with 19%. Statistically significant differences between groups were reported (P-value 0.004). However, it was not specified which groups differed from each other, and which groups did not. Thus, it is, based on the presented results, not sure whether the plant sterol group differed from the control group.

The results of these two small-scale RCTs are in line with findings in healthy people and people with hypercholesterolemia. However, these two RCTs provide too little evidence to specifically base conclusions on for people with ASCVD.

3.3 Combination with LDL-lowering medication

With respect to LDL-lowering medication use, EFSA noted in above-described report that the effects of plant sterols and/or stanols were also present in people who use statins. The above-described reports did not specify whether the use of products fortified with plant sterols or stanols have added value on top of ezetimibe or other LDL-lowering medication. Therefore, the Committee additionally searched for such studies, and three RCTs were found that addressed the combination of plant sterols with ezetimibe.[18,24,25] Based on these three studies, it was not clear to the Committee whether plant sterols have added value on top of ezetimibe. This is because the studies were rather small and did not show entirely consistent results. More specifically, one study in 22 participants showed an additional lowering effect on LDL cholesterol levels of plant sterols on top of ezetimibe.[25] A second study in 40 participants did not confirm this[24], and from a third study with 41 participants it is not clear whether the differences in LDL cholesterol reductions reached by ezetimibe plus plant sterols and ezetimibe alone were statistically significant.[18] The studies and their quality assessment are described in detail in Annex B.

The Committee did not find studies into combinations with other LDL-lowering medications such as PCSK9.

4 Safety and other considerations

In this chapter, the Committee describes the results of the safety evaluations by the SCF and EFSA. In addition, the Committee explains why studies on plasma plant sterols were not taken into account by the Committee.

4.1 Safety

In 2000, the SCF has assessed the safety of plant sterols.[15] The SCF concluded that the use of phytosterols at levels up to 8% per 100 g yellow fat spread is safe for human use. The toxicological evaluation was based on studies on absorption, distribution, metabolism and excretion and on sub-chronic toxicity, genotoxicity, reproductive toxicity, potential estrogenic activity and from human studies. Currently, the European Commission has authorised the placing on the market of the following food formats with added plant sterols or stanols: yellow fat spreads, milk, and yoghurt-type products.

The SCF noted that plant sterols (and stanols) interfere with the absorption of fat-soluble vitamins, beta-carotene in particular. With the ingestion of 20 g/d of products containing 8% plant sterols for 1 year, plasma beta-carotene levels in adults reduce with 20%. The SCF noted that such reductions in plasma beta-carotene levels might become relevant when the vitamin A status is not optimal, which may be the case for pregnant and lactating women as well as younger children. In 2002, the SCF assessed the effects of long-term ingestion of elevated levels of plant sterols with a particular attention on beta-carotene.[16] Based on this assessment, the SCF concluded that, considering there is no evidence for additional benefit on LDL cholesterol above 3 g per person per day, and that the consequences of a persistent decrease of blood levels of beta-carotene on human health are largely unknown, it is prudent to avoid intakes exceeding 3 g/day. In addition, the SCF recommends the consumption of natural sources of beta-carotene to counterbalance the expected reduction in beta-carotene and other fat-soluble vitamins.

In addition, the SCF noted the following in its report of 2002: ‘The absorption of plant sterols is much lower than that of cholesterol. However, consumption of phytosterols leads to a 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, leads 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.’ According to the Committee’s knowledge, there are currently no studies on the effects of long-term exposure to foods fortified with plant sterols on CVD events. The Committee is aware of reports of studies that addressed the relationships of plasma plant sterols with the

long-term risk of CVD in cohort studies in people without sitosterolaemia. These include both conventional cohort studies and a Mendelian randomisation study. Some of these studies suggest that relatively higher plasma plant sterol levels (often standardised to total cholesterol) associate with increased CVD risk, whereas other studies do not confirm this.[26-30] In the Committee's view, the results of these studies are not applicable to answer the question of whether long term consumption of foods fortified with plant sterols might increase CVD risk, and therefore these studies were not evaluated by the Committee. An extensive explanation is given below (paragraph 4.2).

In 2020, The NDA Panel of EFSA gave a scientific opinion on the safety of an extension of use of the novel food 'plant sterol esters' when added to vegetable fat spreads and to liquid vegetable fat-based emulsions for cooking and baking purposes. The panel noted that plant sterol oxidation products levels may exceed safety levels in adults when used at the maximum authorised dose of 3 g/d. The Panel concluded that the safety of the intended extension of use (i.e., cooking and baking) of plant sterols under the proposed conditions of use has not been established.[17]

4.2 Considerations regarding plasma plant sterols

Consumption of plant sterols increases plasma plant sterols. Whether slight elevations in plasma plant sterols might increase the risk of atherosclerosis and CVD has been a matter of debate for several decades.[31-35] This is particularly because the metabolism of plant sterols and cholesterol are closely related, and difficult to disentangle.[36,37] For this reason, the Committee did not evaluate observational studies into plasma plant sterols and risk of CVD events. Below, this is further explained.

With consumption of foods fortified with plant sterols, plasma levels of plant sterols increase. For instance, a MA of Ras et al. (2013) based on 41 intervention studies showed that intake of foods fortified with plant sterols (average plant sterol dose of 1.6 g/d) increased plasma sitosterol with 31% and campesterol with 37%. When standardised to total cholesterol (the ratio of these plant sterols to total cholesterol), these percentages were 42% and 61%, respectively.[38] These two types of plant sterols together contribute approximately 90% to plant sterols in plasma.[39] In the studies included by Ras et al., total plant sterol concentrations remained below 1% of total sterols in the circulation. In addition, the plasma levels were much lower than the plant sterol levels of people with homozygous sitosterolemia. This is a genetic disorder caused by mutations in the ABCG5 or ABCG8 gene, which are involved in sterol absorption. People with such mutations have extremely elevated plant sterol levels (approximately 500 to 1200 µmol/L; compared to approximately 7 to 8 µmol/L reported in studies in people without this disorder) and no or mild elevations in cholesterol.[38] These people have an increased risk of premature atherosclerosis.[40,41] This observation contributed to the question of whether consumption of foods fortified with

plant sterols, which also contribute to elevations in plasma plant sterols, might increase CVD risk. On the other hand, not all sitosterolemic people have been diagnosed with signs of premature atherosclerosis, and neither have people with heterozygous sitosterolemia.[42,43] These latter people generally have only slight elevations in plant sterols, which have been reported to be similar to or higher than the elevations reached with consumption of foods fortified with plant sterols.[34,38]

Several cohort studies on the relationship between plasma plant sterols and the risk of CVD or CHD have been performed in people without sitosterolemia, and showed inconsistent results.[26,27,29,30] The contrasts in absolute plasma plant sterols addressed in in such studies (averages of 6 and 10 µmol/L for sitosterol and campesterol, respectively) have been reported to be slightly greater than reached with consumption of fortified foods (2 and 5 µmol/L for sitosterol and campesterol respectively).[38] Whether (standardised) plasma plant sterols are *causally* related to CVD risk in such studies is a matter of debate. [31-35] People with higher plasma (LDL) cholesterol concentrations generally also have higher absolute plasma plant sterol concentrations. A proposed reason for this is that these people have more plasma lipoprotein particles, which transport both cholesterol and plant sterols. People with more lipoprotein particles can thus have higher absolute plant sterol levels even with a similar plant sterol intake or plant sterol absorption rate. The effects of cholesterol and absolute plant sterols are therefore hard to disentangle. Standardising plasma plant sterols to total cholesterol has often been used in observational cohort studies as a solution. Such ratios have been suggested to reflect sterol or cholesterol absorption, mainly obtained from the diet.[36] Since such ratio's reflect both (dietary) cholesterol and plant sterol absorption, it remains uncertain whether the associations of standardised plasma plant sterols with CVD outcomes in observational studies are due to (dietary) cholesterol, plant sterols or both.

Proteins known to be involved in the regulation of plasma plant sterols include (not an exhaustive list) ABCG5/8 and NPC1L1. In particular, genetic variations in the ABCG5/8 genes have been identified as important predictors of plasma plant sterols in genome wide association studies (GWAS). Several (but not all) of these plant sterol related variants have been associated with increased CHD risk.[31,37,44,45] ABCG5/8 transporters excrete sterols out of the circulation (into the intestinal lumen and bile), with a preference for non-cholesterol sterols. Since these transporters are particularly known to impact plant sterol excretion, it might be concluded from the genetic studies that plant sterols are atherogenic. However, these genetic variants on ABCG5/8 genes have also been related to cholesterol or cholestanol (marker of cholesterol absorption). It can therefore not be excluded that such an increase in CHD risk could be explained by increased cholesterol absorption associated with these variants, and thus not certainly provides evidence that specifically plant sterols increase CHD risk.[35,37,44,45]

This illustrates it is very challenging, and possibly (currently) even impossible, to disentangle the effects of plasma cholesterol and plant sterols in observational studies.

The Committee is aware of a Mendelian randomisation (MR) study in which an attempt was made to disentangle the direct effects of (absolute) plasma sitosterol and the effects mediated through cholesterol on CHD risk. The plasma plant sterol levels across different levels of the genetic score used in the study were not reported. Based on observations in a previous genetic study, it cannot be excluded that the contrasts addressed in this MR study were higher than reached upon consumption of foods fortified with plant sterols.[32]

One of the assumptions for MR studies is that the genetic instrument associates with the exposure of interest, and not with other exposures that may also be risk factors for the disease of interest (i.e., lack of pleiotropy). In the Committee's view, it is questionable whether the effects of sitosterol and cholesterol could be disentangled in the current work and therefore this assumption may not be valid. This is because cholesterol and plant sterol metabolism are closely related (as explained above), and all genetic variants included in the genetic instrument also associate with LDL cholesterol, as reported on the GWAS catalog web page.[46] The authors of the MR study argued they selected genetic variants that were more strongly related to sitosterol than cholesterol in their analyses, and thereby may have reduced the chances of type I pleiotropy. However, the Committee notes this does not take away the fact that biological mechanisms are likely related. Also, smaller sample sizes were used for calculating associations with sitosterol than with cholesterol, and it can therefore not be excluded that associations with plasma sitosterol were to some extent overestimated.

The genetic instrument used in the MR study was particularly based on genetic variants in gene regions involved in sterol absorption. In the Committee's view, it may therefore be argued that a conclusion on the relationship between sterol absorption and CHD risk would be possible based on this study, rather than specifically on plasma sitosterol with CHD risk. Whether the increased CHD risk with relatively higher plasma sitosterol observed in this MR study is due to cholesterol, plant sterols or both remains, in the Committee's view, uncertain.

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Annexes

Annex A Search strategy and study selection

A.1 Search strategy SRs and MAs

PubMed

(“Coronary disease” [MeSH] OR “Acute coronary syndrome” [MeSH] OR “Angina pectoris” [MeSH] OR “Coronary artery disease” [MeSH] OR “Myocardial infarction” [MeSH] OR “Peripheral arterial disease” [MeSH] OR “Intermittent claudication” [MeSH] OR “Stroke” [MeSH] OR “Brain ischemia” [MeSH] OR “Cerebrovascular disorders” [MeSH] OR “Percutaneous coronary intervention” [MeSH] OR “Coronary artery bypass” [MeSH] OR “Coronary disease” [TIAB] OR “Coronary heart disease” [TIAB] OR “Acute coronary syndrome” [TIAB] OR “Angina pectoris” [TIAB] OR “Angina” [TIAB] OR “Ischemic heart disease” [TIAB] OR Ischaemic heart disease [TIAB] OR Coronary artery disease [TIAB] OR “Coronary Arteriosclerosis” [TIAB] OR “Myocardial infarction” [TIAB] OR “Heart attack” [TIAB] OR “Peripheral arterial disease” [TIAB] OR “Peripheral vascular disease” [TIAB] OR “Intermittent claudication” [TIAB] OR “Stroke” [TIAB] OR “Acute stroke” [TIAB] OR “Cerebrovascular Apoplexy” [TIAB] OR “Apoplexy” [TIAB] OR “Ischemic stroke” [TIAB] OR “Ischaemic stroke” [TIAB] OR “Hemorrhagic stroke” [TIAB] OR “Haemorrhagic stroke” [TIAB] OR “Cerebrovascular accident” [TIAB] OR “Acute cerebrovascular accident” [TIAB] OR “Cerebrovascular stroke” [TIAB] OR “Brain vascular accident” [TIAB] OR “Brain ischemia” [TIAB] OR “Cerebral ischemia” [TIAB] OR “Cerebral stroke” [TIAB] OR “Brain accident” [TIAB] OR “Brain infarction” [TIAB] OR “Cerebral infarction” [TIAB] OR “Transient ischemic attack” [TIAB] OR “TIA” [TIAB] OR “Cerebrovascular*” [TIAB] OR “Subarachnoid haemorrhage” [TIAB] OR “Intracerebral hemorrhage” [TIAB] OR “Intracranial hemorrhages” [TIAB] OR “Coronary revascularization” [TIAB] OR “Percutaneous coronary intervention” [TIAB] OR “Coronary artery bypass graft surgery” [TIAB] OR “Percutaneous transluminal coronary angioplasty” [TIAB] OR “Percutaneous transluminal angioplasty” [TIAB] OR “Coronary angioplasty” [TIAB] OR “Atherosclerotic cardiovascular disease” [TIAB] OR “Carotid artery disease” [TIAB] OR “CHD” [TIAB] OR “ACS” [TIAB] OR “IHD” [TIAB] OR “CAD” [TIAB] OR “MI” [TIAB] OR “AMI” [TIAB] OR “PAD” [TIAB] OR “CVA” [TIAB] OR “CVAs” [TIAB] OR “TIA” [TIAB] OR “PCI” [TIAB] OR “CABG” [TIAB] OR “PTCA” [TIAB] OR “PTA” [TIAB] OR “ASCVD” [TIAB])

AND

("Phytosterols"[Mesh] OR “phytosterol*”[TIAB] OR “plant sterol*”[TIAB] OR “plant stanol*”[TIAB] OR “phytostanol*”[TIAB] OR “sitosterol*”[TIAB] OR “sitostanol*”[TIAB] OR “campesterol*”[TIAB] OR “campestanol*”[TIAB] OR “stigmasterol*”[TIAB] or “brassicasterol*”[TIAB])

AND

(“Systematic review”[publication type] OR “Meta-analysis”[publication type] OR “Review Literature as Topic”[MeSH] OR “review”[TIAB] OR "meta-analysis"[TIAB] OR “meta analysis”[TIAB] OR “metaanalysis”[TIAB] OR “quantitative review”[TIAB] OR “quantitative overview”[TIAB] OR “Systematic Reviews as Topic”[MeSH] OR “systematic review”[TIAB] OR “systematic overview”[TIAB] OR “methodologic review”[TIAB] OR “methodologic overview”[TIAB] OR “individual participant data”[TIAB] OR “individual patient data”[TIAB] OR “IPD”[TIAB] OR “individual-level data”[TIAB] OR “pooled analysis”[TIAB] OR “Pooled analyses”[TIAB] OR “multi-center study”[TIAB] OR “multi-cohort study”[TIAB])

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TITLE-ABS(“phytosterol”) OR TITLE-ABS(“plant sterol”) OR TITLE-ABS(“plant stanol”) OR TITLE-ABS(“phytostanol”) OR TITLE-ABS(“sitosterol”) OR TITLE-ABS(“sitostanol”) OR TITLE-ABS(“campesterol”) OR TITLE-ABS(“campestanol”) OR TITLE-ABS(“stigmasterol”) OR TITLE-ABS(“brassicasterol”) TITLE-ABS("phytosterols") OR OR TITLE-ABS(“plant sterols”) OR TITLE-ABS(“plant stanols”) OR TITLE-ABS(“phytostanols”) OR TITLE-ABS(“sitosterols”) OR TITLE-ABS(“sitostanols”) OR TITLE-ABS(“campesterols”) OR TITLE-ABS(“campestanols”) OR TITLE-ABS(“stigmasterols”) OR TITLE-ABS(“brassicasterols”)

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A.2 Search strategy individual RCTs and cohort studies in people with ASCVD

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AND

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Limit: from 2000

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TITLE-ABS("Coronary disease") OR TITLE-ABS("Acute coronary syndrome") OR TITLE-ABS("Angina pectoris") OR TITLE-ABS("Coronary artery disease") OR TITLE-ABS("Myocardial infarction") OR TITLE-ABS("Peripheral arterial disease") OR TITLE-ABS("Intermittent claudication") OR TITLE-ABS(Stroke) OR TITLE-ABS("Brain ischemia") OR TITLE-ABS("Cerebrovascular disorders") OR TITLE-ABS("Percutaneous coronary intervention") OR TITLE-ABS("Coronary artery bypass") OR TITLE-ABS("Coronary heart disease") OR TITLE-ABS(Angina) OR TITLE-ABS("Ischemic heart disease") OR TITLE-ABS("Ischaemic heart disease") OR TITLE-ABS("Coronary Arteriosclerosis") OR TITLE-ABS("Heart attack") OR TITLE-ABS("Peripheral vascular disease") OR TITLE-ABS("Acute stroke") OR TITLE-ABS("Cerebrovascular Apoplexy") OR TITLE-ABS(Apoplexy) OR TITLE-ABS("Ischemic stroke") OR TITLE-ABS("Ischaemic stroke") OR TITLE-ABS("Hemorrhagic stroke") OR TITLE-ABS("Haemorrhagic stroke") OR TITLE-ABS("Cerebrovascular accident") OR TITLE-ABS("Acute cerebrovascular accident") OR TITLE-ABS("Cerebrovascular stroke") OR TITLE-ABS("Brain vascular accident") OR TITLE-ABS("Brain ischemia") OR TITLE-ABS("Cerebral ischemia") OR TITLE-ABS("Cerebral stroke") OR TITLE-ABS("Brain accident") OR TITLE-ABS("Brain infarction") OR TITLE-ABS("Cerebral infarction") OR TITLE-ABS("Transient ischemic attack") OR TITLE-ABS(TIA) OR TITLE-ABS(Cerebrovascular*) OR TITLE-ABS("Subarachnoid haemorrhage") OR TITLE-ABS("Intracerebral hemorrhage") OR TITLE-ABS("Intracranial hemorrhages") OR TITLE-ABS("Coronary revascularization") OR TITLE-ABS("Percutaneous coronary intervention") OR TITLE-ABS("Coronary artery bypass graft surgery") OR TITLE-ABS("Percutaneous transluminal coronary

angioplasty") OR TITLE-ABS("Percutaneous transluminal angioplasty") OR TITLE-ABS("Coronary angioplasty") OR TITLE-ABS("Atherosclerotic cardiovascular disease") OR TITLE-ABS("Carotid artery disease") OR TITLE-ABS(CHD) OR TITLE-ABS(ACS) OR TITLE-ABS(IHD) OR TITLE-ABS(CAD) OR TITLE-ABS(MI) OR TITLE-ABS(AMI) OR TITLE-ABS(PAD) OR TITLE-ABS(CVA) OR TITLE-ABS(CVAs) OR TITLE-ABS(TIA) OR TITLE-ABS(PCI) OR TITLE-ABS(CABG) OR TITLE-ABS(PTCA) OR TITLE-ABS(PTA) OR TITLE-ABS(ASCVD)

AND

TITLE-ABS(“phytosterol”) OR TITLE-ABS(“plant sterol”) OR TITLE-ABS(“plant stanol”) OR TITLE-ABS(“phytostanol”) OR TITLE-ABS(“sitosterol”) OR TITLE-ABS(“sitostanol”) OR TITLE-ABS(“campesterol”) OR TITLE-ABS(“campestanol”) OR TITLE-ABS(“stigmasterol”) OR TITLE-ABS(“brassicasterol”) TITLE-ABS("phytosterols") OR OR TITLE-ABS(“plant sterols”) OR TITLE-ABS(“plant stanols”) OR TITLE-ABS(“phytostanols”) OR TITLE-ABS(“sitosterols”) OR TITLE-ABS(“sitostanols”) OR TITLE-ABS(“campesterols”) OR TITLE-ABS(“campestanols”) OR TITLE-ABS(“stigmasterols”) OR TITLE-ABS(“brassicasterols”)

AND

TITLE-ABS-KEY(“cohort stud*”) OR TITLE-ABS-KEY(“longitudinal stud*”) OR TITLE-ABS-KEY(“prospective stud*”) OR TITLE-ABS-KEY(“Observational study”) OR TITLE-ABS-KEY ("Clinical Trial") OR TITLE-ABS-KEY ("Cross-Over Studies”) OR TITLE-ABS-KEY("Double-Blind Method") OR TITLE-ABS-KEY("Single-Blind Method") OR TITLE-ABS-KEY("Controlled Before-After Studies") OR TITLE-ABS-KEY("Historically Controlled Study") OR TITLE-ABS-KEY(randomized) OR TITLE-ABS-KEY(randomised) OR TITLE-ABS-KEY(RCT) OR TITLE-ABS-KEY(controlled*) OR TITLE-ABS-KEY(placebo) OR TITLE-ABS-KEY(“clinical trial”) OR TITLE-ABS-KEY(trial) OR TITLE-ABS-KEY(intervention)

AND NOT

TITLE-ABS-KEY ("Systematic Review") OR TITLE-ABS-KEY (Review) OR TITLE-ABS-KEY ("Meta-Analysis") OR TITLE-ABS-KEY ("Meta Analysis”) OR TITLE-ABS-KEY ("Network Meta-Analysis”) OR TITLE-ABS-KEY ("Primary Prevention”)

Limit: from 2000

A.3 Selection of individual RCTs and cohort studies in people with ASCVD

Step 1. Identification
236 records retrieved:

- PubMed: 87
- Scopus: 148
- Other sources: 1

61 duplicates excluded

Step 2. Screening
175 records screened,
168 records excluded after first selection

Step 3. Eligibility
7 full-texts assessed,
5 records excluded after second selection due to:

- Different study population
- No exposure of interest

Step 4. Inclusion
2 records of RCTs included

Annex B RCTs on plant sterols and ezetimibe

The MAs that are described in paragraph 2.5.1 and individual RCTs that are described in paragraph 2.5.2 were searched for RCTs that investigated the effect of products fortified with plant sterols or stanols on top of ezetimibe or other lipid-lowering medication (except statins). Three RCTs were found that addressed the combination with ezetime.[18,24,25] Additional searches on PubMed for similar articles and articles siting these studies did not yield additional RCTs relevant on this topic. Below the three RCTs that were found are described.

The RCT of Gomes et al. (2017)[18] has already been described in paragraph 3.2 by the Committee. In short, the study examined the differences in effects on LDL cholesterol between four groups: 1) control group; 2) 2 g/d plant sterols; 3) 10 mg/d ezetimibe; 4) 2 g/d plant sterols plus 10 mg/d ezetimibe. All participants remained on their regular statin use. Statistically significant differences across groups were reported (P-value 0.004). However, it was not specified which groups differed from each other, and which groups did not. Thus, it is, based on the presented results, not sure whether ezetimibe plus plant sterols (27% LDL cholesterol reduction) has added value above ezetimibe alone (19% LDL cholesterol reduction).
Regarding the quality of the study, the Committee noted that the study report provided limited information regarding the data-analysis plan. Besides this, the Committee has no other comments related to the quality of this study.

The RCT by Jakulj et al. (2005)[24] is a four-arm crossover trial that investigated the effect of plant sterols, (open-label) ezetimibe treatment and their combination on LDL cholesterol levels in 40 people with hypercholesterolemia. There was a run-in period of 2 weeks during which participants were not allowed to consume any plant sterol- or stanol enriched food products or other dietary supplements. For participants who regularly consumed foods enriched with plant sterols or stanols a run-in period of 6 weeks was initiated. After the run-in period, participants were randomised into 4 groups: 1) 10 mg/d ezetimibe and 25 g/d control spread; 2) 10 mg/d ezetimibe and 25 g/d spread containing 2 g plant sterols; 3) 25 g/d spread containing 2 g plant sterols; 4) 25 g/d control spread. After 4 weeks of treatment, participants crossed over to the next treatment. During the intervention period, participants were not allowed to use any other lipid-lowering medication or food products. LDL-cholesterol levels were calculated with the Friedewald equation. One participant was excluded from data analysis because of high triglyceride concentrations and possible noncompliance. Compared to placebo treatment, plasma LDL cholesterol significantly decreased by 5% during plant sterol treatment, 22% during ezetimibe treatment and 25% during plant sterol and ezetimibe treatment. The LDL cholesterol reduction reached with combination treatment of plant sterols and ezetimibe was not statistically different from the reduction

reached by treatment with ezetimibe alone. Financial supporters were not reported. None of the authors had a conflict of interest. Regarding the quality of the study, the Committee noted that the per-protocol was tested, since non-compliant participants were excluded. This resulted in the exclusion of only one participant and therefore it likely did not affect the results. Furthermore, the study report provided limited information regarding the data-analysis plan. Besides this, the Committee has no other comments related to the quality of this study.

The double-blind triple-crossover RCT of Lin et al. (2011)[25] included 22 participants with moderately elevated LDL cholesterol levels. People taking prescribed medication known to affect lipid metabolism were excluded. Participants were randomly assigned to 1 of the 6 possible sequences of 3 treatments: 1) ezetimibe placebo and plant sterol placebo; 2) 10 mg/d ezetimibe and plant sterol placebo; 3) 10 mg/d ezetimibe and 2.5 g/d plant sterol supplement. Each treatment lasted 3 weeks with a 1-week wash-out period in between. In addition, all participants had to follow a diet consisting of 57% carbohydrates, 15% protein, 28% fat and a daily multivitamin supplement. The energy requirement of each participant was calculated individually, and all foods and beverages were prepared and provided by the study feeding centre accordingly. Participants had to consume their breakfast and dinner at the feeding centre. LDL-cholesterol levels were calculated with the Friedewald equation. One participant dropped out during the study and was excluded from data analysis. Compliance with the study treatments was reported to be 99 to 100%. The ezetimibe treatment decreased the LDL cholesterol statistically significantly with 16% compared with the placebo treatment. The ezetimibe and plant sterol treatment further decreased LDL cholesterol with 7%. This decrease was statistically significantly larger than with placebo treatment and than with ezetimibe treatment alone.
The study was partially funded by Merck & Co, Inc, Whitehouse Station, NJ, a company which, among other things, produces ezetimibe. In addition, one of the authors had a financial interest in Ligeline Technologies, Inc, which is a start-up company commercializing emulsified phytosterols. The overall risk of bias of this study was judged as low by the Committee.

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).
The Health Council receives most requests for advice from the Ministers of Health, Welfare and Sport, Infrastructure and Water Management, Social Affairs and Employment, and Agriculture, Nature and Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.
Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

This publication can be downloaded from www.healthcouncil.nl.

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