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## Food and Drug Administration

## 21 CFR Part 101

## Food Labeling; Health Claim; Phytosterols and Risk of Coronary Heart Disease; Proposed Rule

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Part 101**

**[Docket Nos. FDA–2000–P–0102, FDA–2000–P–0133, and FDA–2006–P–0033; Formerly Docket Nos. 2000P–1275, 2000P–1276, and 2006P–0316, Respectively]**

# Food Labeling; Health Claim; Phytosterols and Risk of Coronary Heart Disease

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Proposed rule.

**SUMMARY:** The Food and Drug Administration (FDA) is proposing to amend the regulation authorizing a health claim on the relationship between plant sterol esters and plant stanol esters and reduced risk of coronary heart disease (CHD) for use on food labels and in food labeling. The agency is taking this action based on evidence previously considered by the agency, and FDA's own review of data on esterified and nonesterified plant sterols and stanols (collectively, phytosterols) [1] published since the agency first authorized the health claim by regulation. FDA is also taking these actions, in part, in response to a health claim petition submitted by Unilever United States, Inc. The proposal would amend the authorized use of the claim by modifying the nature of the substances that may be the subject of the claim for conventional foods to include nonesterified, or free, phytosterols, by expanding the types of foods that may bear the claim to include a broader range of foods, by modifying the daily dietary intake of the substance specified in the claim as necessary for the claimed benefit, by adjusting the minimum amount of the substance required for a food to bear the claim, and by making other minor changes.

**DATES:** Submit written or electronic comments by February 22, 2011.

**ADDRESSES:** You may submit comments, identified by Docket Nos. FDA–2000–P–0102, FDA–2000–P–0133, and FDA–2006–P–0033, by any of the following methods:

## Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: http://www.regulations.gov.* Follow the instructions for submitting comments.

## Written Submissions

Submit written submissions in the following ways:

- *Fax:* 301–827–6870.
- *Mail/Hand delivery/Courier (for paper, disk, or CD–ROM submissions):* Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

*Instructions:* All submissions received must include the agency name and docket numbers for this rulemaking. All comments received will be posted without change to *http://www.regulations.gov,* including any personal information provided. For detailed instructions on submitting comments and additional information on the rulemaking process, *see* the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

*Docket:* For access to the docket to read background documents or comments received, go to *http://www.regulations.gov* and insert the docket numbers, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:** Blakeley Denkinger, Center for Food Safety and Applied Nutrition (HFS–830), 5100 Paint Branch Pkwy., College Park, MD 20740, 301–436–1450.

**SUPPLEMENTARY INFORMATION:**

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## I. Background

The Nutrition Labeling and Education Act of 1990 (NLEA) (Pub. L. 101–535) amended the Federal Food, Drug, and Cosmetic Act (the act) in a number of important ways. The NLEA clarified FDA's authority to regulate health claims on food labels and in food labeling by amending the act to add section 403(r) to the act (21 U.S.C. 343(r)). Section 403(r) of the act specifies, in part, that a food is misbranded if it bears a claim that expressly or by implication characterizes the relationship of a nutrient to a disease or health-related condition unless the claim is made in accordance with section 403(r)(3) (for conventional foods) or 403(r)(5)(D) (for dietary supplements).

The NLEA directed FDA to issue regulations authorizing health claims (*i.e.,* labeling claims that characterize the relationship of a nutrient to a disease or health-related condition) for conventional foods only if the agency determines, based upon the totality of publicly available scientific evidence (including evidence from well-designed studies conducted in a manner that is consistent with generally recognized scientific procedures and principles) that there is significant scientific

[1] The term "phytosterols" is used as a collective term for plant sterols and their hydrogenated stanol forms, whether used in the free form or esterified with fatty acids. As discussed in more detail elsewhere in this proposal, phytosterol is a term commonly used by manufacturers and distributors of these substances.

agreement (SSA), among experts qualified by scientific training and experience to evaluate such claims, that the claim is supported by such evidence (21 U.S.C. 343(r)(3)(B)(i)). Congress delegated to FDA the authority to establish the procedure and standard for health claims for dietary supplements (21 U.S.C. 343(r)(5)(D)).

FDA issued regulations establishing general requirements for health claims in labeling for conventional foods on January 6, 1993 (58 FR 2478). Among the regulations issued under that final rule were: (1) Section 101.14 (21 CFR 101.14), which sets out the rules for the authorization of health claims by regulation based on significant scientific agreement, and prescribes general requirements for the use of health claims; and (2) section 101.70 (21 CFR 101.70), which provides a process for petitioning the agency to authorize health claims about the substance-disease relationship and sets out the types of information that any such petition must include. Each of these regulations became effective on May 8, 1993. On January 4, 1994 (59 FR 395), FDA issued a final rule applying the requirements of §§ 101.14 and 101.70 to health claims for dietary supplements.

On February 1, 2000, Lipton, a subsidiary of Unilever United States Inc. (Unilever), submitted to FDA a health claim petition (Docket No. FDA–2000–P–0102 (formerly Docket No. 2000P–1275)) seeking authorization of a claim characterizing a relationship between consumption of plant sterol esters and the risk of CHD. The petition limited its request to health claims in the labeling of spreads and dressings for salad [2] containing at least 1.6 gram (g) of plant sterol esters per reference amount customarily consumed (RACC) and the risk of CHD. On February 15, 2000, McNeil Consumer Healthcare (McNeil) submitted to FDA a health claim petition (Docket No. FDA–2000–P–0133 (formerly Docket No. 2000P–1276)) requesting that the agency authorize a health claim characterizing the relationship between plant stanol esters and the risk of CHD. Both petitioners requested that FDA exercise its authority under section 403(r)(7) of the act to make any authorizing regulation effective on publication, pending consideration of public comment and publication of a final rule.

On September 8, 2000 (65 FR 54686),[3] the agency issued an interim final rule (IFR) in response to these two health claim petitions to provide for health claims on the relationship between plant sterol/stanol esters and the reduced risk of CHD (codified in § 101.83 (21 CFR 101.83)). FDA concluded that, based on the totality of the publicly available scientific evidence, there was significant scientific agreement among qualified experts that a health claim for plant sterol/stanol esters and a reduced risk of CHD was supported by such evidence (65 FR 54686 at 54700).

Specifically, the agency determined that there is significant scientific agreement that diets that include plant sterol esters and plant stanol esters may reduce the risk of CHD. FDA found that high blood (serum or plasma) total and low density lipoprotein (LDL) cholesterol are major modifiable risk factors in the development of CHD. The agency determined that the scientific evidence established that including plant sterol and plant stanol esters in the diet helps to lower blood total and LDL cholesterol levels.

Current § 101.83 now provides for a health claim on the label or labeling of a food meeting certain criteria provided the claim among other things: (1) States that plant sterol and plant stanol esters should be consumed as part of a diet low in saturated fat and cholesterol, (2) uses the term plant (or vegetable oil) sterol esters or plant (or vegetable oil) stanol esters, (3) specifies that the daily dietary intake necessary to reduce the risk of CHD is 1.3 g or more for plant sterol esters or 3.4 g or more for plant stanol esters, (4) specifies the contribution a serving of the product makes to the daily dietary intake level, and (5) specifies that the daily dietary intake of plant sterol or stanol esters should be consumed in two servings eaten at different times of the day with other foods.

The IFR was effective upon publication on September 8, 2000, with a 75-day comment period that closed on November 22, 2000. On June 6, 2001, the agency issued a notice of an extension of the period for issuance of a final rule (66 FR 30311). In this notice, the agency stated that, due to the complexities of the issues involved and the lack of agency resources, the agency would be unable to issue a final rule within the prescribed 270 days from date of publication of the IFR.

After the comment period had closed, the agency received two requests to extend the comment period. Because several additional substantial issues had been raised in these comments, FDA reopened the comment period on October 5, 2001 (66 FR 50824). The agency specifically requested comment on the following: (1) The eligibility of nonesterified (free) plant sterols and plant stanols to bear a health claim, (2) daily intake levels necessary to reduce the risk of CHD, (3) the eligibility of mixtures of plant sterols and plant stanols to bear a health claim, (4) the significance of serum apolipotrotein B concentration as a surrogate marker for CHD risk, and (5) issues regarding safe use of plant sterol and stanols in foods and the necessity of an advisory label statement.

On February 14, 2003, FDA issued a letter announcing its intentions to consider the exercise of enforcement discretion, pending publication of the final rule, with respect to certain requirements of the health claim (Ref. 1). Under the conditions of the letter, FDA said it would consider enforcement discretion if: (1) The food contains at least 400 milligrams (mg) of phytosterols per RACC; (2) mixtures of phytosterol substances (*i.e.,* mixtures of sterols and stanols) contain at least 80 percent beta-sitosterol, campesterol, stigmasterol, sitostanol, and campestanol (combined weight); (3) the food meets the requirements of § 101.83(c)(2)(iii)(B), (c)(2)(iii)(C), and (c)(2)(iii)(D); [4] (4) products containing phytosterols, including mixtures of sterols and stanols in esterified or nonesterified forms, use a collective term in lieu of the terms required by § 101.83(c)(2)(i)(D) [5] in the health claim to describe the substance (*e.g.,* "plant sterols" or "phytosterols"); (5) the claim

[2] The agency is using the term "dressings for salad" throughout this document in lieu of the term "salad dressing" used by the petitioners because the standard of identity for "salad dressing" in § 169.150 (21 CFR 169.150) refers to a limited class of dressings for salad, *i.e.,* those that contain egg yolk and meet certain other specifications and resemble mayonnaise type products. "Salad dressing" as defined in § 169.150 does not include a number of common types of dressings for salad, such as Italian dressing.

[3] A correction notice published in the **Federal Register** on November 24, 2000 (65 FR 70466).

[4] Section 101.83(c)(2)(iii)(B)—The food must be "low in saturated fat" and "low in cholesterol" as defined in § 101.62 (21 CFR 101.62); § 101.83(c)(2)(iii)(C)—the food must meet the limits for total fat in § 101.14(a)(4) (*e.g.,* for individual foods, 13.0 g fat per RACC, per labeled serving and if the RACC is 30 g or less or 2 tablespoons or less, per 50 g) except that spreads and dressings for salad are not required to meet the limit per 50 g if the label of the food bears a disclosure statement per § 101.13(h) (*e.g.,* "See nutrition information for fat content"); and § 101.83(c)(2)(iii)(D)—the food must meet the minimum nutrient contribution requirement in § 101.14(e)(6) (*e.g.,* except for dietary supplements, the food contains 10 percent or more of the Daily Value of vitamin A, vitamin C, iron, calcium, protein, or fiber per RACC prior to any nutrient addition) unless it is a dressing for salad.

[5] The IFR required that the substance for the claim be specified as "plant sterol esters" or "plant stanol esters" except that if the sole source of the substance was vegetable oil, the terms "vegetable oil sterol esters" or "vegetable oil stanol esters" may be used.

specifies that the daily dietary intake of phytosterols that may reduce the risk of CHD is 800 mg or more per day, expressed as the weight of nonesterified phytosterol; (6) vegetable oils for home use that exceed the total fat disqualifying level bear the health claim along with a disclosure statement that complies with § 101.13(h) (21 CFR 101.13(h));[6] and (7) use of the claim otherwise complies with § 101.83.

## II. Petition and Grounds for Amending the Health Claim on Plant Sterols/Stanols and CHD

In response to the IFR, and the October 5, 2001 (66 FR 50824), reopening of the comment period, the agency received approximately 37 comments from a variety of sources. These comments came from professional organizations, industry, consumer groups, health care professionals, academia, and research scientists. The majority of the comments supported authorization of the health claim for phytosterol esters and CHD but requested modification of one or more provisions.

The agency has conducted an extensive re-evaluation of the scientific evidence regarding the relationship between consumption of phytosterols and the risk of CHD. This re-evaluation focused primarily on evidence from intervention studies that address the specific amendments that are being considered in this proposed rule. (These studies are summarized in Tables 1 and 2 at the end of this document and are discussed below.) FDA's process for this re-evaluation took into consideration all available scientific evidence of which FDA was aware and was consistent with FDA evidence-based review approach to health claims (Ref. 2).

The more recent scientific evidence affirms the agency's conclusion regarding the validity of the relationship between consumption of phytosterol esters and a risk of CHD under the SSA standard. FDA has no reason at this time, based on either public comment or on currently available scientific evidence, to reconsider that basic conclusion. The re-evaluation, however, did cause the agency to reconsider the scope of the substances eligible for the health claim and the requirements for use of the health claim in the labeling of food.

Based on evidence from those intervention studies, and in light of the comments received in response to the IFR, the agency has determined that current § 101.83 should be amended to reflect the current state of the science under the SSA standard. Because the agency has not provided a formal opportunity for public comment on the modifications proposed to current § 101.83, and because of the time that has elapsed since publishing the IFR, the agency has decided to issue a proposed rule to amend current § 101.83 rather than finalizing, with modification, the IFR. This approach provides an opportunity for public comment prior to issuance of the final rule.

On May 5, 2006, Unilever submitted a health claim petition under section 403(r)(4) of the act (Docket No. FDA–2006–P–0033 (formerly Docket No. 2006P–0316)). The petition requested that FDA amend § 101.83 to permit use of the health claim for phytosterols in a food that provides the full daily intake in a single serving. On August 18, 2006, FDA notified the petitioner that it had completed its initial review of the petition and that the petition had been filed for further action in accordance with section 403(r)(4) of the act. The agency is issuing this proposed rule, in part, in response to Unilever's petition.

## III. Eligibility for a Health Claim/Overview of Data

FDA concluded in the IFR that there was significant scientific agreement that the consumption of phytosterol esters may reduce the risk of CHD. FDA's prior evaluation of the scientific evidence to substantiate a relationship between phytosterols and CHD risk focused on results from intervention studies designed to investigate the effect of phytosterol ester consumption on blood total and LDL cholesterol levels. FDA's evaluation of the scientific evidence to substantiate a relationship between phytosterol ester consumption and CHD risk included the review of 20 phytosterol-ester intervention studies that measured blood (serum or plasma) total or LDL cholesterol levels.

Since issuance of the IFR, there have been a substantial number of studies conducted and published on the relationship between esterified and nonesterified phytosterols and risk of CHD. As part of the re-evaluation of the scientific evidence, FDA requested the Agency for Healthcare, Research and Quality (AHRQ) to identify intervention studies that had been conducted since 2000 on the relationship between phytosterols and CHD risk. FDA identified additional relevant intervention studies based on comments submitted in response to the IFR, the 2001 reopening of the comment period and by conducting its own literature review. In total, FDA identified 66 intervention studies in which the cholesterol-reducing effect of conventional foods containing phytosterols was evaluated. FDA identified seven intervention studies in which the cholesterol-reducing effect of dietary supplements containing phytosterols was evaluated. Consistent with FDA's prior evaluation and its evidence-based review approach to the evaluation of health claims, the agency recognizes elevated blood (serum or plasma) total cholesterol and LDL cholesterol levels to be valid surrogate endpoints for CHD risk (Ref. 3). Although other types of study endpoints, such as measurement of intestinal absorption of cholesterol, are useful for examining issues such as mechanism of action, they do not provide direct evidence of an effect on disease risk.[7] Thus, FDA evaluated only intervention studies that used the valid surrogate endpoints of CHD (*i.e.,* blood total and LDL cholesterol), to evaluate the potential effects of phytosterol intake on CHD risk. Consistent with the agency's prior evaluation of phytosterol esters, FDA also reviewed intervention studies that evaluated the effect of phytosterol intake in individuals who were generally healthy and not yet diagnosed with CHD.

Following FDA's evidence-based review approach to the scientific evaluation of health claims, the agency excluded intervention studies that included patients diagnosed with CHD. Of the 66 intervention studies on conventional foods containing phytosterols identified by FDA, scientific conclusions could not be drawn from 15 intervention studies for the following reasons. Five intervention studies did not include an appropriate control group (Refs. 4, 5, 6, 7, and 8). Without an appropriate control group, it cannot be determined whether changes in the endpoint of interest were due to phytosterol consumption or to unrelated and uncontrolled extraneous factors. Four intervention studies did not conduct statistical analysis between the control and treatment group (Refs. 9, 10, 11, and 12). Statistical analysis of the substance/disease relationship is a critical factor because it provides the comparison between subjects consuming phytosterols and those not consuming phytosterols to determine whether there is a reduction of CHD risk. When statistics are not performed on the specific substance/disease relationship, it cannot be determined

[6] *E.g.,* "See nutrition information for fat content."

[7] Although FDA sought comment on whether use of serum apolipoprotein B is an appropriate surrogate endpoint for CHD (66 FR 50824 at 50825 and 50826), the agency has concluded that it is not because it has not been adequately validated.

whether there is a difference between the two groups. Five intervention studies provided a combination of phytosterols and other food components (*e.g.,* polyunsaturated oils, soy protein, beta-glucan and other viscous fibers) that may be beneficial in reducing total and/or LDL cholesterol levels (Refs. 13, 14, 15, 16, and 17). Therefore, it is not possible to evaluate the independent relationship between phytosterols and CHD risk. One study did not provide baseline and post-study blood total and LDL cholesterol levels, including statistical data (Ref. 18). Without knowing if baseline and/or post-intervention total and/or LDL levels were significantly different, it is difficult to interpret the findings of the intervention. Thus, FDA identified 51 intervention studies from which scientific conclusions could be drawn about the relationship between phystosterols in conventional foods and risk of CHD. (These studies are summarized in table 1 at the end of this document and are discussed below).

The intervention studies included in this review are studies that tested phytosterols, derived from either vegetable oils or from tall oil;[8] as sterols, their stanol derivatives, or sterol/stanol mixtures; and used in the form of fatty acid esterified phytosterols or nonesterified phytosterols. A number of techniques were used to solublize and disperse nonesterified phytosterols in food (*e.g.,* lecithin emulsion, microcrystalline forms, dissolving in heated oil). The majority of intervention studies used phytosterol-enriched conventional foods, most frequently margarine-like spreads. A very limited number of intervention studies provided phytosterols as ingredients in dietary supplements. With few exceptions, the subjects were instructed to consume the enriched foods with meals, and either once a day or up to three times a day. Intake levels in these intervention studies ranged from 0.45 to 9 g per day, though most intervention studies added phytosterols to the diet in the range of about 1 to 3 g per day.[9] With a few exceptions, the participants in these intervention studies were moderately hypercholesterolemic. The results of these intervention studies are consistent with the results of the intervention studies that had been considered in the IFR in that consumption of 1 to 3 g of phytosterols per day in phytosterol-enriched foods resulted in statistically significant reductions (5 to 15 percent) in blood LDL cholesterol levels relative to a placebo control (*see* table 1 at the end of this document).

As discussed elsewhere in this proposal, FDA tentatively concludes that the results of the intervention studies involving the consumption of dietary supplements containing phytosterols are limited and inconsistent in demonstrating that such dietary supplements reduce blood cholesterol levels. The available scientific evidence indicates that dietary supplements containing phytosterol esters reduce cholesterol as effectively as conventional foods containing phytosterols. Although one intervention study showed cholesterol-lowering efficacy for one formulation of dietary supplement containing nonesterified phytosterols, there also is evidence that other types of nonesterified phytosterol formulations were not effective in reducing cholesterol. We tentatively conclude that the available evidence is insufficient to establish what factors are key in predicting which nonesterified phytosterol formulations will be effective and which will not be when consumed as ingredients in dietary supplements.

## IV. Review of the Preliminary Requirements

A health claim characterizes the relationship between a substance and a disease or health-related condition (§ 101.14(a)(1)). A substance means a specific food or component of food, regardless of whether the food is in conventional food form or a dietary supplement. (§ 101.14(a)(2)). To be eligible for a health claim, if to be consumed at other than decreased dietary levels, the food or food component must contribute taste, aroma, nutritive value, or some other technical effect to the food and be safe and lawful under the applicable safety provisions of the act at levels necessary to justify the claim (§ 101.14(b)(3)).

As noted in the IFR, CHD is a disease for which the U.S. population is at risk and it therefore qualifies as a disease for which a health claim may be made under § 101.14(b)(1) (65 FR 54686 at 54687). Current § 101.83 authorizes a health claim regarding CHD for two substances: (1) Plant sterol esters prepared by esterifying a mixture of plant sterols from edible oils with food-grade fatty acids; the mixture consisting of at least 80 percent beta-sitosterol, campesterol, and stigmasterol (combined weight) and (2) plant stanol esters prepared by esterifying a mixture of plant stanols derived from edible oils, or from byproducts of the kraft paper pulping process, with food-grade fatty acids; the mixture consisting of at least 80 percent sitostanol and campestanol (combined weight) (§ 101.83(c)(2)(ii)). The regulation does not currently authorize health claims for mixtures of the two substances. Moreover, the regulation requires a health claim regarding one of the two substances to specify which one is the subject of the claim (§ 101.83(c)(2)(i)(C)).

For reasons discussed elsewhere in this preamble, FDA is proposing to amend § 101.83 to expand the substances eligible for the authorized health claim regarding CHD. Under the proposed amendments, phytosterols would be the subject of the regulation. As the agency noted in the IFR, plant sterols occur throughout the plant kingdom and are present in many edible fruits, vegetables, nuts, seeds, cereals, and legumes in both nonesterified and esterified forms (65 FR 54686 at 54687 and 54688). As the hydrogenated form of plant sterols, plant stanols are also present in foods such as wheat, rye, corn, and certain vegetable oils (65 FR 54686 at 54688). Therefore, phytosterols qualify as substances for which a health claim may be made under § 101.14(a)(2).

As was true of phytosterol esters, the scientific evidence suggests that phytosterols achieve their intended effect by functioning to assist the digestive process. Upon the same reasoning provided for phytosterol esters in the IFR, therefore, phytosterols provide nutritive value through assisting in the efficient functioning of a classical nutritional process and of other metabolic processes necessary for the normal maintenance of human existence (*see* 65 FR 54686 at 54688). Accordingly, the agency concludes that the preliminary requirement of § 101.14(b)(3)(i) is satisfied.

Finally, under § 101.14(b)(3)(ii), phytosterols, at levels necessary to justify the claim, must be safe and lawful under the applicable food safety provisions of the act. For conventional foods, this evaluation involves considering whether the substance is generally recognized as safe (GRAS), listed as a food additive, or authorized by a prior sanction issued by FDA. (*See* § 101.70(f).) Dietary ingredients in dietary supplements are not subject to the food additive provisions of the act (*see* section 201(s)(6) of the act (21 U.S.C. 321(s)(6))). Rather, they are subject to the adulteration provisions in section 402 of the act (21 U.S.C. 342) and, if applicable, the new dietary

[8] As explained in more detail in section V.A.3 in this proposed rule, tall oil is the term FDA is using in this proposed rule to describe the byproducts of the kraft process of wood pulp manufacture.

[9] Weight of phytosterols is represented as nonesterified sterols and/or stanols. One g of nonesterified stanols is equivalent to 1.7 g stanol esters. One g of nonesterified sterols is equivalent to 1.6 g sterol esters.

ingredient provisions in section 413 of the act (21 U.S.C. 350b).

Through the agency's GRAS notification program, FDA has received numerous submissions from food manufacturers regarding the GRAS status of phytosterols when used in certain conventional foods at levels necessary to justify the claim under the proposed amendments to § 101.83. These submissions have included data to support the manufacturer's self-determinations that phytosterols under the intended conditions of use identified in the submissions are GRAS.[10] FDA did not object to the conclusions in those submissions. The GRAS submissions include conditions of use for a variety of conventional foods, but not all conventional foods. The agency has not made its own determination that phytosterols are GRAS. However, FDA is not aware of any scientific evidence that phytosterols, whether free or esterified, would be harmful. For those conventional foods that have been the subject of a GRAS notification reviewed by FDA with conditions of use that meet the eligibility criteria for the use of the health claim, and for which FDA had no further questions, FDA concludes that the preliminary requirement under § 101.14(b) that phytosterols be safe and lawful has been met for use in such conventional foods. We note, in section C.1 of this document, the minimum level of phytosterols necessary for a food to contain in order to be eligible to bear a claim is 0.5 g per RACC. Not all conventional foods for which a GRAS notification for phytosterols was submitted, to which the agency had no further questions, are under conditions of use in food that would be consistent with the eligibility requirements for the health claim, *e.g.,* certain foods may contain phytosterols at a level that is less than the minimum of 0.5 g per RACC. Such foods would not be eligible to bear the health claim if the rule is finalized as proposed. The agency notes that authorization of a health claim for a substance should not be interpreted as an affirmation that the substance is GRAS.

FDA has also received new dietary ingredient (NDI) notifications, under section 413(a)(2) of the act, for the use of plant stanol esters (Ref. 19) and for all plant sterols derived from tall oil (Ref. 20) as dietary ingredients.[11] In FDA's judgment, the data submitted with these NDIs, considered in combination with the GRAS notifications it has also received for phytosterols in conventional foods, provide an adequate basis to conclude that a dietary supplement containing phytosterol esters would reasonably be expected to be safe. Therefore, FDA concludes that the preliminary requirement under § 101.14 that the use of phytosterols in dietary supplements be safe and lawful is satisfied. However, the agency notes that the authorization of a health claim for phytosterol esters in dietary supplements does not relieve manufacturers and distributors of such products from ensuring that their products are not adulterated under section 402 or 413 of the act.

## V. Proposed Modifications to Current § 101.83

### *A. Nature of the Substance*

#### 1. Esterification

Current § 101.83 limits the substances eligible for the health claim to those specified in the two original health claim petitions as follows: (1) Plant sterols derived from vegetable oils and prepared by esterifying, with food-grade fatty acids, a mixture of plant sterols, consisting of at least 80 percent beta-sitosterol, campesterol, and stigmasterol (combined weight); and (2) plant stanol esters derived from vegetable oils or from byproducts of the kraft paper pulping process derived from vegetable oils or from byproducts of the kraft paper pulping process and prepared by esterifying, with food-grade fatty acids, a mixture of plant stanols, consisting of at least 80 percent sitostanol and campestanol (combined weight) (§ 101.83(c)(2)(ii)). The regulation does not authorize a health claim for nonesterified phytosterols. Several comments received in response to the IFR requested that the agency permit foods containing nonesterified phytosterols to bear the health claim.

In finding that the phytosterol esters specified in the current regulation reduce the risk of CHD under the SSA standard, FDA expressed agreement in the IFR with the petitioners that the fatty acid portion of plant sterol/stanol esters is likely to be readily hydrolyzed by digestive lipases upon ingestion and that the resultant free phytosterol is left to be incorporated into intestinal micelles in a manner that prohibits the absorption of cholesterol. The phytosterol is therefore the active portion of the ester (65 FR 54686 at 54690, 54691, 54694, and 54705). Although the scientific evidence on which FDA relied in issuing the IFR included studies of both esterified and nonesterified phytosterols FDA had not considered, in the IFR, cholesterol-lowering efficacy of nonesterified phytosterols.

In response to the IFR, FDA received a number of comments asserting that the IFR should be modified to allow use of the health claim for nonesterified phytosterols, as well as phytosterol esters. Other comments argued that nonesterified phytosterols should not be eligible for the health claim because the available evidence on the efficacy of nonesterified plant sterols and stanols is too limited and the characterization of the substance is too scant to support their inclusion in the final rule. In FDA's notice to reopen the comment period (66 FR 50824, October 5, 2001), the agency asked for any additional data on the effectiveness of nonesterified phytosterols in reducing the risk of CHD.

Esterification with fatty acids was one of the initial techniques used to increase lipid solubility of phytosterols and facilitate incorporation of phytosterols into foods. However, other techniques have also been demonstrated effective in enhancing the solubility of nonesterified phytosterols in conventional foods. Techniques for solubilization of phytosterols include the following: (1) Dissolving them into heated fats (Refs. 21 and 22), (2) re-crystallization by cooling after dissolution in heated oil (Refs. 23 and 24), (3) mechanically pulverizing crystalline phytosterols to a fine particle size (Refs. 25 and 26), and (4) emulsifying them with lecithin (Ref. 27).

Nonesterified phytosterols dissolved in oils are as effective in lowering cholesterol as are equivalent amounts of phytosterol esters. However, due to the limited lipid solubility of nonesterified phytosterols, the amount of fat needed to dissolve an effective amount of phytosterols is substantially greater for nonesterified phytosterols than for phytosterol esters. The solubility of sitosterol/sitostanol in rape seed oil mayonnaise increased about tenfold when esterified with fatty acids (Ref. 28).

Although current § 101.83 provides only for a claim about phytosterol esters, the evidence that was considered in the IFR included five intervention

[10] *See, e.g.,* GRAS Notification Numbers (GRN) 000039, GRN 000048, GRN 000176, GRN 000177, GRN 000112, GRN 000181, GRN 000053, and GRN 000206).

[11] Section 413(a) of the act requires that manufacturers and distributors of dietary supplement ingredients that had not been used for food or as a dietary supplement ingredient prior to October 15, 1994, or that are in a form that has been chemically modified from the form in which it was used in food, submit to FDA at least 75 days before the ingredient is introduced into interstate commerce, information that is the basis on which the manufacturer or distributor determined that the dietary supplement containing the ingredient will reasonably be expected to be safe.

studies that investigated the effects of nonesterified phytosterols on serum total and/or LDL cholesterol levels (Refs. 21, 28, 29, 30, and 31). In addition, 12 intervention studies published since the IFR have involved nonesterified phytosterols added to conventional foods (Refs. 22, 24, 25, 26, 27, 32, 33, 34, 35, 36, 37, and 38) (*see* table 1 at the end of this document). In these 17 intervention studies, subjects consumed conventional foods providing from 0.7 to 5 g per day of nonesterified plant sterols, plant stanols, or plant sterol/stanol mixtures during intervention periods of 3 weeks to 6 months. Thirteen of the seventeen intervention studies reported finding statistically significant reductions in blood total and/or LDL cholesterol from the consumption of foods containing nonesterified phytosterols.

Two intervention studies directly compared the cholesterol lowering efficacy of similar amounts of nonesterified and esterified phytosterols in conventional foods (Refs. 35 and 38) (*see* table 1 at the end of this document). Nestel *et al.,* 2001 (Ref. 35) reported that consumption of 2.4 g per day of soy phytosterols, as either plant sterol esters or as nonesterified plant stanols, suspended in conventional foods and consumed with meals over a 4-week period, significantly lowered serum LDL cholesterol levels and that there was no statistically significant difference in the cholesterol-lowering effect between the two forms of phytosterols. Abumweiss *et al.,* 2006 (Ref. 38) reported that 1.7 g per day of phytosterols, provided as either nonesterified plant sterols or fatty acid esterified plant sterols dissolved in margarine did not significantly lower total or LDL cholesterol compared to the placebo.

In the majority of these 17 intervention studies, nonesterified phytosterols were suspended in fat-free or low-fat foods (*e.g.,* orange juice, low-fat dairy foods or other fat-free beverage, bread, cereal, and jam); in other studies nonesterified phytosterols were suspended in high-fat foods (*e.g.,* margarine, butter, chocolates and meats) (*see* table 1 at the end of this document). In most of these intervention studies, the study design specified that the food enriched with phytosterols be consumed with meals. In the few nonesterified phytosterol intervention studies that did not specify the phytosterol-enriched foods be consumed with meals (Refs. 24 and 25), the types of food used (meats, bread, jam, and margarine) make it likely that they would have been consumed concurrently with other foods.

Based on the totality of available scientific evidence, FDA agrees with the comments asserting that the blood cholesterol-lowering efficacy of conventional foods containing nonesterified forms of phytosterols is comparable to that of fatty acid esterified phytosterols. Although esterification with fatty acids is one technique that facilitates dispersion of phytosterols in foods with a high fat content, FDA tentatively concludes that there is significant scientific agreement that fatty acid esterification is not necessary for phytosterols to be incorporated into food matrices or for phytosterols to be effective in lowering blood cholesterol when added to conventional foods. FDA also tentatively concludes that, for conventional foods, it is reasonable to expand the substance that is the subject of the claim to include both nonesterified and esterified phytosterols.

Therefore, the agency is proposing to amend current § 101.83(c)(2)(ii) to define the substances eligible for the health claim to include both phytosterols esterified with certain food-grade fatty acids and, for the conventional foods for which the claim is authorized, nonesterified phytosterols as substances for which the health claim may be made. As discussed elsewhere in this document, however, FDA is not proposing that dietary supplements containing only nonesterified phytosterols be eligible for the health claim.

2. Mixtures of Plant Sterols and Plant Stanols

Current § 101.83 distinguishes between plant sterol esters and plant stanol esters. The plant sterol component of the plant sterol ester that is the subject of current § 101.83 must be comprised of at least 80 percent (combined weight) of beta-sitosterol, campesterol, and stigmasterol (§ 101.83(c)(2)(ii)(A)(*1*)). Similarly, the plant stanol component of the plant stanol ester that is the subject of the health claim must be comprised of at least 80 percent (combined weight) sitostanol and campestanol (§ 101.83(c)(2)(ii)(B)(*1*)). The effective cholesterol-lowering daily intake specified in the current regulation for plant sterol esters is 1.3 g per day (equivalent to 0.8 g per day of nonesterified sterol) and that for plant stanol esters is 3.4 g per day (equivalent to 2 g per day of nonesterified stanol) (§ 101.83(c)(2)(i)(G)).

The agency requested comment on the variability of beta-sitosterol, campesterol, and stigmasterol composition in the plant sterol ester products reported to be effective in lowering cholesterol (65 FR 54686 at 54705) and requested similar information with respect to the variability of stanol composition of plant stanol products (65 FR 54686 at 54706). FDA further requested comment on the requirements that sterol composition of plant sterol esters be at least 80 percent (combined weight) beta-sitosterol, campesterol, and stigmasterol (65 FR 54686 at 54705) and that the stanol composition of plant stanol esters be at least 80 percent (combined weight) sitostanol and campestanol. The 2001 reopening of the IFR comment period (66 FR 50824) specifically sought submission of additional data on the effectiveness of plant sterol and stanol mixtures in reducing serum cholesterol levels.

Some comments requested that the scope of the health claim be broadened to include mixtures of plant sterols and stanols as eligible substances. One comment stated that for purposes of the health claim the effective cholesterol-lowering daily intake level for plant sterols, plant stanols, or plant sterol/stanol mixtures must be considered the same because available scientific evidence shows plant sterols and plant stanols to be equivalent in their serum cholesterol-lowering effect. Other comments asserted that the IFR should not be broadened to include plant sterol/stanol mixtures because these substances have not been the subject of a health claim petition. These comments asserted that FDA should only consider health claims for other phytosterol substances based on petitions submitted by proponents of such claims.

The totality of scientific evidence includes reports from five intervention studies of cross-over design that directly compared the cholesterol-lowering effects of similar intake levels of plant sterols and plant stanols within each study and at intake levels ranging from 1.8 and 3 g per day (Refs. 22, 35, 39, 40, and 41) (*see* table 1 at the end of this document). Three of the five intervention studies reported that equivalent intake levels of plant sterols and plant stanols were equally effective in lowering of blood total and/or LDL cholesterol levels (Refs. 22, 39, and 41). The other two intervention studies reported that plant sterols resulted in a greater reduction in LDL cholesterol compared to an equivalent intake level of plant stanols (Refs. 35 and 40).

There are nine intervention studies that investigated the cholesterol-lowering effects of mixtures of plant sterols and plant stanols added to conventional foods (Refs. 21, 22, 24, 25,

32, 34, 37, 42, and 43) (*see* table 1 at the end of this document). Eight of the nine studies, which provided 1.7 to 5 g per day of such mixtures foods consumed with meals, reported finding significant LDL cholesterol reductions of 5 to 15 percent relative to a placebo control. The magnitude of the effect on lowering LDL cholesterol did not vary meaningfully between the intervention studies involving mixtures of plant sterols and plant stanols and interventions studies involving plant sterols or plant stanols alone. Only one of the plant sterol/stanol mixture intervention studies reported finding no statistically significant lowering of LDL cholesterol (Ref. 34). The phytosterol composition of the mixtures used in most of these intervention studies was approximately 75 to 85 percent sterols and 10 to 15 percent stanols; two intervention studies used phytosterol mixtures that contained 50 percent sterol and 50 percent stanol (Refs. 42 and 22).

Based on the intervention studies demonstrating no meaningful difference between the effectiveness of plant sterols and plant stanols in lowering cholesterol and the intervention studies demonstrating that mixtures of plant sterols and plant stanols effectively lower cholesterol, FDA tentatively concludes that there is significant scientific agreement among qualified experts to support the relationship between foods containing mixtures of plant sterols and plant stanols and CHD.

FDA is therefore proposing to combine current § 101.83(c)(2)(ii)(A)(*1*) and (c)(2)(ii)(B)(*1*), and to adopt the term "phytosterol" as inclusive of both plant sterols and plant stanols. Proposed § 101.83(c)(2)(ii) would specify the eligible substance as "phytosterols." The proposal would also add a new paragraph (§ 101.83(a)(3)) in the background section of amended § 101.83 to define the term "phytosterols" and to clarify the regulation's use of that collective term. As discussed in section V.4 of this document, the proposal would further establish the permissible terminology that could be used to describe the substances subject to the health claim (§ 101.83(c)(2)(i)(D)).

3. Sources of Phytosterols

Current § 101.83(c)(2)(ii) specifies that eligible plant sterol esters must be derived from edible oils and that eligible plant stanols must be derived from either edible oils or from byproducts of the kraft paper pulping process. Some comments to the IFR urged FDA to broaden the nature of the substance to include both sterols and stanols derived from either vegetable oils or from wood oils.

The restriction on the source of plant sterol esters to edible oils in current § 101.83(c)(2)(ii)(A)(*1*) reflects the original health claim petition's specifications. The petition for a health claim characterizing a relationship between plant sterol esters and CHD limited itself to plant sterols derived from edible oils (*i.e.,* those edible oils that are vegetable oils). The origin of FDA's use of the "byproducts of the kraft paper pulping process" in current § 101.83(c)(2)(ii)(B)(*1*) was the terminology used by the original health claim petition for plant stanol esters. The petitioner submitted documentation to support its self-determination that plant stanol esters, whether obtained from vegetable oils or byproducts of the kraft paper pulping process, were GRAS (65 FR 54686 at 54706). FDA notes, however, that some of the intervention studies that were considered for purposes of re-evaluating the scientific basis for the authorized health claim identified the source of the phytosterols as "tall oil." Tall oil is a byproduct of the wood pulp industry, usually recovered from pine wood "black liquor" of the kraft paper process, containing rosins, fatty acids, long chain alcohols and phytosterols (Ref. 44). FDA is proposing to use the term "tall oil" in lieu of "byproducts of the kraft paper pulping process."

The phytosterols derived from tall oil are predominantly sterols. These wood-derived plant sterols are hydrogenated to convert a predominantly plant sterol product to plant stanols. The available scientific evidence includes five of six intervention studies that demonstrated cholesterol-lowering effects of conventional foods containing plant sterols derived from tall oil (Refs. 21, 24, 32, 37, and 43) (*see* table 1 at the end of this document). Jones (Ref. 34) did not observe a significant reduction in total or LDL cholesterol levels when 1.8 g of nonesterified sterols from tall oil was consumed in a nonfat or low fat beverage. The composition of the phytosterols used in these intervention studies was approximately 85 to 90 percent sterols and 10 to 15 percent stanols. FDA concurs with the comments that argued that there is no justification for not including plant sterols derived from byproducts of the kraft paper pulping process. FDA is proposing to amend the nature of the substance paragraph in current § 101.83(c)(2)(ii) to specify that the source for any phytosterol eligible for the claim may be either vegetable oils or tall oil.

Amended § 101.83(c)(2)(ii) would specify that eligible plant sterols and stanols are derived from vegetable oils or from tall oil.

4. Designation of Substance as Phytosterols

Current § 101.83(c)(2)(i)(D) requires that the claim statement identify the substance as either "plant sterol esters," or "plant stanol esters," except that if the sole source of the plant sterols/stanols is vegetable oil, the claim may use the term "vegetable oil sterol esters" or "vegetable oil stanol esters." Because FDA is now proposing to expand the substance that is the subject of the health claim to include, in addition to plant sterol/stanol esters, nonesterified phytosterols and mixtures of sterols and stanols, the agency is proposing to replace the terms "plant sterol esters" and "plant stanol esters" with the single term "phytosterols" throughout § 101.83.

In addition, FDA does not believe that requiring the claim to distinguish plant sterol esters from nonesterified plant sterols would provide meaningful information to the average consumer. On the other hand, it is likely that consumer recognition of the potential health benefit of phytosterol-enriched foods would be served by encouraging consistent use of a single term to identify the variations of phytosterol substances proposed to be included in the health claim. FDA believes that permitting the health claim statement to use the term "phytosterol" to identify all forms of the substance rather than distinguishing between sterol and stanol forms of esterified and nonesterified forms would encourage manufacturers to take that approach.

Therefore the agency proposes amending current § 101.83(c)(2)(i)(D) to include the single term "phytosterols." To be consistent with other revisions made to substances eligible for the health claim in this proposal, we are also proposing to permit accurate use of the terms "plant sterols," "plant stanols," or "plant sterols and stanols," and to permit "vegetable oil phyosterols" or "vegetable oil sterols and stanols" if the sole source of the plant sterols or stanols is vegetable oil.

5. Determining the Amount and Nature of the Substance

Current § 101.83(c)(2)(ii)(A)(*2*) and (c)(2)(ii)(B)(*2*) specify that, when FDA measures phytosterols in foods bearing the claim, it will use particular analytical methods, which are the methods specified in the original health claim petitions. The analytical methods specified in the current regulation are direct saponification/gas

chromatographic methods for the determination of phytosterols in various food matrices. FDA is proposing to amend the health claim to revise the analytical methods for phytosterols, because the current methods would be inadequate to measure phytosterols in the range of foods eligible to bear the health claim under the proposed amendments to the regulation.

In table 3 of this document, FDA has summarized the key features of several recent methods used for quantitation of phytosterols. Analytes, sample handling, matrices studied, and types and lengths of gas chromatography columns are listed. The types of validation data obtained for these methods are also listed. Each of these methods provides starting points for possible extensions to other analytes and other food matrices. The validation data provide guidelines regarding the types of validation that would be needed should these methods be extended or modified.

The agency solicited comments on the suitability of the petitioners' analytical methods for ensuring that foods bearing the health claim contain the qualifying levels of phytosterol esters (65 FR 54686 at 54706 and 54707). Comments received from several manufacturers recommended that, until a general method is developed and validated for determining the phytosterol content of foods, the regulation should allow manufacturers to use any reliable analytical method for determining the amount of phytosterols in their products and that the records of their testing, or records of other reliable methods to verify phytosterol content such as production records, should be available to FDA upon request.

FDA emphasizes that the purpose for identifying a specific analytical method in a health claim regulation is not to bind manufacturers to the use of any one analytical method. Rather, the purpose is to inform manufacturers of the analytical method that will be used by FDA to verify that foods bearing the claim comply with the requirements of the claim. Because there is no Association of Official Analytical Chemists (AOAC) Official Method for phytosterols in foods, FDA has considered the comments from manufacturers that the agency could review manufacturers' records (production and/or testing) as a method of determining compliance with the requirements of the claim regulation. A specific quantitative analytical method for the substance that is the subject of the health claim is one means for verifying compliance with the requirements of a health claim, although it is not an absolute requirement for a health claim regulation. In the absence of a validated analytical method for determining the amount of a substance in a food, FDA has previously included a record inspection requirement to determine the amount and nature of a substance in the food to assure that it was in compliance with the requirements of the health claim. In the soy protein/CHD health claim regulation (§ 101.82(c)(2)(ii)(B)), manufacturers of foods bearing the claim must maintain records sufficient to substantiate the level of soy protein when the food contains other sources of protein and make such records available to FDA upon request.

Although FDA recognizes that using food manufacturers' production and/or analytical records is one option for compliance verification, recent developments in analytical methodology have provided an additional possibility for verifying compliance with the claim requirements. For the reasons discussed below, FDA is proposing to replace both the Unilever and McNeil methods specified in the current regulation with AOAC Official Method 994.10, "Cholesterol in Foods" (Ref. 45) as modified by Sorenson and Sullivan (Ref. 46) for assaying phytosterols. FDA recognizes that this method may need to undergo further validation studies if analytes other than those already studied are included in the analyses.

When adopted in the IFR, as the analytical methods FDA would use for determining plant stanol ester content of foods, neither the McNeil nor the Unilever methods had been subjected to validation through a collaborative study or peer-verified validation process, nor had they been published in the scientific literature (65 FR 54686 at 54706 and 54707). FDA is not aware that this situation has changed for the McNeil methods. The Unilever analytical method has subsequently been validated through a collaborative study and published (Ref. 47). However, this method quantifies total 4-desmethyl sterol content only and is not recommended for identification of unknown sterols. As such, this method is not suitable for one of the primary analytical needs for determining compliance with the claim requirements (*i.e.,* identifying the phytosterols present in a food). Further, the method was validated only for measurement of plant sterols in vegetable oil blends and plant sterol concentrates. For these reasons, FDA is proposing to remove the McNeil and Unilever methods cited in § 101.83(c)(2)(ii)(A)(*2*) and (c)(2)(ii)(B)(*2*) from the regulation.

TABLE 3—SUMMARY OF KEY FEATURES OF SEVERAL RECENT METHODS USED FOR QUANTITATION OF PHYTOSTEROLS

| Method | Description | Analytes, analytical ranges, other features | Validation data available, matrices studied | Comments |
|---|---|---|---|---|
| 1. McNeil—§ 101.83(c)(2)(ii)(B)(*2*). | Direct saponification, silyl derivatization, GC.<br>Lipids are saponified at high temp with ethanolic KOH. The unsaponifiable fraction is extracted into hexane. Sterols are derivatized to trimethylsilyl (TMS) ethers and quantified by capillary GC with FID<br>Internal standard: 5β-cholestan-3α-ol System suitability standards: cholestanol + stigmastanol.<br>Column: capillary, 30 m × 0.32 mm × 0.25 μm film thickness; cross-linked 5% phenyl-methyl silicone or methyl silicone gum (HP–5). | Analytes: sitosterol, sitostanol, campesterol, campestanol.<br>Ranges: 3–8 g/100 g dressing; 6–18 g/100 g tub spread; 2.5–7.5 g/100 g snack bars; 464–696 mg/softgel capsules | In-house validation data on linearity, accuracy, precision, and reproducibility.<br>Matrices: dressings, tub spreads, snack bars, softgel capsules | Method is applicable to the determination of added phytosterols.<br>Alkaline saponification hydrolyses sterol-ester bonds; analytes are nonesterified sterols. |
| 2A. Unilever—§ 101.83(c)(2)(ii)(A)(*2*). | Direct saponification, no derivatization, GC. | | | |

TABLE 3—SUMMARY OF KEY FEATURES OF SEVERAL RECENT METHODS USED FOR QUANTITATION OF PHYTOSTEROLS—Continued

| Method | Description | Analytes, analytical ranges, other features | Validation data available, matrices studied | Comments |
|---|---|---|---|---|
| | Lipids are saponified at high temp with ethanolic KOH..<br>Unsaponifiable fraction is extracted into heptane. Quantitation by GC with FID<br>Internal standard: β-cholestanol (CAS No. 80–97–7)<br>Column: capillary, 10 m × 0.32 mm × 0.12 μm film thickness; CP–Sil-5CB | Analytes: total 4-desmethyl sterols.<br>Range: 7–60 g/100 g product | Validation results for recovery, and repeatability.<br>Matrices: margarines, dressings, fats, fat blends, and phytosterol ester concentrates | Method has been validated through a collaborative study; however, this method quantifies total 4-desmethyl sterol content only and is not recommended for identification of unknown sterols. Method is not suitable for one of the primary analytical needs for determining compliance with the claim requirements (*i.e.,* identifying the phytosterols present in a food). Method validated only for measurement of plant sterols in vegetable oil blends and plant sterol concentrates. |
| 2B. Duchateau *et al.,* 2002 (Ref. 47). | Direct saponification, no derivatization, GC.<br>Sample is saponified with ethanolic KOH at 70° C for 50 min. Unsaponifiable fraction is extracted into heptane. Quantitation by GC with FID<br>Internal standard: β-cholestanol (5α-cholestane-3β-ol)<br>Reference standards: cholesterol, campesterol, stigmasterol, β-sitosterol<br>Column: capillary, 10 m × 0.32 mm × 0.12 μm film thickness; CP–Sil-5CB | Analytes: cholesterol, brassicasterol, campesterol, stigmasterol, β-sitosterol, Δ5-avenasterol.<br>Ranges: 15–20 g/100 g vegetable oils; 8 g/100 g vegetable oil spreads; 60 g/100 g phytosterol ester concentrates | International collaborative study performed with 8 samples from 4 different products and batches. Validation data for recovery, accuracy, and repeatability. Instrument details (GC brand, type; columns, injector type, temperature program) for all participants provided. | Method is that of Unilever (2A).<br>Phytosterols analyzed as nonesterified sterols. |
| 3. AOAC Official Method 994.10 "Cholesterol in Foods." Direct saponification-gas chromatographic method (Ref. 45). | Direct saponification, silyl derivatization, GC.<br>Lipids are saponified at high temperature (not specified) with ethanolic KOH. Unsaponifiable fraction containing cholesterol and other sterols is extracted with toluene. Sterols are derivatized to TMS ethers and quantified by GG with FID<br>Internal standard: 5α-cholestane.<br>Column: capillary, 25 m × 0.32 mm × 0.17 μm film thickness; cross-linked 5% phenyl-methyl silicone or methyl silicone gum (HP–5, Ultra 2 of HP–1). | Analyte: cholesterol Test sample should contain ≤ 1 g fat or ≤ 5 g water. Suggested sample weights provided for pure oils, salad dressings, substances with high moisture content..<br>LOQ: 1.0 mg/100 g Calibration curve 2.5–200 μg/ml | Collaborative study matrices: Butter cookies, vegetable bacon baby food, chicken vegetable baby food, skinless wieners, NIST egg powder (SRM 1845) commercial powdered eggs, Cheese Whiz. | The method is applicable to the determination of ≥ 1 mg cholesterol/100 g of foods, food products.<br>Collaborative study reference: *Journal of AOAC International,* 78(6):1522–1525, 1995. (Ref. 48). |

TABLE 3—SUMMARY OF KEY FEATURES OF SEVERAL RECENT METHODS USED FOR QUANTITATION OF PHYTOSTEROLS—Continued

| Method | Description | Analytes, analytical ranges, other features | Validation data available, matrices studied | Comments |
|---|---|---|---|---|
| 4. Sorenson and Sullivan, 2006 (Ref. 46). | Direct saponification, silyl derivatization, GC.<br>Modification of AOAC Official Method 994.10 (*see* item 3. of this table) to include determination of phytosterols<br>Lipids are saponified at high temperature (not specified) with ethanolic KOH. Unsaponifiable fraction containing cholesterol and other sterols is extracted with toluene. Sterols are derivatized to TMS ethers and quantified by GG with FID<br>Internal standard: 5α-cholestane<br>Column: capillary, 25 m × 0.32 mm × 0.17 μm film thickness; cross-linked 5% phenyl-methyl silicone or methyl silicone gum (HP–5, Ultra 2 of HP–1) | Analytes: campesterol, stigmasterol, β-sitosterol.<br>LOQ: 1.0 mg/100 g Calibration curve: 2.5–200 μg/ml | Single laboratory validation: precision, stability, accuracy, and ruggedness.<br>Matrices: powdered saw palmetto berry, saw palmetto dried fruit $CO_2$ extracts, saw palmetto 45% powdered extract, dietary supplement samples | Full collaborative study said to be in progress. |
| 5. Quaker Method #210 (Ref. 49). | Direct extraction, silyl derivatization, GC.<br>Lipids are extracted from homogenized food sample into toluene. Sterols are derivatized to TMS ethers and quantified by capillary GC with FID<br>Internal standard: 5α-cholestane (CAS No. 481–21–0).<br>Reference standards: mixture of nonesterified sitosterol, sitostanol, campesterol, campestanol<br>Column: capillary, 30 m × 0.25 mm × 0.25 μm film thickness; (DB–5) | Analytes: sitosterol, sitostanol, campesterol, campestanol..<br>Range: 0.7–2.25 g/100 g bars; 0.13–0.38 g/100 g beverages; 3–9 g/100 g cereals | In-house validation data for specificity, accuracy linearity, precision, and stability..<br>Matrices: food bars, beverages, ready-to-eat cereals | Intended for use in only relatively low-fat foods enriched with nonesterified plant sterols/stanols.<br>Applicable for determination of added nonesterified phytosterols. |
| 6. Toivo, J. *et al.* 2001 (Ref. 50). | Acid hydrolysis, saponification, silyl derivatization, GC.<br>First step uses HCL hydrolysis to liberate glycosylated phytosterols bound in food matrices. Lipids are extracted into hexane:ether, dried and the lipid extract is saponified at high temp with ethanolic KOH. Unsaponifiable fraction is extracted into cyclohexane. Sterols are derivatized to TMS ethers and quantified by capillary GC with FID.<br>Internal standard: dihydrocholesterol (cholestanol).<br>Reference standard: dihydrocholesterol (cholestanol), cholesterol, cholesteryl palmitate, and mixture of soybean steryl glucosides containing sitosterol, campesterol, and stigmasterol as their glucosides.<br>Column: capillary, 60 m × 0.25 mm × 0.1 μm film thickness; cross-linked 5% diphenyl-95% dimethyl polysiloxane. | Analytes: cholesterol, sitosterol, sitostanol, campersterol, campestanol, stigmasterol, Δ5-avenasterol.<br>Range: 0.5–800 mg/100 g for individual phytosterols. | Single laboratory validation includes method optimization, accuracy, and repeatability..<br>Matrices: flour, canola oil, corn meal, dried onion, sunflower seed, diet composite. | Intended for use in determining levels of endogenous phytosterols in foods.<br>Acid hydrolysis step included to release conjugated forms of phytosterols. Important for grains, flours; not so for oils. Use of acid hydrolysis prior to or following lipid extraction discussed.<br>Method has been used for analysis of hundreds of foods to create database of phytosterol in foods. |

**ABREVIATIONS:** GC—gas chromatography; TMS—trimethylsilyl; FID—flame ionization detector; KOH—potassium hydroxide; CAS—Chemical Abstract Service; LOQ—limit of quantitation.

At the present time, the method that appears to be the most appropriate for the current regulation is that of Sorenson and Sullivan (2006) (Ref. 46). This method, which has undergone AOAC's single laboratory validation procedures, is a modification of AOAC Official Method 994.10 for the determination of cholesterol in foods. AOAC Official Method 994.10 was validated in a variety of food matrices (Ref. 48) and, with the modifications and validation data provided by Sorenson and Sullivan (Ref. 46), can likely be extended further to include campestanol and sitostanol and additional food matrices.

At this time, FDA is not aware of any publicly available analytical methods that have already been validated through collaborative studies that apply to a wider range of food matrices and that adequately resolve the specific phytosterols that are the subject of this health claim (*i.e.,* β-sitosterol, campesterol, stigmasterol, sitostanol, and campestanol) from other phytosterols potentially present in foods. FDA is therefore requesting submission of validation data for any analytical methods that may apply to a wider range of food matrices or more fully validated for separation and quantitation of the specific phytosterols of this health claim.

FDA is tentatively concluding that the modification of AOAC Official Method 994.10 provided by Sorenson and Sullivan (Ref. 46) for the evaluation of campesterol, stigmasterol, and beta-sitosterol is an appropriate method for use to assess compliance for this health claim for those foods for which such method has been validated. This method will need to be validated to include campestanol and sitostanol and to include additional matrices for other foods that may be eligible for this claim. Method validation is a process that is used to establish that, if the method is performed properly, it produces results which are of acceptable quality. The validation process involves determining statistical parameters of a method to decide if the method is fit for a specified purpose. Methods documented by published interlaboratory validation data are generally selected over those that are not. Attributes of methods include the following: Range, limit of detection, limit of quantitation, accuracy, precision (repeatability and reproducibility), specificity (selectivity), sensitivity, robustness (ruggedness), practicality, and applicability. We request comment on whether validated methods are available for analytes and matrices that are not included in the Sorenson and Sullivan method. If so, FDA may adopt such methods in a final rule. If no other validated methods are available, FDA would likely require, in a final rule, a requirement for manufacturers to maintain records to demonstrate that the method used to identify the presence of the phytosterols in its product, that bears the phytosterol health claim, and the level of each phytosterol source in such product, is capable of accurately quantifying phytosterols in the product. FDA also would likely require that manufacturers maintain records of test results. Further, FDA would likely require that the manufacturer make such records available to FDA upon request.

FDA is proposing to replace the analytical methods now specified in current § 101.83 (Unilever's method in § 101.83(c)(2)(ii)(A)(*2*) and McNeil's methods in § 101.83(c)(2)(ii)(B)(*2*)) with Sorenson and Sullivan's modifications of AOAC Official Method 994.10 (Ref. 46), for those foods for which the Sorenson and Sullivan method has been validated.

*B. Nature of the Claim*

1. Effective Cholesterol-Lowering Daily Dietary Intake

Current § 101.83(c)(2)(i)(G) requires that the health claim specify the daily dietary intake of plant sterol or stanol esters that is necessary to reduce the risk of CHD and the contribution one serving of the product makes to the specified daily dietary intake level. Current § 101.83(c)(2)(iii)(A) further specifies that the amount of plant sterol or stanol esters that a food product eligible to bear the health claim is required to contain per RACC. Such amount is one half of the daily dietary intake level associated with reduced CHD risk (*i.e.,* the total daily intake divided between two meals). FDA concluded in the IFR that the daily dietary intake levels of plant sterol and stanol esters that are associated with reducing the risk of CHD, based on the consistently demonstrated effective lowering of blood total and/or LDL cholesterol, were at least 1.3 g per day of plant sterol esters (equivalent to 0.8 g per day expressed as plant sterol) and at least 3.4 g per day of plant stanol esters (equivalent to 2 g per day expressed as plant stanols) (65 FR 54686 at 54704).

In its original health claim petition, Unilever (then acting under its subsidiary Lipton) proposed 1.6 g per day of plant sterol esters (equivalent to 1 g per day expressed as nonesterified plant sterols) as the daily dietary intake level of plant sterols necessary to justify a claim about reduced risk of CHD. The agency agreed that an intake level of 1 g per day of nonesterified plant sterols had been demonstrated to consistently reduce blood total and LDL cholesterol, but the agency also considered three intervention studies (Refs. 29, 30, and 51) in which a daily intake level of approximately 0.8 g per day plant sterols was reported to significantly lower blood cholesterol. The agency therefore concluded that the intake level of plant sterols consistently shown to lower blood total and LDL cholesterol was 0.8 g per day or more of nonesterified plant sterols (equivalent to 1.3 g per day or more expressed as plant sterol esters) (65 FR 54686 at 54704).

McNeil proposed a total daily intake of at least 3.4 g per day of plant stanol esters (equivalent to 2 g per day expressed as nonesterified plant stanols), which represents an amount that had been consistently shown to be effective in reducing blood cholesterol (65 FR 54686 at 54704). The agency found no consistent scientific evidence for blood cholesterol-lowering associated with plant stanol ester intake levels less than 3.4 g per day. Although one study (Refs. 28 and 52) reported significant lowering of blood cholesterol at 1.36 g plant stanol esters per day (equivalent to 0.8 g per day expressed as nonesterified stanols), another study (Ref. 53) reported no significant reduction of blood cholesterol levels at approximately the same plant stanol ester intake level.

FDA requested comment on the determination of the daily intake of plant sterol esters and plant stanol esters associated with the risk of CHD (65 FR 24686 at 24704). A majority of comments to the IFR suggested that the efficacy of plant sterols and stanols was similar and that the daily intake levels should be the same for both substances. Many of these comments suggested that the equivalent amount should be in line with the minimum effective level for plant sterol esters. Some comments argued for adopting approximately 2 g per day (expressed as nonesterified phytosterols) as a more highly effective level, but most comments favored the lower level. Some comments provided scientific data and analysis to support this contention; others did not.

The phytosterol intervention studies that FDA considered in this reevaluation (*see* table 1 at the end of this document) included dietary phytosterol intervention levels ranging between 0.45 g per day (Ref. 54) and 9 g per day (Ref. 55). Most commonly, phytosterol intake levels ranged from 1 to 3 g per day. Intervention studies demonstrated statistically significant reductions in total and/or LDL

cholesterol levels for plant sterol intake levels ranging from 1 to 3 g per day. Similar to plant sterols, intervention studies demonstrated statistically significant reductions in total and/or LDL cholesterol levels for plant stanol intake levels ranging from 1.6 to 3 g per day. There are also five intervention studies of cross-over design that directly compared the cholesterol-lowering effects of similar intake levels of plant sterols and plant stanols within each study and at intake levels ranging from 1.8 and 3 g per day across the five intervention studies (Refs. 22, 35, 39, 40, and 41). All five of these intervention studies demonstrated that both plant sterols and plant stanols significantly reduce blood total and/or LDL cholesterol levels. Three of the five intervention studies reported that equivalent intake levels of plant sterols and stanols were equally effective in lowering of blood LDL cholesterol levels (Refs. 22, 39, and 41). The other two intervention studies reported that plant sterols resulted in a greater reduction in LDL cholesterol compared to an equivalent intake level of plant stanols (Refs. 35 and 40).

Based on the scientific evidence regarding the relationship of consuming phytosterols with a reduced risk of CHD, FDA tentatively concludes that 2 g of phytosterols per day is the daily dietary intake necessary to achieve the claimed effect. Two g per day of plant sterols is the midpoint of the daily intake range of 1 to 3 g used in the majority of intervention studies designed to evaluate their effectiveness in lowering cholesterol. Two g of phytosterols per day is also at the lower end of the daily intake range in the intervention studies designed for evaluating the effectiveness of plant stanols and mixtures of plant stanols and sterols. In addition, 2 g per day is commonly cited as an optimal level for cholesterol-lowering effects (Refs. 3, 56, 57, and 58) and FDA's own evaluation of the publicly available evidence supports that conclusion. FDA has thus tentatively determined that, for purposes of authorizing a health claim relating phytosterol consumption and CHD risk, the daily dietary intake necessary to achieve the claimed effect for phytosterols is 2 g per day. The agency invites comments on this tentative determination.

Current § 101.83(c)(2)(i)(G) identifies the daily dietary intake levels of plant sterols/stanols in terms of "___ grams or more per day * * *." Likewise, the model health claims provided in the IFR preface the daily dietary intake levels with the phrase "at least," *e.g.,* "Food containing at least 1.7 g per serving * * * for a total daily intake of at least 3.4 g * * *" (§ 101.83(e)). The agency is also proposing to eliminate the "or more" and "at least" qualifications from the specification of the daily dietary phytosterol intake level. The agency is proposing to amend § 101.83(c)(2)(i)(G) to require that a claim that is the subject of this regulation specify that the daily dietary intake of phytosterols that is necessary to justify the CHD risk reduction claim is 2 g per day.

2. Servings per Day

Current § 101.83(c)(2)(i)(H) requires the health claim to specify that the daily dietary intake of plant sterol or stanol esters should be consumed in two servings eaten at different times of the day with other foods. FDA explained that the conditions for the consumption of phytosterols to be specified in the claim were consistent with the way phytosterols were used in those intervention studies showing significant blood cholesterol-lowering effects of phytosterols. In these intervention studies, the study subjects were instructed to consume the daily intake of phytosterols divided over two or three servings at different times of the day or were instructed to replace a portion of their typical dietary fat with equal portions of phytosterol-enriched test margarines over the course of the day, usually during meals (65 FR 54686 at 54705). FDA also noted that given the limited variety of phytosterol-enriched foods to be included in the claim, it would be difficult for many consumers to eat more than two servings of phytosterol-enriched foods per day. FDA further noted that recommending more than two servings per day of phytosterol-enriched foods would not be appropriate, considering the fat content of the phytosterol-enriched conventional foods (primarily fat-based foods) to be eligible to bear the claim (65 FR 54686 at 54708).

FDA requested comments on whether it was reasonable, in light of the fat content of products eligible to bear a claim and the limited number of available products, to divide the daily dietary intake of plant sterol esters and plant stanol esters by two and specify that the product should be consumed in two servings eaten at different times of the day (65 FR 54686 at 54707 and 54708, respectively). Some comments supported the agency's requirement that the label specify that the daily dietary intake of phytosterols should be consumed in two servings at different times during the day. Several comments stated that the claim statement should state "at least two * * *" or "two or more * * *" servings a day rather than two servings per day and asserted that consumers would benefit more from consuming phytosterols on more occasions during the day. Most comments disagreed with the agency's two servings per day requirement. Some of these comments noted that, because the technology exists to disperse phytosterols into non-fat foods, there is no reason to deviate from the usual assumption that the total daily intake of a food component is divided among four eating occasions. Several comments requested that the claim make the servings per day statement optional rather than a mandatory component of the claim. One comment said that optional claim language about the number of servings of phytosterol-enriched foods per day could vary, depending on the phytosterol content of a food.

The 2006 Unilever petition (Docket No. FDA–2006–P–0033 (formerly Docket No. 2006P–0316)) asserted that there is now significant scientific agreement that phytosterols will significantly reduce cholesterol levels when consumed once per day. The petition requested that § 101.83 be amended to permit a food containing 2g of phytosterols to state that consuming phytosterols once per day has been associated with a reduced risk of CHD. FDA is proposing to amend § 101.83 to permit the health claim Unilever requested.

The design of most phytosterol intervention studies specified that the daily intake of phytosterols be divided between two or three servings eaten at different times with meals. However, scientific evidence that has become available since issuance of the IFR demonstrates that dividing the daily intake over two or more servings is not necessary for the cholesterol-lowering effect of phytosterols. Seven of the more recently completed phytosterol intervention studies had their study subjects consume all phytosterol-enriched test foods in one serving per day (Refs. 8, 35, 38, 42, 43, 59, and 60) (*see* table 1 at the end of this document).

Six of the seven "once-per-day" studies that FDA considered reported significant reductions of total and/or LDL cholesterol in phytosterol groups compared to the control group (Ref. 38). AbuMweis *et al.,* 2006 reported no cholesterol-lowering effect, at 1.0 to 1.8g per day, when the phytosterols were incorporated into margarine and consumed as part of the breakfast meal for 4 weeks. Each of the six studies that reported once-per-day consumption of phytosterols to be effective in reducing cholesterol had incorporated the phytosterols into test foods (margarine,

bread, low fat milk, cereal, yogurt, or ground beef) that were consumed with a meal. These once-per-day studies reported that daily intakes ranging from 1.6 to 3 g per day resulted in reductions in cholesterol of between 5.6 and 12.4 percent compared to controls. The cholesterol-lowering effect from "once-per-day" consumption was similar to the cholesterol reductions observed for comparable daily intake levels divided over multiple servings eaten at different times of the day.

Based on this evidence, FDA tentatively concludes that the requirement for the health claim to specify that the daily dietary intake of phytosterols should be consumed in two servings eaten at different times during the day is no longer consistent with the available scientific evidence for the cholesterol-lowering effect of phytosterol consumption. FDA also notes that the other reasons cited in the IFR for requiring the claim statement to specify that phytosterols should be eaten in two different servings (*i.e.,* the health claim was to be available to a limited number of foods and the conventional foods were mostly high fat content), would no longer be valid arguments due to other changes in the claim criteria that are being proposed at this time.

Therefore the agency is proposing to amend § 101.83(c)(2)(i)(H) by removing the requirement that the health claim include a recommendation that phytosterols be consumed in two servings eaten at different times of the day.

3. Consuming Phytosterols With Meals

Current § 101.83(c)(2)(i)(H) requires that the health claim specify that phytosterols should be consumed in two servings eaten at different times of the day with other foods. As discussed in section V.B.2 of this document, FDA has concluded that requiring the claim to state that the total daily dietary intake of phytosterols should be divided over two servings eaten at different times is no longer supported by available scientific evidence. The agency is also proposing to amend § 101.83 to require the claim to recommend that phytosterols be consumed with "meals."

The design used in a majority of phytosterol intervention studies specified that the phytosterol-enriched test foods were to be consumed with meals. The experimental design of most all other intervention studies that did not specify the phytosterol-enriched test foods were to be consumed "with meals" involved fat-based phytosterol-enriched test foods (margarine, butter, mayonnaise) and specified that the phytosterol test food be used to replace an equivalent amount of the subjects' typical daily fat consumption. As such, it is likely that in these studies the phytosterol-enriched foods would have been consumed with other foods. One intervention study investigated the impact of consuming phytosterols with meals (Ref. 43). The study subjects in this study were instructed to consume a daily single serving of phytosterol-enriched yogurt either in the morning at least 0.5 hour before breakfast, or with lunch. Significant lowering of total and LDL cholesterol was reported for both phytosterol-enriched yogurt consumed while fasting and when consumed with a meal; however, the cholesterol-lowering effect was significantly greater when consumed with a meal than when not consumed with a meal (Ref. 43).

Intestinal absorption of cholesterol requires cholesterol be incorporated into mixed micelles of the intestinal digesta. Intestinal micelles form when dietary fatty acids, pancreatic juice, and bile salts come together at the same time in the small intestine. The process of eating food stimulates secretion of pancreatic juice and of bile salts into the intestine. The presumptive primary site of phytosterol interaction with cholesterol is within the micelles, where phytosterols are thought to block the transfer of cholesterol from micelles to intestinal mucosal cells. This mechanism supports the theory that the effectiveness of dietary phytosterols in reducing blood cholesterol levels depends upon the phytosterols being consumed concurrently with food and dietary fat to ensure maximal incorporation of phytosterols into intestinal micelles. Current § 101.83 authorizes a health claim only for phytosterols esterified with fats and incorporated into types of fat-based foods (margarines and salad dressings) that typically are consumed with other foods and therefore the theoretical conditions that facilitate interference with cholesterol absorption (*i.e.,* phytosterols consumed with food and with dietary fat) would be met.

Changes to current § 101.83 in this proposed rule include: (1) Expanding the substance of the claim to include nonesterified phytosterols in conventional foods, (2) removing restrictions on types of conventional foods eligible for the claim such that fat-free foods and beverages will not be precluded from making the claim, and (3) removing the requirement that the claim statement specify that phytosterols should be consumed in two servings eaten at different times during the day. The cholesterol-lowering efficacy of phytosterols, when not consumed with dietary fat and a substantial amount of food, has not been demonstrated. Without a recommendation that phytosterols be consumed with meals or snacks, it is probable that the types of foods (including dietary supplements) likely to be enriched with phytosterols for the purpose of bearing the health claim would be consumed without sufficient dietary fat or amounts of food to be consistent with the circumstances under which phytosterols are likely to be effective in lowering cholesterol.

FDA is proposing to amend § 101.83(c)(2)(i)(H) to require that the health claim specify that phytosterol-enriched foods should be consumed "with meals or snacks." The "with meals or snacks" specification will replace the current requirement that the claim specify the daily dietary phytosterol intake should "be consumed in two servings eaten at different times of the day with other foods."

*C. Nature of the Food Eligible To Bear the Claim*

1. Qualifying Amount of Phytosterols per Serving

Current § 101.83(c)(2)(iii) requires that, in order to bear the health claim, a product must contain at least 0.65 g of plant sterol esters (equivalent to 0.4 g nonesterified plant sterols) or 1.7 g of plant stanol esters (equivalent to 1 g nonesterified plant stanols) that comply with paragraphs § 101.83(c)(2)(ii)(A)(*1*) and (c)(2)(ii)(B)(*1*) respectively, per RACC. These values are one-half of the plant sterol/stanol ester daily intake specified in the IFR as that necessary to achieve the CHD risk-reduction benefit. As discussed in section V.B.2 of this document, FDA is proposing to amend § 101.83 to remove the current requirement that the health claim specify that phytosterols should be consumed in two servings at different times of the day. Also, the proposed changes to § 101.83 would result in a greater variety of phytosterol-enriched foods eligible for the claim than now included in current § 101.83, including conventional foods with a lower fat content. Therefore, FDA is reconsidering the initial decision to base the minimum amount of phytosterol in a food eligible to use the health claim on two servings per day.

The agency generally assumes that a typical food consumption pattern includes three meals and one snack per day (*see* 58 FR 2302 at 2379, January 6, 1993). Currently available evidence demonstrates that it is feasible and effective to enrich low fat and fat free foods with phytosterols. Due to the

wider variety of conventional foods that may potentially be fortified with phytosterols (as evidenced by the variety of phytosterol-enriched test foods used in intervention study reports published since 2000), it may be feasible for consumers to select four servings per day without having to depend exclusively on conventional foods with a high fat content. As a result, FDA believes it would be reasonable to base the minimum qualifying amount of phytosterol in a food on four servings per day. As discussed in section V.B.1 of this document, FDA has tentatively concluded that, for the purpose of the health claim, the phytosterol daily dietary intake necessary to achieve the claimed effect is 2 g per day. Dividing this daily intake over four servings per day, the minimum eligible phytosterol content of a food would be 0.5 g per RACC, expressed as the weight of nonesterified phytosterols.

Therefore, the agency is proposing to amend § 101.83(c)(2)(iii)(A) to permit health claims on foods that contain at least 0.5 g per RACC of phytosterols, expressed as the weight of nonesterified phytosterols, and that comply with paragraph (c)(2)(ii) of this section. Further, the agency is proposing to add new § 101.83(c)(2)(iii)(C) to limit the claim to conventional foods containing phytosterols for which the agency has received a GRAS notification, to which it had no further questions, and the conditions of use are consistent with the eligibility requirements for the health claim. We note that not all conventional foods for which a GRAS notification for phytosterols was submitted, to which the agency had no further questions, are under conditions of use in food that would be consistent with the eligibility requirements for the health claim, *e.g.,* certain foods may contain phytosterols at a level that is less than the minimum of 0.5 g per RACC. Such foods would not be eligible to bear the health claim if the rule is finalized as proposed.

2. Nature of the Food

Current § 101.83(c)(2)(iii)(A)(*1*) limits the plant sterol ester-enriched food products eligible to bear the health claim to spreads and dressings for salad. Current § 101.83(c)(2)(iii)(A)(*2*) limits the plant stanol ester-enriched food products eligible to bear the health claim to spreads, dressings for salad, snack bars, and dietary supplements in softgel form. The term "spreads" was used in the IFR to include both margarine and vegetable oil spreads resembling margarine but having a fat content less than that required by the food standard for margarine (§ 166.110 (21 CFR 166.110)). The term "dressings for salad" was used in the IFR to include both salad dressing and similar vegetable oil-based food products with vegetable oil content less than that required by the food standard for salad dressing (§ 169.150 (21 CFR 169.150)), which is typically a product that resembles mayonnaise.

FDA explained in the IFR that the use of the plant sterol ester claim was being restricted to the labeling of spreads and dressings for salads because of the following: (1) The petitioner limited its requested health claim to those two types of foods, (2) the petitioner had satisfied the requirement of § 101.14(b)(3)(ii) only with respect to the use of plant sterol esters as an ingredient in spreads and dressings for salads, and (3) the petitioner had provided a quantitative analytical method for measurement of plant sterol esters only in spreads and dressings for salads (65 FR 54686 at 54707). FDA noted that it would consider broadening the types of plant sterol ester-containing foods eligible to bear the claim if data were submitted to establish the use of plant sterol esters in other food products at levels necessary to justify the claim is safe and lawful and if a validated analytical method that permits accurate determination of the amount of plant sterol esters in other types of foods was available (65 FR 54686 at 54707). The agency advanced analogous reasoning for limiting the foods eligible to bear the authorized health claim for plant stanol esters to spreads, dressings for salad, snack bars and dietary supplements in softgel form (65 FR 54686 at 54708).

Many comments received in response to the IFR addressed the restrictions on the types of foods eligible for the claim. Most of the comments objecting to the IFR's specification of eligible food categories recommended that the final rule be expanded to include additional types of foods or asserted that the final rule need not restrict the types of food eligible for the claim. These comments argued: (1) That evidence now available from clinical trials established the cholesterol-lowering effectiveness of phytosterols when incorporated into many types of foods, including low fat and fat free foods, and (2) that thus there was no evidence to suggest that the food matrix chosen to carry the phytosterol will have an effect on cholesterol-lowering efficacy. Some comments asserted that it is unnecessary to limit the claim to fat-based food matrices because the technology is available to disperse nonesterified plant sterols and stanols in a wide variety of non-fat food matrices and because the key factor is that the plant sterols be consumed with fat, not that the plant sterols be dispersed in fat. Other comments noted that a growing number of GRAS notifications, to which the agency has not objected, expand the categories of food in which phytosterols may be used safely and lawfully beyond the foods listed in current § 101.83. Some comments urged authorizing the health claim for other categories of foods, subject to availability of validated quantitative analytical methodology for phytosterols in other food matrices. Other comments argued that it is not necessary to restrict use of the claim to types of foods for which the petitioners had provided product-specific phytosterol analytical methods. Rather, these comments contended, that it is feasible to measure phytosterols in other food matrices using established general sterol methods and the food industry should be permitted to use any reliable methods, including maintaining production records, to document compliance with the phytosterol content requirements of the claim. Some comments asserted that making more types of foods eligible for use of the claim would encourage consumer use of phytosterol-enriched foods through a broader array of food options accommodating a greater variety of consumer tastes. One comment opposed broadening of the categories of foods eligible to bear the claim, arguing that proliferation of the types of foods bearing the claim would likely result in phytosterol intake exceeding acceptable daily intake levels and that the long-term safety of higher intake levels has not been evaluated.

Finally, some comments received in response to the IFR requested that FDA expand the regulation to permit health claims for plant sterol/stanol ester-containing dietary supplements in a variety of forms including tablets, capsules, softgel capsules, and chewable wafers. Others were concerned that products in "pill" form and intended for use to help lower blood cholesterol looked too much like over the counter drugs.

a. *Conventional foods.* All the intervention studies involving phytosterol-enriched conventional foods cited in the IFR were studies in which the phytosterols were added to the diet as phytosterol-enriched margarines, butter, mayonnaise, or shortening. Subsequently, evidence from intervention studies employing a wider variety of phytosterol-enriched conventional foods has become available (*see* table 1 at the end of this document). Phytosterol-enriched conventional foods used in intervention studies now include the following: Margarine and reduced-fat spreads

resembling margarine, shortening, dressings for salad, mayonnaise, grain products (bread, croissants, muffins, and breakfast cereal), dairy products (yogurt, reduced-fat cheese, butter, and dairy-based beverage), beverages (orange juice, fat-free lemon-flavored drink, and unspecified fat-free drink), meat (ground beef and cold cuts), and chocolate. The more recent intervention studies showed that daily dietary phytosterol (nonesterified and esterified) intake of approximately 1 to 3 g per day from a variety of types of food enriched with phytosterols, including fat-free foods, resulted in significant cholesterol-lowering comparable to that resulting from consuming phytosterol-enriched spreads and margarines (*see* table 1 at the end of this document). The data from available intervention studies show the average percent reduction of blood LDL cholesterol resulting from a daily phytosterol of intake between 1 and 3 g per day is independent of the types of foods enriched with phytosterols. FDA therefore concurs with the comment that, with respect to conventional foods, there is no scientific evidence to suggest the food matrix into which the phytosterols are added is an important factor affecting the cholesterol-lowering efficacy of phytosterols.

Therefore, the agency is proposing to amend § 101.83(c)(2)(iii)(A) by eliminating the enumeration of specific conventional foods that may bear a health claim and thereby broadening the conventional foods eligible to bear the claim to those meeting the other requirements of paragraph (c)(2)(iii).

b. *Dietary supplements.* While there is an abundance of evidence from intervention studies to demonstrate the cholesterol-lowering efficacy of phytosterol-enriched conventional foods, relatively few trials have been conducted with dietary supplements containing phytosterols. There is scientific evidence from four intervention studies to demonstrate the cholesterol-lowering efficacy of dietary supplements containing phytosterol esters (Refs. 61, 62, 63, and 64). In the intervention study conducted by Rader and Nguyen (Ref. 61) (*see* table 2 at the end of this document), participants were moderately hypercholesterolemic, but otherwise healthy adults. They consumed three phytosterol ester or placebo softgel capsules daily for 3 weeks. The phytosterol ester-containing softgel capsules provided 1 g of phytosterols per day. A significantly greater reduction in blood total and LDL cholesterol was reported in the phytosterol ester group than in the placebo group.

The cholesterol-lowering efficacy of dietary supplements containing phytosterols esters has also been confirmed in three additional intervention studies (Ref. 62, 63, and 64). Woodgate *et al.* (Ref. 64) provided six softgel supplements that provided phytosterol esters equating to 1.6 g of nonesterified phytosterols for 4 weeks. There was a significantly greater reduction in total cholesterol levels in the group that received the phytosterol-ester supplement compared to the placebo group. Participants in the trial by Acuff *et al.* (Ref. 62) were hypercholesterolemic, but otherwise healthy adults. They consumed two phytosterol ester or placebo capsules daily for 4 weeks. The sterol ester-containing capsules provided 0.8 g per day phytosterols. A significant blood LDL cholesterol reduction in the sterol ester group relative to the placebo group was reported. Earnest *et al.* (Ref. 63) provided four sterol ester-containing capsules or a placebo for 12 weeks. The sterol ester-containing capsule provided 2.6 g per day of phytosterols. There was a significantly greater reduction in blood total and LDL cholesterol in the group that received the sterol ester-containing capsules compared to the placebo group. Statistical differences in the change in blood LDL cholesterol between the sterol ester and placebo group was not determined. In conclusion, esterified phytosterols were effective in reducing total and/or LDL cholesterol levels in the blood in all three studies.

There have been three intervention studies published on the efficacy of nonesterified phytosterols in reducing blood cholesterol levels (Refs. 65, 66, and 67) (*see* table 2 at the end of this document). Nonesterified phytosterols consumed as ingredients in a gelatin capsule supplement were reported to have no effect on blood cholesterol (Ref. 65). The intervention study supplemented moderately hypercholesterolemic men, consuming a Step I diet, with 3 g of nonesterified phytosterols per day. The phytosterols were suspended in safflower oil (20 percent sitostanol by weight in safflower oil) contained within gelatin capsules and consumed with meals. No changes in either blood total or LDL cholesterol were observed between Step I diet alone and a Step I + sitostanol supplements. The concentration of 20 percent sitostanol in the gelatin capsule is much greater than the solubility of sitostanol of 1 percent (Ref. 68). Thus, it has been speculated that much of the sitostanol was undissolved (Ref. 57), and therefore not adequately dispersed in the intestinal contents.

Although a nonesterified phytosterol/soy lecithin emulsion formulation has been shown to be effective in lowering cholesterol under certain circumstances (Refs. 66 and 67), the results have been inconsistent and highlight how difficult it is to predict the effectiveness of nonesterified phytosterols in lowering cholesterol when consumed as ingredients in dietary supplements. McPherson *et al.* (Ref. 66) reported that consumption of 1.26 g stanols per day as the spray-dried phytostanol/lecithin emulsion tablet formulation resulted in a significant lowering of LDL cholesterol in humans; whereas, consumption of 1 g per day as the spray-dried phytostanol/lecithin emulsion capsule formulation had no significant effect on blood cholesterol. This study identified several physical differences between the capsule and tablet preparations, but does not provide data sufficient to identify the physical characteristics responsible for the differences between capsule and tablet preparations in their abilities to affect cholesterol absorption. However, the effectiveness of nonesterified phytosterol/soy lecithin vesicle tablets (1.8 g per day) on blood cholesterol reduction was confirmed in a subsequent intervention study done with subjects taking statin drugs for hypercholesterolemia (Ref. 67). The available scientific evidence for the cholesterol-lowering effects of phytosterols in dietary supplements shows that formulation of the supplement product is an important factor in the effectiveness of the product in lowering cholesterol and that esterifying the phytosterol is one way to ensure effectiveness. One explanation for the inconsistent results obtained from dietary supplements containing nonesterified phytosterols may be the importance of phytosterol dispersal and solubility in the gastrointestinal tract. The effectiveness of phytosterols to interfere with cholesterol absorption depends on their ability to be soluble, adequately dispersed within the intestinal contents, and incorporated into the mixed micelles (Refs. 57 and 61).

Because nonesterified phytosterols have poor solubility, manufacturers must use a technique such as esterification to facilitate absorption and dispersal of the phytosterols in the conventional food itself. For example, as noted in section V.A.1 of this document, the solubility of phytosterols in rape seed oil mayonnaise increased about ten-fold when esterified with fatty acids (Ref. 28). No such techniques are necessarily required, as a practical

matter, for adding phytosterols to dietary supplements, which commonly come in tablets or capsules. Esterification, however, still serves to make the phytosterols more soluble and thus suitable for dispersal in the gastrointestinal tract and incorporation into the mixed micelles.

The available scientific evidence shows that esterified phytosterols are effective in lowering cholesterol and thus reducing the risk of CHD. At this time, however, FDA finds that the totality of available scientific evidence for the cholesterol-lowering effects of nonesterified phytosterols in dietary supplements is inconsistent and tentatively concludes that the scientific evidence for a relationship between dietary supplements containing nonesterified phytosterols and CHD does not meet the significant scientific agreement standard. FDA is therefore proposing to amend § 101.83(c)(2)(iii)(B) to make the use of the health claim available to phytosterol ester-containing dietary supplements that meet all the specific requirements of the claim stated in § 101.83 and the general health claim requirements of § 101.14. However, FDA is not proposing to include nonesterified phytosterol-containing dietary supplements as foods eligible for the claim.

FDA invites submission of additional data that demonstrate the cholesterol-lowering efficacy of nonesterified phytosterols consumed as ingredients in dietary supplements. At this time, there are no USP standards for disintegration and dissolution for dietary supplements containing phytosterols. Therefore, FDA is also requesting data to provide a justification for inclusion or exclusion of specific dietary supplement formulations using USP standards. FDA will reevaluate its tentative conclusion regarding the eligibility of dietary supplements containing both esterified and nonesterified phytosterols in light of any additional data received.

3. Other Requirements

a. *Disqualifying total fat level.* Under the general requirements for health claims, foods are ineligible for health claims if they contain more than 13 g of total fat: (1) Per RACC; (2) per labeled serving size; and (3) when the RACC is small (30 g or less or 2 tablespoons or less), per 50 g of food (§ 101.14(a)(4) and 101.14(e)(3)). FDA may waive this disqualifying level for an individual nutrient in a health claim based on a finding that the claim will assist consumers in maintaining healthy dietary practices despite the content of that nutrient in the food (§ 101.14(e)(3)). FDA had concluded in the IFR that permitting the use of the phytosterol health claim on labels of spreads and dressings for salad would assist consumers to develop a dietary approach that would result in significantly lower cholesterol levels and an accompanying reduction in the risk of heart disease. Consequently current § 101.83(c)(1) and (c)(2)(iii)(C) permit the disqualifying level for total fat level on a "per 50 g" basis for foods with a small RACC (*i.e.,* more than 13 g of fat per 50 g) to be waived for spreads and dressings for salad, which ordinarily have a high fat content, provided the label bears a disclosure statement that complies with § 101.13(h) (*i.e.,* "*See* nutrition information for fat content") (65 FR 54686 at 54706). Current § 101.83 does not exempt spreads and dressings for salads from the total fat disqualifying level per RACC, and per label serving size.

The agency requested comments to the IFR on its decision to exempt phytosterol-enriched spreads and dressings for salad from the disqualifying level for total fat per 50 g (65 FR 54686 at 54710). The agency also suggested that, despite its reluctance to grant broad exceptions to the disqualifying levels, it was willing to consider additional exemptions on a limited case-by-case basis and said that manufacturers of products other than spreads and dressings for salad may submit comments with supporting information or petition the agency for an exemption from the total fat disqualification levels in § 101.14(e)(3).

FDA received a variety of comments in response to this aspect of the IFR. Some comments agreed with FDA's exemption for spreads and dressings for salad from the disqualifying level for total fat per 50 g, while other comments asserted that this exemption was not justified and argued that foods with a high fat content should not be eligible for a health claim. Some comments suggested that the exemption should be extended to other foods, such as vegetable oils, which have a similar nutrient composition to the foods currently exempted by § 101.83(c)(2)(iii)(C), or extended to include all foods with a small serving size. Some comments asserted that there should be an expedited approach to permit additional exemptions to the fat-disqualifying level.

The agency believes that the limited exemption from the disqualifying level of total fat on a per 50 g basis for foods with a small reference amount continues to be appropriate for dressings for salads and for spreads that resemble margarine. One of the factors in FDA's decision to provide a limited exemption to the total fat disqualifying level under § 101.14(a)(4) was that, without this exemption for spreads and dressings for salad, the number of foods eligible for this health claim would be limited to such an extent that the public health value of the claim would be undermined (65 FR 54686 at 54710). FDA is now proposing to remove the current restrictions on food categories eligible to bear the phytosterol/CHD health claim. Consequently the variety of phytosterol-enriched foods not high in total fat and eligible to bear the health claim available to consumers would significantly increase. Therefore, the agency does not find it necessary to expand the limited total fat "per 50 g" disqualifying level exemption to other foods with small servings out of concern that the number of foods eligible for the claim is limited. The type of food identified as "spreads" in current § 101.83 was intended by the agency to be specifically vegetable oil spreads resembling margarine formulated with a reduced total fat content relative to the minimum 80 percent fat content required under the standard of identity for margarine (§ 166.110). FDA realizes that without additional specification, the term "spread" could be interpreted to include other types of foods as well, such as mayonnaise and peanut butter-type spreads. Because FDA has tentatively concluded that it is not necessary to extend the limited exemption from disqualifying total fat level per 50 g beyond the limited food categories initially included, the agency is proposing to clarify in amended § 101.83(c)(2)(iii)(D) that the spreads that are exempt from § 101.14(a)(4) are vegetable oil spreads that resemble margarine.

Some comments recommended an exemption from the total fat disqualifying level be made to provide for the use of the health claim by liquid vegetable oils. These comments argued that liquid vegetable oils have fat composition as do the vegetable oil spreads and dressings for salads that can use the health claim. FDA recognizes that providing for disclosure of the total fat level rather than disqualification reflects an evolution in expert opinion on total fat intake and risk of CHD. The "Dietary Guidelines for Americans, 2005" (Ref. 69) recommends that Americans limit fat intake to between 20 to 35 percent of calories, with most fats coming from sources of polyunsaturated and monounsaturated fatty acids such as fish, nuts and vegetable oils, and limit intake of fats and oils high in saturated and/or trans fatty acids. Substituting liquid vegetable oils,

containing predominantly unsaturated fatty acids, for solid fats high in saturated fat and cholesterol is one dietary modification that can contribute to reducing dietary saturated fat and cholesterol.

Several current qualified health claims (*see* FDA's 2003 Consumer Health Information for Better Nutrition Initiative (Ref. 70)) are about a relationship of the unsaturated fatty acids of certain vegetable oils (olive oil, canola oil, and corn oil) used to replace similar amounts of saturated fat without increasing calories consumed, and CHD risk (Refs. 71, 72, and 73). When deliberating the merits of these vegetable oil unsaturated fatty acid qualified health claims, FDA concluded that there was credible but limited scientific evidence that label statements informing consumers that they might lower their risk of CHD by consuming foods high in unsaturated fatty acids, such as vegetable oils, in place of similar foods high in saturated fatty acids, without increasing calorie consumption, is information that can help consumers develop a dietary approach to lower CHD risk. FDA also concluded that such information is consistent with current dietary guidelines, which emphasize that consuming diets low in saturated fat and cholesterol is more important in reducing CHD risk than is consuming diets low in total fat. FDA therefore decided that the disqualifying total fat level for health claims would not be a criterion in permitting the qualified health claims for unsaturated fats of vegetable oils. Consistent with the position taken in permitting the unsaturated fatty acids in vegetable oils and CHD qualified health claims, FDA finds that rather than disqualifying phytosterol-enriched liquid vegetable oils on the basis of total fat content, disclosure of the total fat content along with the phytosterol health claim, will help consumers develop a dietary approach to lowering blood cholesterol levels.

Liquid vegetable oils are composed entirely of fat, and the amount of fat in a RACC (1 tablespoon, about 13.6 g) exceeds the disqualifying total fat level of 13 g. The limited exemption from the disqualifying total fat level on a per 50 g basis provided for spreads and dressings for salads, if extended to liquid vegetable oils, would still not make liquid vegetable oils eligible for a health claim. Therefore, FDA is proposing to exempt liquid vegetable oils from the total fat disqualifying level on a per RACC, per label serving size, and per 50 g basis.

The agency is proposing to amend § 101.83(c)(2)(iii)(D) to specify that the limited exemption from the disqualifying total fat level "per 50 g basis" for "spreads" applies specifically to vegetable oil spreads resembling margarine and not to other spreadable food products such as peanut butter and mayonnaise. In addition to the current exemption per 50 g for dressings for salad, the agency is also proposing to exempt liquid vegetable oils from the requirement per RACC, per labeled serving, and per 50 g.

b. *Low saturated fat and low cholesterol criteria.* Current § 101.83(c)(2)(iii)(B) requires foods that bear the health claim to meet the nutrient content requirements in § 101.62 for a "low saturated fat" and "low cholesterol" food.

One comment to the IFR objected to the "low saturated fat" requirement for the phytosterol CHD health claim on the basis that it would severely limit the availability of sterol/stanol containing foods. The comment recommended that the requirement for "low" amounts of saturated fat are not appropriate for foods that contain equal amounts of saturated fat, monounsaturated fat, and polyunsaturated fat.

There is strong and consistent scientific evidence that diets high in saturated fat and cholesterol are associated with elevated total and LDL cholesterol, and that elevated blood cholesterol levels are a major modifiable risk factor for CHD. The "Dietary Guidelines for Americans, 2005" recommends lowering dietary saturated fat and cholesterol as a primary lifestyle change for reducing heart disease risk (Ref. 69).

The variety of phytosterol-enriched foods tested in intervention studies since publication of the IFR indicates a range of food products, many of which are low fat or fat-free, that manufacturers contemplate marketing. There also are a number of foods in the food categories now eligible for the health claim under current § 101.83 that can qualify as "low saturated fat" and "low cholesterol." As a result, FDA does not agree that requiring foods bearing the claim be "low saturated fat" and "low cholesterol" would significantly limit the number of food products eligible to use the claim. Consequently, the agency is not proposing to amend the requirement that foods eligible for the claim be "low in saturated fat" and "low in cholesterol."

*c. Trans fat considerations.* FDA is concerned about the presence of *trans* fats in foods bearing the phytosterols and risk of coronary heart disease claim. There is a positive linear trend between *trans* fatty acid intake and LDL cholesterol concentration, and therefore there is a positive relationship between *trans* fatty acid intake and the risk of CHD (Ref. 74). In the Institute of Medicine (IOM) report, *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids,* in the discussion on dietary fats, total fat and fatty acids, the IOM states that *trans* fatty acids are not essential and provide no known benefit to human health (Ref. 74). The IOM sets tolerable upper intake levels (UL) for the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. In their 2005 report, the IOM does not set a UL for *trans* fatty acid because any incremental increase in *trans* fatty acid intake increases the risk of CHD (Ref. 74).

*Trans* fats are naturally occurring in some foods made from ruminant animals (*e.g.,* cattle and sheep) such as dairy products and meats (Ref. 69). *Trans* fatty acids are created when unsaturated fatty acids are chemically changed through the process of hydrogenation [12] to create a more solid food product (Ref. 69). Sources of *trans* fatty acids include partially hydrogenated and hydrogenated vegetable oils used in making shortening, margarine, baked goods such as biscuits and pie crusts, snack foods, fried foods, and margarine (Ref. 69). Since *trans* fats are naturally occurring in some foods that contribute essential nutrients such as protein, calcium and vitamin D, consuming zero percent of energy as *trans* fats would require substantial adjustments to the diet that may have undesirable effects (Ref. 74). To date, there have been no reports issued by authoritative sources that provide a level of *trans* fat in the diet above which there is a known increased risk of CHD and below which there is no risk of CHD. Recommendations are for Americans to limit *trans* fat as much as possible while consuming a nutritionally adequate diet (Refs. 3 and 74).

The agency is taking several approaches to address *trans* fats. On July 11, 2003 (68 FR 41507), FDA published an advance notice of proposed rulemaking (ANPRM), in part, to solicit information and data that

[12] Hydrogenation is the addition of a carbon-carbon double bond to a chain of unsaturated fatty acids. This produces a single carbon-carbon bond with two hydrogens attached to each carbon. This process converts liquid oils into more solid fats, which are used in making products such as margarine and shortening. *Trans* fats are a by-product of hydrogenation of vegetable oils (Ref. 75).

could potentially be used to establish new nutrient content claims about *trans* fatty acids; to establish qualifying criteria for *trans* fat in current nutrient content claims for saturated fatty acids and cholesterol, lean and extra lean claims, and health claims that contain a message about cholesterol-raising lipids; and, in addition, to establish disclosure and disqualifying criteria to help consumers make heart-healthy food choices. On March 1, 2004 (69 FR 9559), FDA reopened the comment period to allow interested persons to consider the report issued by the Institute of Medicine of the National Academy of Science in December 2003 entitled "Dietary Reference Intakes: Guiding Principles for Nutrition Labeling and Fortification." FDA extended the comment period on April 19, 2004 (69 FR 20838) to receive comment on a Food Advisory Committee Nutrition Subcommittee meeting discussing the scientific evidence for determining a maximal daily intake value of *trans* fat and how *trans* fat compares to saturated fat with respect to reducing coronary heart disease. Specifically, the agency requested comment on whether the available scientific evidence supported listing the percent Daily Value (DV) for saturated fat and *trans* fat together or separately on the Nutrition Facts label and what the maximal daily intake of *trans* fat may be. In addition, the agency published an ANPRM on November 2, 2007 (72 FR 62149) to request, in part, comment on what new reference values the agency should use to calculate the DV for a number of nutrients and what factors the agency should consider in establishing such values. FDA asked specific questions in the November 2, 2007 ANPRM about *trans* fat labeling. Comments are being reviewed by the agency from these ANPRMs for consideration in defining nutrient content claims for *trans* fat and in deciding what levels of trans fat may be appropriate in foods bearing health claims about a reduced risk of coronary heart disease.

FDA received a citizen petition from the Center for Science in the Public Interest (CSPI) in 2004 and one from Dr. Fred Kummerow in 2009 asking the agency to revoke the GRAS status of partially hydrogenated oils. The agency is in the process of reevaluating the GRAS status of partially hydrogenated oils in response to the two citizen petitions. Finally, the agency is evaluating current analytical methods for the detection of *trans* fat in foods and is working on improving the sensitivity of these methods so that *trans* fat may be reliably detected at lower levels in foods.

The agency is concerned that products containing phytosterols and bearing the health claim may also contain significant amounts of *trans* fat that could undermine the beneficial effects from consumption of the phytosterols in the product. The agency is not aware of any studies that were designed to determine the amount of *trans* fat that could offset the beneficial effects of phytosterols. Based on the available data, 0.8g/day of *trans* fat was the highest intake level from margarine at which there was a significant reduction in total and LDL cholesterol levels when the consumption of phytosterols was approximately 2 g/day (Ref. 41). The agency requests comment on whether these data, alone or in combination with other data or information, would support a limitation on the level of *trans* fat in foods, as an eligibility criterion, for foods that could bear the phytosterol and risk of coronary heart disease claim. Foods that contain more than this level of *trans* fat would be disqualified from bearing a claim. In addition, the agency requests comment on whether there are data that may support another level of *trans* fat that the agency should consider as an eligibility criterion for foods bearing such a claim. The agency also requests comment on available information that provides clarification on the effect of *trans* fat in products that also contain phytosterols.

d. *Minimum nutrient contribution requirement.* Current § 101.83(c)(2)(iii)(D) requires that a conventional food bearing a health claim for phytosterol esters meet the minimum nutrient contribution requirement specified in § 101.14(e)(6), unless it is a dressing for salad. Section 101.14(e)(6) requires that, except for dietary supplements or where provided in other health claim regulations, foods eligible to bear a health claim contain 10 percent or more of the Reference Daily Intake or Daily Reference Value for vitamin A, vitamin C, iron, calcium, protein, or fiber per reference amount prior to any nutrient addition. The minimum nutrient contribution requirement is necessary to ensure that the value of a health claim will not be trivialized or compromised by its use on a food of little or no nutritional value. In the IFR, the agency concluded that, while important, the minimum nutrient requirement for dressings for salad is outweighed by the public health importance of communicating the cholesterol-lowering benefits from consumption of plant sterol/stanol esters (65 FR 54686 at 54711). FDA found that the value of the health claim would not be trivialized or compromised by its use on dressings for salad because dressings for salad are typically consumed with foods rich in fiber and other nutrients. However, the agency decided that there was not a sufficient rationale to justify an exemption from this requirement for the remaining phytosterol-enriched foods that would have otherwise been eligible to bear the health claim. *Id.*

The agency requested comments in the IFR on its decision to exempt only dressings for salad from the minimum nutrient requirement. FDA further stated that manufacturers of foods that do not meet the minimum nutrient requirement may submit comments with supporting information by a petition to the agency requesting an exemption from this requirement. *Id.*

Comments were mixed as to whether the minimum nutrient contribution requirement should be applied to other foods eligible for the health claim. Some agreed with FDA's exemption from the minimum nutrient contribution requirement for dressings for salad, while other comments suggested that no foods should be exempt. Other comments suggested additional specific foods such as fruit drinks, smoothies, liquid vegetable oils, vegetable oil spreads or snack bars or groups of foods such as small servings to which the minimum nutrient requirement exemption might be extended either through fortification or waiving of the requirement.

The purpose of the minimum nutrient contribution requirement is to ensure that health claims are used to promote only those foods that are consistent with dietary guidelines and to ensure that health claims are not to be trivialized or compromised by their use on foods of little or no nutritional value (*e.g.,* jelly beans) (58 FR 2478 at 2481 and 2521). FDA exempted dressings for salad from the minimum nutrient requirement in current § 101.83 in recognition that dressings for salad are typically consumed with other foods (specifically salads and vegetables) that are rich in a number of important nutrients and fiber. FDA is not persuaded by the rationales put forward for other foods, as a general matter. It does, however, concur that extending the exemption from this requirement for certain vegetable oil spreads and liquid vegetable oils is justified because they provide unsaturated fatty acids that can be used in place of saturated fatty acids in the diet.

A key recommendation of the "Dietary Guidelines for Americans, 2005" (Ref. 69) is that most fats in the diet should

come from sources of polyunsaturated and monounsaturated fatty acids such as fish, nuts, and vegetable oils. Using liquid vegetable oils in the diet as substitutes for solid and hardened fats is an approach to developing a heart-healthy diet that is consistent with the "Dietary Guidelines for Americans, 2005." Liquid vegetable oils, like dressings for salad, will likely be consumed in small portions with foods rich in fiber and other nutrients. Vegetable oils contain none of the six core nutrient components of the minimum nutrient content requirement for health claims and therefore are ineligible for health claims unless an exemption is provided in a specific health claim regulation. The agency has concluded that the public health benefit of providing for use of the health claim on labels of certain liquid vegetable oil outweighs the concerns that health claims are trivialized by their use with foods of little nutritional value, and therefore is proposing that liquid vegetable oils be exempt from the minimum nutrient requirement in amended § 101.83. As noted in section V.C.2.a of this document, FDA is proposing to also exempt liquid vegetable oils from the disqualifying level for total fat; however liquid vegetable oils will be subject to the requirement that foods bearing the phytosterol/CHD health claim be "low saturated fat" foods.

Margarine, a standardized food under § 166.110 including those that are nutritionally modified and labeled under 21 CFR 130.10 must contain not less than 10 percent of the recommended dietary allowance (RDA) for vitamin A per reference amount customarily consumed. Margarine substitutes may need to be fortified with Vitamin A to be nutritionally equivalent to margarine to avoid being categorized as "imitation" margarine (§§ 101.3(e)(2) and 104.20(e) (21 CFR 101.3(e)(2) and 104.20(e))). As FDA stated in the rulemaking for § 101.14, permitting foods to be fortified with nutrients for the sole purpose of making a health claim that complies with the minimum nutrient requirement would be misleading and inconsistent with FDA's fortification policy in § 104.20 (58 FR 2478 at 2521). FDA also stressed, however, that "the exclusion of fortification pertains only to fortification to specifically meet the requirements of this provision and not to the fortification of the food itself" (*id.*). Vegetable oil spreads that resemble and substitute for margarine may be required to be fortified with Vitamin A to avoid being categorized as an "imitation" (as explained in this paragraph) and those not required to be so fortified may be optionally fortified under § 104.20. Such spreads usually serve as substitutes for products higher in saturated fats and cholesterol. Thus, the agency believes that permitting vegetable oil spreads resembling margarine to meet the minimum nutrient contribution requirement through the addition of Vitamin A is consistent with FDA's fortification policy and appropriate as an exemption to the requirement in § 101.14(e)(6) that the food contain 10 percent or more of a nutrient prior to any nutrient addition.

The agency is not convinced that additional modifications to current § 101.83(c)(1) and (c)(2)(iii)(D) to provide exemptions from the minimum nutrition contribution requirement for additional foods are warranted. Because the agency is proposing to drop the limitation on eligible food categories and extend the claim to include nonesterified phytosterols and mixture of plant sterols and stanols, there would be a greater variety of lower fat, heart healthy phytosterol-enriched foods that would be able to bear the health claim without extending the minimum nutrient contribution requirement. Further, the agency believes that dropping the requirement in § 101.14(e)(6) altogether could lead to indiscriminate use of health claims on foods with little or no nutritional value such as snack and confectionary items. Therefore, the agency is not proposing to provide further exemptions to the minimum nutrient contribution requirement.

While FDA will consider any further requests for exemptions that it receives via the petition process as expeditiously as possible, it still expects that any such request will be accompanied with adequate justification for the exemption. The agency does not plan to set up an expedited notification process for such a review.

In short, the agency is proposing to amend § 101.83(c)(2)(iii)(E) to permit liquid vegetable oils to be exempt from the minimum nutrient requirement. FDA is also proposing to amend this provision to permit the minimum nutrient contribution requirement for vegetable oil spreads resembling margarine to be met by the addition of vitamin A consistent with FDA's fortification policy.

*D. Model Claims*

Current § 101.83(c)(2)(i) prescribes specific requirements for health claims that link plant sterol/stanol esters to reduced risk of CHD. Current § 101.83(e) provides examples of model health claims that may be used to comply with the requirements in § 101.83(c)(2)(i). As discussed in previous sections of this document, we are proposing modifications to § 101.83 that would entail revision of specific requirements for health claims and the examples of model health claims. Consequently, the agency is proposing to revise § 101.83(c)(2)(i) and (e) accordingly.

*E. Cautionary Statements*

Current § 101.83 does not require cautionary or advisory statements regarding the potential effect of consuming phytosterols on the absorption of other nutrients or on certain subpopulation groups, and FDA did not address the use of such statements in the IFR. However, the agency subsequently became aware that regulatory bodies in other countries had concluded that requiring such statements on the labels of products containing phytosterols or limiting the use of phytosterols in food was necessary to guard against such effects. When the IFR comment period was reopened, FDA requested comments on "whether changes to [§ 101.83], advisory labeling, or other actions are needed" to address concerns regarding the effect of consuming plant/sterol esters on the absorption of beta-carotene and on certain subpopulation groups (66 FR 50824 at 50826).

Some comments focused on the safety of consuming plant/sterol esters for certain subpopulation groups, such as those taking drugs to lower cholesterol or those suffering from phytosterolemia, an autosomal recessive disorder characterized by increased intestinal absorption of dietary cholesterols and phytosterols. Those comments disagreed whether the labels of foods bearing the health claim should provide an advisory statement. Other comments asserted that consuming phytosterols inhibits intestinal absorption of fat soluble vitamins and carotenoids and that requiring an advisory statement on foods bearing the health claim is necessary to prevent adverse health consequences, especially in vulnerable subpopulation groups, such as children or pregnant or lactating women.

Section 201(n) of the act states that, in determining whether labeling is misleading, the agency shall take into account not only representations made about the product, but also the extent to which the labeling fails to reveal facts material in light of such representations made or suggested in the labeling with respect to consequences which may result from use of the article to which the labeling relates under the conditions of use as are customary or usual (*see* 21

CFR 1.21). Thus, the omission of certain material facts from the label or labeling on a food causes the product to be misbranded within the meaning of sections 403(a)(1) and 201(n) of the act. Under that authority, FDA has considered the use of cautionary statements to address each of the public health issues identified by other regulatory bodies and the similar concerns raised in comments.

With respect to the comments about the effects of consuming phytosterols on individuals suffering from rare conditions that make them hypersensitive to phytosterols, FDA tentatively concludes that no cautionary statement regarding those effects in the labeling of foods bearing the health claim or any other action is necessary. For the consumers at whom such a cautionary statement would be directed, *i.e.,* those aware that they have a phytosterol-sensitive condition, the health claim itself and the required ingredient declaration (*see* 21 CFR 101.4(a)) should provide sufficient warning that the product contains phytosterols. Such consumers could consult with their medical practitioner regarding the possible consequences of consuming phytosterols.

As for a cautionary statement regarding potential adverse interactions with cholesterol-lowering drugs, FDA tentatively concludes that § 101.83 should not require such a statement in the labeling of food bearing the health claim. FDA is unaware of any scientific evidence demonstrating that consuming phytosterols while on cholesterol-lowering drugs results in any adverse health consequences. The agency thus sees no justification for requiring a statement specific to consumers taking cholesterol-lowering drugs. We invite the submission of any data or other evidence demonstrating adverse health consequences under such circumstances.

With respect to the comments about the potential effect of phytosterols on the absorption of certain nutrients in the population as a whole or in certain subpopulation groups, FDA tentatively concludes that the available scientific evidence does not support a need for a cautionary statement regarding that potential effect. As noted in this section of the document, the potential effect of phytosterol-enriched foods on lowering plasma fat soluble vitamins and carotenoids has been a concern to regulatory bodies in some other countries. The European Commission (EC) Scientific Committee on Food (SCF) recommended that the beta-carotene lowering effect of phytosterol-enriched foods be communicated to the consumer, together with appropriate dietary advice regarding the regular consumption of fruits and vegetables (Refs. 76 and 77). As a result, EC regulations for the labeling of foods with added phytosterols require a label statement stating that: (1) Phytosterol-enriched foods may not be nutritionally appropriate for pregnant or breastfeeding women and children under the age of 5 years; and (2) phytosterol-enriched foods should be used as part of a balanced and varied diet, including regular consumption of fruit and vegetables to help maintain carotenoid levels (Refs. 78 and 79). Similarly, Food Standards Australia New Zealand (FSANZ) requires that phytosterol-enriched foods have a label statement advising that the product should be consumed in moderation as part of a diet low in saturated fat and high in fruits and vegetables, and that the product is not recommended for infants, children, or pregnant or lactating women unless under medical supervision (Ref. 80).

FDA reviewed 19 intervention studies that evaluated the effect of phytosterol intake on the intestinal absorption of fat soluble vitamin and carotenoid, by measuring plasma levels (Refs. 24, 26, 35, 37, 39, 41, 51, 55, 59, 81, 82, 83, 84, 85, 86, 87, 88, 89, and 90). Collectively, these studies provided phystosterols ranging from 0.8 to 9 g per day. After adjusting for plasma total or LDL cholesterol levels, only one study showed that vitamin E levels were significantly reduced with phytosterol intake (3 g per day) (Ref. 88). Vitamin E levels were not altered at higher phytosterol intake levels (3.2 to 9 g per day) (Refs. 51, 55, 88, and 89). There was no effect of phytosterol intake on adjusted levels of other fat soluble vitamins (*i.e.,* vitamin A, vitamin D, vitamin K).

While phytosterol intake was shown in some studies to reduce adjusted levels of beta-carotene (the major pro-vitamin A carotenoid) to a statistically significant degree at phytosterol intake levels ranging from 3 to 9 g per day (Refs. 51, 55, 87, 88, 89, and 90) there was no effect on serum retinol levels (a biomarker of vitamin A status). Some studies also showed a reduction in carotenoids such as lutein and lycopene, but these food components likewise do not have an established health benefit at a particular level. Thus, FDA has no basis for concluding that any reduction in the intestinal absorption of these nutrients caused by consuming phytosterols amounts to an adverse health consequence.

FDA has determined that available scientific evidence does not demonstrate that consuming phytosterols has an effect on intestinal absorption of fat soluble vitamins. Furthermore, although there is some evidence that consuming phytosterols reduces plasma levels of carotenoids such as beta-carotene, lutein, and lycopene, those carotenoids have no established health benefits at particular levels. Therefore, the agency is not proposing that § 101.83 require a cautionary statement regarding a potential effect on fat soluble vitamins or carotenoids.

In conclusion, the agency finds that the failure of a food bearing the health claim to include any of the foregoing cautionary statements would not render the food's labeling misleading under section 403(a)(1) of the act. We are therefore not proposing that § 101.83 require any of the foregoing cautionary statements. Furthermore, the available science does not persuade FDA that the use of phytosterols at the levels necessary to justify the claim render the food unsafe or unlawful under the relevant safety provisions of the act, even in the absence of such cautionary statements. But FDA again notes that authorization of a health claim for a substance should not be interpreted as an affirmation that the substance is safe and lawful for all uses.

### *F. Status Under Section 301(ll) of Foods Containing Nonesterified and Esterified Phytosterols*

Section 301(ll) of the act (21 U.S.C. 331(ll)) prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the act (21 U.S.C. 355), a biological product licensed under section 351 of the Public Health Service Act (42 U.S.C. 262), or a drug or a biological product for which substantial clinical investigations have been instituted and their existence made public, unless one of the exemptions in section 301(ll)(1)–(4) applies. In this proposal to amend the regulation authorizing a health claim on the relationship between plant sterol esters and plant stanol esters and reduced risk of CHD for use on food labels and in food labeling, FDA did not consider whether section 301(ll) of the act or any of its exemptions would apply to foods containing nonesterified or esterified phytosterols. Accordingly, this proposed rule should not be construed to be a statement that foods that contain nonesterified or esterified phytosterols, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll) of the act. Furthermore, this language is included in all health claim proposed

and final rules and should not be construed to be a statement of the likelihood that section 301(ll) of the act applies.

## VI. Enforcement Discretion

Pending issuance of a final rule, FDA intends to consider the exercise of its enforcement discretion on a case-by-case basis when a health claim regarding phytosterols is made in a manner that is consistent with the proposed rule. Beginning 75 days from the date the proposed rule publishes, FDA does not intend to exercise its enforcement discretion based on the letter issued in 2003 (Ref. 1). The act's enforcement provisions commit complete discretion to the Secretary of Health and Human Services (and by delegation to FDA) to decide how and when they should be exercised (*see Heckler* v. *Chaney,* 470 U.S. 821 at 835 (1985); *see also Shering Corp.* v. *Heckler,* 779 F.2d 683 at 685–86 (DC Cir. 1985) (stating that the provisions of the act "authorize, but do not compel the FDA to undertake enforcement activity")). Until the agency issues a final rule amending the requirements of § 101.83, the agency believes that its exercise of enforcement with respect to claims that do not comply with current § 101.83 but do comply with the proposed rule is appropriate. Food bearing the health claim would be required to comply with any revised requirements established in the final rule when the final rule becomes effective.

## VII. Environmental Impact

FDA has determined under 21 CFR 25.32(p) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

## VIII. Analysis of Economic Impacts

*Preliminary Regulatory Impact Analysis*

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is not a significant regulatory action as defined by the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the costs to all businesses would be low and will not likely have a significant economic impact on a substantial number of small businesses, the agency believes that the proposed rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and Tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $135 million, using the most current (2009) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount and has determined that this proposed rule does not constitute a significant rule under the Unfunded Mandates Reform Act.

*A. Need for the Rule*

The scientific evidence relating to phytosterols and the risk of CHD has developed to warrant proposing to amend the existing health claim for plant sterol/stanol esters and CHD. If finalized, this rule would allow manufacturers of products that meet certain conditions to provide the most scientifically reliable, up-to-date information on the relationship between diets that include phytosterols and the risk of CHD. In addition, this rule would allow an increased number of foods to be eligible to make this health claim, by including foods other than the limited number in the current regulation, and increasing the variety of composition of the phytosterol ingredients included under the regulation, *i.e.,* inclusion of plant sterol and plant stanol mixtures, inclusion of forms of phytosterols in conventional foods other than those esterified with fatty acids, and inclusion of additional forms of dietary supplements. The greater availability of foods containing the required minimum amounts of phytosterols and with up-to-date information on their labels would provide additional health benefits for consumers that are consistent with the current state of scientific evidence. FDA announced, in February 2003, its decision to consider exercise of enforcement discretion, within certain parameters, in regards to the use of the phytosterol/CHD health claim in order to provide greater flexibility in the application of the claim than that allowed under the IFR. The proposed rule would reduce any uncertainty that may arise on the part of manufacturers from the real and perceived lack of permanency inherent in the policy of enforcement discretion.

*B. An Overview of the Changes in Behavior From the Regulatory Options*

FDA's benefit-cost analysis assumes the existing regulatory requirements of § 101.83, rather than upon the 2003 enforcement discretion criteria, as the baseline upon which to measure the impact of this proposed rule. The regulatory options considered are as follows:

- Option 1—Take no new regulatory action,
- Option 2—Implement the proposed rule,
- Option 3—Restrict coverage of the proposed option to only conventional foods and not allow dietary supplements to make a phytosterols/CHD health claim, and
- Option 4—Restrict the proposed option to require manufacturers of any product claiming reduced risk of CHD from phytosterols consumption, for which the analytical method for determining the quantity of phytosterols is different than either the McNeil or Unilever methods, to provide FDA with access to documentation substantiating the amount of phytosterols contained in the food product.

There would be no changes from current behavior by consumers and manufacturers for option 1. No products would need to be re-labeled or reformulated, and consumer information on the relationship between diets containing phytosterols and the risk of CHD currently found on food labels would remain unchanged.

For option 2, the proposed rule, manufacturers of vegetable spreads, salad dressings, snack bars, and dietary supplements in softgel form that currently use the plant sterol/stanol esters health claim would be required to re-label their products to conform to the claim language required under the proposed rule. Manufacturers of plant sterol ester-enriched products would also be required to reformulate these products if they contain no more than the minimum 0.65 g sterol ester/RACC (equivalent to 0.4 g nonesterified plant sterol) required under the IFR for plant

sterol esters, and if they want to continue to make the claim. The IFR requires a minimum of 1.7 g/RACC of plant stanol esters (equivalent to 1 g of nonesterified plant stanol), so manufacturers of plant stanol ester-enriched products, including dietary supplements in softgel form that currently make a phytosterols/CHD health claim, would not be required to reformulate to continue to make the claim. Consumers would benefit from more up-to-date information on food labels, the increase in the intake of phytosterols, and the wider range of foods and dietary supplements that would likely contain phytosterols, which may contribute to an increase in the intake of phytosterols and a reduction in the risk from CHD.

For ensuring compliance with the labeling requirements for vegetable spreads, salad dressings, snack bars, and dietary supplements in softgel form, the protocol for sampling and testing the products directly for phytosterols content would be changed to the Sorenson and Sullivan method from the McNeil or Unilever methods. The Sorenson and Sullivan method would also be used to ensure compliance with the labeling requirements for the variety of products newly allowed to claim a relationship between diets containing phytosterols and the reduction in risk from CHD.

Option 3 would restrict coverage of the proposed requirements to only conventional foods, so that manufacturers of some plant stanol ester-containing dietary supplements in softgel form that currently claim reduced risk of CHD from plant sterol/stanol esters consumption would no longer be allowed to make that claim. These manufacturers are assumed to re-label their products to either make no claim or to make a structure/function claim. Benefits from the consumption of dietary supplements in softgel form may be reduced.

For option 4, the behavioral changes by manufacturers and consumers are assumed to be the same as those from the proposed option. To ensure compliance with the labeling requirements for vegetable spreads, salad dressings, snack bars, and dietary supplements, sampling and testing the products directly for phytosterols content using either the McNeil or Unilever methods would be used. Ensuring compliance with the labeling requirements for the variety of food products and dietary supplements that would be newly allowed to claim benefits from the relationship between phytosterols consumption and the risk of CHD, for which the analytical method for making this determination is different than either the McNeil or Unilever methods would require FDA access to, and analyses of, documents that substantiate the amount of phytosterols contained in these products.

*C. Costs of Option 2 (the Proposed Rule)*

The costs of the proposed rule are from the re-labeling required of products that currently make the plant sterol/stanol esters-CHD health claim to conform to the claim language required under the proposed rule. Manufacturers of plant sterol ester-enriched products may also incur reformulation costs associated with the increase in the phytosterols content required to make the health claim under the proposed rule.

Vegetable spreads, salad dressings, snack bars, and dietary supplements that currently make a plant sterol/stanol esters and CHD health claim would have to be re-labeled because of this rule. All current manufacturers of these products would bear the costs of unused label inventory as well as the costs of designing and printing new labels to comply with the updated health claim requirements. Some manufacturers of plant sterol ester-enriched vegetable spreads and salad dressings will decide to reformulate their products in order to meet the higher minimum amounts of phytosterols per serving required for plant sterol esters to make a phytosterols-CHD health claim under the proposed rule. Moreover, some manufacturers of plant stanol ester-enriched snack bars may decide not to make a phytosterols-CHD health claim due to the required new language that specifies that the daily dietary intake of phytosterols should be consumed with meals; snack bars may be less likely than vegetable spreads or salad dressings to be consumed with meals.

FDA does not have any information on how many labels would have to be redesigned, or the number of products that would be reformulated because of the proposed rule. Many existing products would not need to reformulate because the qualifying amount of plant stanol content in the IFR—1.7 g plant stanol esters per RACC, or the equivalent of 1 g of nonesterified stanols—is higher than the qualifying amount of phytosterols (plant sterols/stanols) per RACC in this proposed rule (0.5 g per RACC). Some products that currently enrich with plant sterol esters in order to make the plant sterol/stanol esters and CHD health claim may need slight reformulation since the qualifying amount in the IFR—0.65 g plant sterol esters per RACC, or the equivalent of 0.4 g of nonesterified sterols—is slightly lower than the qualifying amount of phytosterols per RACC required in this proposed rule. However, there is evidence suggesting that some food products now enriching with plant sterol esters are formulated with more than 0.5 g phytosterol per RACC. For example, the phytosterol content of the sterol ester-enriched product Benecol spread (Ref. 111) exceeds the 0.5 g per RACC and would not need to reformulate.

The agency uses the FDA Labeling Cost Model to estimate the costs of redesigning the labels and the costs of lost label inventory for estimated small fractions of the vegetable spreads, salad dressings, snack bars and dietary supplements sectors (Ref. 112). In order to use the FDA Labeling Costs Model to estimate the re-labeling costs, FDA estimates the percentage of each of the sectors that would incur costs from the proposed rule. These percentages are then applied to the sector-wide results obtained by the Labeling Cost Model.

For estimating the percentage of the dietary supplements sector that currently make a plant sterol/stanol esters and CHD health claim, FDA uses information from the 1999 report by Research Triangle Institute for FDA entitled "Dietary Supplements Sales Information" (Ref. 113). Research for that report found that of the approximately 20 categories of claims made by dietary supplements, approximately 20 percent make a claim regarding circulatory system benefits. FDA assumes that 67 percent of the claims regarding circulatory system benefits are either structure/function claims or nutrient content claims, and 50 percent of the remaining 33 percent address the risk of CHD, then about 3.3 percent of all dietary supplements address the risk of CHD (*i.e.,* 20 percent × 33 percent × 50 percent).

FDA uses representative scanner data on sales and forms that dietary supplements take over the period 2001–2005, to estimate that 2 percent of all dietary supplement sales are in softgel form. Consistent with the estimated percent for dietary supplements overall, FDA assumes that 3.3 percent of all dietary supplements in softgel form may have a health claim that addresses the risk of CHD, and that no more than 10 percent of those with health claims that address the risk of CHD may make a phytosterols health claim. Consequently, FDA estimates that between 0 and 0.007 percent of dietary supplements sold may currently make a plant sterol/stanol esters and CHD health claim and would be re-labeled (2 percent of all dietary supplements × 3.3

percent that make a claim that addresses CHD × 0 to 10 percent that may make a phytosterols-CHD health claim).

To estimate the percent market shares of conventional food products to apply to the Labeling Cost Model, the agency uses results from FDA's 2001 Food Label and Package Survey (FLAPS), from which LeGault, *et al.* report that 4.4 percent of all food products sold make at least one of the FDA-approved health claims (Ref. 114). In order to estimate the market share of foods that may make a plant sterol/stanol esters and CHD health claim, FDA takes the estimated percentage of total sales of products that make any claim (4.4 percent) and multiply it by the percentage of health claims that were found to address the risk of CHD (41.7 percent). FDA assumes that 10 percent of all packaged food sales with claims that address the risk of CHD may make a phytosterols-CHD health claim. Consequently, FDA estimates that approximately 0.2 percent of all food sales in the vegetable spreads and salad dressings sectors may make a plant sterol/stanol esters and CHD health claim (*i.e.,* 4.4 percent × 41.7 percent × 10 percent, rounded to the nearest tenth of a percent).

To account for the smaller likelihood that manufacturers of snack bars that currently make a plant sterol/stanol esters and CHD health claim will continue to do so under the proposed rule, FDA divides the estimate for vegetable spreads by 2 to obtain the market share for the snack bar sector that would incur re-labeling costs.

While the names of most of the sectors used by both the Labeling Cost Model and Reformulation Cost Model correspond closely with those that are currently identified in the IFR, there is no snack bar sector identified in the models. Consequently, FDA uses the labeling costs for the "Salty Snacks—Other" category to approximate those for the snack bar category. FDA assumes that firms will have 1 year to come into compliance. The estimated low, medium, and high costs of re-labeling generated by the labeling cost model for these sectors made assuming a 12-month compliance period are provided in table 4 of this document. Because 12 months represents a compliance period likely to be shorter than the actual period, actual costs may be lower.

TABLE 4—RE-LABELING COSTS ASSUMING A 12-MONTH COMPLIANCE PERIOD

| Product group | Low | Medium | High |
|---|---|---|---|
| Salty Snacks—Other | $27,000 | $38,000 | $52,000 |
| Margarines | 3,000 | 4,000 | 8,000 |
| Fats and Oils | 25,000 | 35,000 | 57,000 |
| Salad Dressings and Toppings | 30,000 | 42,000 | 67,000 |
| Dietary Supplements—Liquid | 900 | 1,000 | 2,000 |
| Total | 86,000 | 121,000 | 186,000 |

FDA uses the Reformulation Cost Model to estimate the costs of reformulating products for estimated fractions of the vegetable spreads, salad dressings, snack bar, and dietary supplement sectors in which it is likely that firms currently make a plant sterol/stanol esters and CHD health claim (Ref. 115). FDA assumes that most conventional food products that currently make a plant sterol/stanol esters and CHD health claim currently meet the minimum per-serving requirements in the proposed rule. FDA assumes that some conventional food products that enrich with plant sterol esters will have to be reformulated in order to meet the minimum per-serving requirements. FDA assumes that 25 percent of conventional food products that currently make a plant sterol/stanol esters and CHD health claim will reformulate to keep the claim. FDA assumes that no dietary supplements in softgel form that currently make a plant sterol/stanol esters and CHD health claim would have to reformulate in order to meet the minimum per-serving requirements in the proposed rule.

FDA assumes that any reformulation costs incurred by manufacturers of these products will involve minor changes to recipes and ingredients. The estimated costs of reformulating generated by the reformulation cost model for sectors that correspond closely with those identified in the IFR used to compute labeling costs are made assuming a 12-month compliance period and are provided in Table 5 of this document. Discarded inventories are the primary cost of reformulation when the model is computed under these assumptions. FDA requests comments on the magnitude of the reformulation cost generated by the model, as well as the assumption that discarded inventories would be the primary source of reformulation costs.

To characterize uncertainty about the total reformulation costs, FDA assumes that the estimated total reformulation costs is distributed normally with a mean equal to the addition of all of the costs estimated for the individual sectors ($5,200), and a standard deviation equal to that for the data across sectors ($650). FDA requests comments on these estimates. The confidence interval that contains the true amount of total reformulation costs with 95 percent probability under the stated assumptions is reported in the bottom row of Table 5.

TABLE 5—REFORMULATION COSTS ASSUMING A 12-MONTH COMPLIANCE PERIOD

| Product group | Reformulation costs |
|---|---|
| Salty Snacks—Other | $500. |
| Vegetable oils | $1,500. |
| Margarines | $1,500. |
| Salad Dressings—Refrigerated. | $150. |
| Salad Dressings—Bottled, Unrefrigerated. | $1,500. |
| Total | Between $700 and $9,000. |

*D. Benefits of Option 2 (the Proposed Rule)*

1. The Importance of the Health Risk Addressed by the Claim

CHD is the leading cause of death and permanent disability in the United States (Ref. 116). The National Center for Health Statistics in the Centers for Disease Control and Prevention (CDC) reports that in 2002 there were approximately 23 million non-institutionalized adults diagnosed with CHD, resulting in approximately 700,000 deaths. According to the same source, CHD patients made approximately 20.8 million office-based

physician visits and approximately 1.1 million hospital outpatient visits in that year. In addition, there were approximately 4.4 million hospital discharges of CHD patients, with average lengths of stay of approximately 4.4 days. As an indication of the extent to which this disease is disabling, CDC reports that approximately 66 percent of heart patients fail to fully recover (Refs. 116 and 117).

2. The Benefits Model

The benefit of the proposed rule relative to the IFR is the reduced risk of CHD that may result from consumers substituting a greater number of foods containing phytosterols for currently consumed alternatives that do not reduce the risk of CHD. The proposed rule would increase the number of food products eligible to use the phytosterols-CHD health claim from only foods enriched with esterified sterols and stanols, to include conventional foods enriched with nonesterified and esterified phytosterols, as well as mixtures of sterols and stanols, and additional forms of dietary supplements. Consequently, a wide variety of low and non-fat foods that are currently not authorized to make the plant sterol/stanol esters-CHD health claim may do so under the proposed rule.

FDA anticipates that foods for which GRAS notifications for phytosterols use have been submitted may be qualified to make a phytosterols-CHD health claim under this proposed rule. Phytosterol GRAS notifications to which FDA has no objections include, but are not limited to, the use of phytosterols as ingredients in: Margarine and vegetable oil spreads, salad dressings, mayonnaise, edible vegetable oils, snack bars, dairy and dairy-like substitutes (including those for yogurt, ice cream, cream cheese, and milk and milk based beverages), baked foods, ready-to-eat breakfast cereals, pasta and noodles, sauces, salty snacks, processed soups, puddings, confections, white breads and white bread products, vegetable meat analogues, fruit and vegetable juices, and coffee. The increase in the number of conventional foods in which phytosterol-enrichment has been self-determined to be GRAS and that may be qualified to make a health claim under the proposed rule, suggests an increase in consumption of conventional foods with phytosterols-CHD health claims.

The higher effective daily intake of phytosterols required to be communicated on the health claim may also increase the dietary intake of phytosterols. The effective daily intake of phytosterols that must be stated in the health claim has been increased to 2 g per day of phytosterols (expressed as weight of nonesterified phytosterols) for both plant sterols and plant stanols in the proposed rule. The IFR specified effective daily intake levels of 1.3 g per day of plant sterol esters (equivalent to 0.8 g of nonesterified plant sterols) and 3.4 g per day of plant stanol esters (equivalent to 2 g of nonesterified plant stanols).

FDA assumes that the proposed change in the minimum amount of phytosterols required for eligible foods to 0.5 g of phytosterols per RACC would have no impact on the number of plant stanol-enriched foods that make the claim because the 0.5 g of phytosterols per RACC required minimum in this proposed rule is less than the qualifying amount of plant stanol esters required under the IFR (1 g/RACC as nonesterified stanol). FDA also assumes that the proposed change in the minimum amount of phytosterols required for eligible foods would have no impact on the number of plant sterol-enriched foods that make the claim because the 0.5 g of phytosterols per RACC required minimum in this proposed rule is only slightly higher than the qualifying amount required under the IFR for plant sterol esters (0.4 g/RACC as nonesterified sterol). Finally, the proposed new claim language specifying that phytosterols should be consumed with meals, rather than specifying that phytosterols should be consumed in two servings eaten at different times of day with other foods, may result in fewer snack foods making the health claim.

3. The Increase in Dietary Intake of Phytosterols

FDA estimates the increase in the market share of newly labeled products that may make a phytosterols-CHD health claim as a first step to model the increase in dietary intake of phytosterols. The agency refines this estimate of the increase in dietary intake to account for the possibility that increased consumption of foods newly permitted to make a health claim under this proposed rule contain the same levels of phytosterols as foods currently consumed but not allowed to make a claim. FDA further refines its estimate of the increase in dietary intake of phytosterols from this proposed rule to account for the consumption of meals away from home that are not subject to packaged food labeling regulations; the portion of dietary intake of phytosterols from meals away from home is assumed to not be affected by the proposed rule.

The increase in dietary intake of phytosterols will be less than the increase in the market share of packaged food products that may make a health claim if meals are consumed away from home and consequently not subject to packaged food labeling regulations, or if consumption of foods newly permitted to make a health claim under this proposed rule contain the same levels of phytosterols as foods currently consumed that are not allowed to make a claim. FDA uses data from the U.S. Department of Agriculture (USDA) to estimate the fraction of total food consumption (both in-home as well as away-from-home consumption) that is subject to packaged food labeling requirements. Food consumed at home accounts for about 57 percent of all food expenditures (Ref. 118). FDA assumes that half of the remaining sales of newly labeled foods that may make a phytosterols-CHD health claim will reflect purchases of existing products that contain threshold levels of phytosterols but are not currently allowed to make a phytosterols-CHD health claim. If FDA applies these estimates to the 0.2 percent for the market share of packaged food products that may make the health claim permitted by this proposed rule, FDA estimates that the percent increase in dietary intake of phytosterols as a result of this proposed rule may be 0.06 percent (*i.e.,* (0.2 percent × 57 percent)/2) of current levels.

Finally, the increase in dietary intake of phytosterols does not necessarily lead to health benefits for all consumers. Healthful characteristics, including the phytosterols content, are just some of several considerations consumers use when making food purchases. Consumers who choose newly formulated foods that make the phytosterols-CHD health benefits over foods that do not contain phytosterols may include both those at risk of CHD as well as those who are not at risk. If a substantial number of those who are at risk of CHD will increase their intake of phytosterols because of the phytosterols-CHD health claims permitted by this proposed rule, then FDA can expect some positive effects on public health.

*E. Costs and Benefits of Option 3*

Option 3 would restrict coverage of the proposed requirements to only conventional foods, so that manufacturers of some plant stanol ester-containing dietary supplements in softgel form that currently claim reduced risk of CHD from plant sterol/stanol esters consumption would no longer be allowed to make that claim. These manufacturers would need to re-label their products to either make no

claim or to make a structure/function claim. Benefits from the consumption of dietary supplements in softgel form may be reduced.

There would be re-labeling costs for some dietary supplements in softgel form that currently make the plant stanol esters-CHD health claim based on the current regulation, but are no longer permitted to make that claim in the proposed rule. The re-labeling costs incurred for the dietary supplements under option 3 will be larger than those incurred by dietary supplement manufacturers under the proposed option; all dietary supplements that currently make a plant sterol/stanol esters and CHD health claim would have to be re-labeled to either make no claim or to make a structure/function claim—either of which implies larger changes to the label. FDA assumes the costs of a full label redesign will be incurred by manufacturers of dietary supplements that currently make a plant sterol/stanol esters and CHD health claim. Because dietary supplements would no longer be permitted to make the plant sterol/stanol esters and CHD health claim, there may also be reformulation costs incurred by manufacturers of some dietary supplements that choose to reduce current levels of phytosterols contained as an ingredient in the final product. However, these costs are considered to be a voluntary reallocation of resources rather than compliance costs.

*F. Costs and Benefits of Option 4*

FDA assumes that manufacturers of any product making the phytosterols-CHD health claim, for which the analytical method for determining the quantity of phytosterols is different than either the Unilever or McNeil methods, may incur costs from the requirement to provide access to documentation that substantiates the amount of phytosterols in a food product. FDA considers the costs incurred for requiring FDA to have access to these documents for an estimated small number of firms to be a reallocation of resources rather than compliance costs, since claiming the health benefits from phytosterols is strictly voluntary; any product for which a testing method different than either the Unilever or McNeil methods is required would be different than a vegetable spread, salad dressing, or snack bar and would have voluntarily chosen to make a phytosterols-CHD health claim following passage of this proposed rule. The costs of ensuring compliance with phytosterols-content requirements in products for which the analytical method for making this determination is different than either the McNeil or Unilever methods would be higher than for the proposed rule if the FDA inspection resources required to access and analyze documents that substantiate the amount of phytosterols contained in products were greater than those required to sample and test the products directly with the Sorenson and Sullivan method.

## IX. Small Entity Analysis (or Initial Regulatory Flexibility Analysis)

FDA has examined the economic implications of this proposed rule as required by the Regulatory Flexibility Act (5 U.S.C. 601–612). If a rule has a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires the agency to analyze regulatory options that would minimize the economic impact of the rule on small entities.

Small businesses that are currently making a plant sterol/stanol esters and CHD health claim may incur re-labeling costs to satisfy the change in the language required on the health claim, and reformulation costs to satisfy the increased minimum per-serving quantity of phytosterols required for a product to make a health claim. FDA uses the 2002 Economic Census to estimate the number of small businesses in the vegetable spreads, salad dressings, snack bars, and dietary supplements sectors that may incur costs from this proposed rule as well as the costs that they would incur. Based on the Economic Census there are approximately 3,065 firms in the sectors described by North American Industry Classification System (NAICS) codes 311225 (Fats and oils refining and blending), 311941 (Mayonnaise, dressing, and other prepared sauce manufacturing, 311942 (Spice and extract manufacturing), 311919 (Other snack food manufacturing), 311999 (All other miscellaneous food manufacturing), and 325412 (Pharmaceutical preparation manufacturing). Approximately 95 percent of these firms have fewer than 500 employees and are considered small (Ref. 119). Moreover, FDA estimates from this data that firms with fewer than 500 employees account for approximately 75 percent of the sales revenues from these sectors.

In order to estimate the number of food manufacturers that may make a plant sterol/stanol esters and CHD health claim, FDA assumes that half of the small firms from the sectors described in the previous paragraph manufacture a product that is eligible to make a health claim. Consistent with FDA's 2001 FLAPS (Ref. 114), FDA multiplies those making a health claim by the percentage of health claims that were found to address the risk of CHD (41.7 percent). FDA assumes that 10 percent of all packaged food sales with claims that address the risk of CHD may make a phytosterols-CHD health claim.

Consequently, FDA estimates that 128 firms with fewer than 500 employees would manufacture one product that makes the plant sterol/stanol esters and CHD health claim and would incur compliance costs from this proposed rule (*i.e.,* 95 percent of 3,065 food and dietary supplements manufacturers, multiplied by 50 percent for only those that manufacture products making a health claim, multiplied by 41.7 percent for manufacturing products that make a health claim addressing the risk of CHD, and multiplying by 10 percent for making the plant sterol/stanol esters and CHD health claim. Because each individual food product currently making the plant sterol/stanol esters and CHD health claim would need to be re-labeled, fewer labels would need to be redesigned or discarded for a small manufacturer than for a large manufacturer. FDA uses data from the 2002 Economic Census indicating that 75 percent of total sales revenue—and by extension re-labeling costs—for the entire sector can be attributed to small manufacturers. FDA multiplies the re-labeling cost estimates for the entire sector of between $86,000 and $186,000 obtained in the cost-benefit analysis by 75 percent, and then divides by the number of small firms to obtain the cost per small firm. Consequently, FDA estimates that the average one-time re-labeling cost per small business would be between approximately $700 and $1,500.

FDA assumes that only some manufacturers that currently enrich conventional food products with plant sterol esters will incur reformulation costs. FDA assumes that 25 percent of small manufacturers of conventional food products that make a plant sterol/stanol esters and CHD health claim would need to reformulate a product as a result of this proposed rule. Consistent with the earlier discussion in this document, FDA estimates that 95 percent of the reformulation costs, or approximately $5,000, would be incurred by approximately 30 small manufacturers with fewer than 500 employees. FDA obtains an estimate of the reformulation costs per small manufacturer of approximately $160. FDA requests comments on the estimate of reformulation costs per manufacturer. Small businesses that currently are not making a plant sterol/stanol esters and CHD health claim will incur labeling and reformulation costs only if they

choose to take advantage of the marketing opportunity presented by this proposed rule.

## X. Paperwork Reduction Act of 1995

FDA concludes that the labeling provisions of this proposed rule are not subject to review by the Office of Management and Budget because they do not constitute a "collection of information" under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). Rather, the food labeling health claim on the association between consumption of phytosterols and CHD risk is a "public disclosure of information originally supplied by the Federal Government to the recipient for the purpose of disclosure to the public" (*see* 5 CFR 1320.3(c)(2)).

## XI. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. Section 4(a) of the Executive order requires agencies to "construe * * * a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State law conflicts with the exercise of Federal authority under the Federal statute." Federal law includes an express preemption provision that preempts "any requirement respecting any claims of the type described in [21 U.S.C. 343(r)(1)] made in the label or labeling of food that is not identical to the requirement of [21 U.S.C. 343(r)] * * *." 21 U.S.C. 343–1(a)(5). However, the statutory provision does not preempt any State requirement respecting a statement in the labeling of food that provides for a warning concerning the safety of the food or component of the food (Pub. L. 101–535, section 6, 104 Stat. 2353 (1990)). If this proposed rule is made final, the final rule would create requirements for various health claims for phytosterols in the label or labeling of food under 21 U.S.C. 343(r).

## XII. Comments

Interested persons may submit to the Division of Dockets Management (*see* **ADDRESSES**) either electronic or written comments regarding this document. It is only necessary to send one set of comments. It is no longer necessary to send two copies of mailed comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

## XIII. References

The following references have been placed on display in the Division of Dockets Management (*see* **ADDRESSES**) and may be seen between 9 a.m. and 4 p.m., Monday through Friday, except on Federal Government holidays. (FDA has verified the Web site addresses, but is not responsible for any subsequent changes to the Web sites after this document publishes in the **Federal Register.**)


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2. Center for Food Safety and Applied Nutrition, Food and Drug Administration. "Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims." January 2009. Available at: *http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/FoodLabelingNutrition/ucm073332.htm.*

3. National Heart, Lung, and Blood Institute, National Institutes of Health. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Pressure in Adults (Adult Treatment Panel III) Executive Summary. National Institutes of Health, Bethesda, MD, 2001. Available at *http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3xsum.pdf.*

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## List of Subjects in 21 CFR Part 101

Food labeling, Incorporation by reference, Nutrition, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 101 be amended as follows:

## PART 101—FOOD LABELING

1. The authority citation for 21 CFR part 101 continues to read as follows:

**Authority:** 15 U.S.C. 1453, 1454, 1455; 21 U.S.C. 321, 331, 342, 343, 348, 371; 42 U.S.C. 243, 264, 271.

2. Section 101.83 is revised to read as follows:

### § 101.83 Health claims: phytosterols and risk of coronary heart disease (CHD).

(a) *Relationship between diets that include phytosterols and the risk of CHD.* (1) Cardiovascular disease means diseases of the heart and circulatory system. Coronary heart disease (CHD) is one of the most common and serious forms of cardiovascular disease and

refers to diseases of the heart muscle and supporting blood vessels. High blood total cholesterol and low density lipoprotein (LDL) cholesterol levels are associated with increased risk of developing CHD. Lowering of blood total and/or LDL cholesterol has been shown conclusively to lower risk for CHD, and thus is the primary target of cholesterol-lowering therapy. The relationship between total and LDL cholesterol levels and CHD risk is continuous over a broad range of LDL cholesterol levels from low to high. High CHD rates occur among people with high total cholesterol levels of 240 milligrams per deciliter (mg/dL) (6.21 millimole per liter (mmol/L)) or above. Borderline high risk blood cholesterol levels range from 200 to 239 mg/dL (5.17 to 6.18 mmol/L). An optimal blood LDL cholesterol level is less than 100 mg/dL (2.6 mg/L); borderline high LDL levels range from 130 to 160 mg/dL (3.4 to 4.1 mmol/L); and a high LDL cholesterol level is above 160 mg/dL.

(2) Populations with a low incidence of CHD tend to have relatively low blood total cholesterol and LDL cholesterol levels. These populations also tend to have dietary patterns that are not only low in total fat, especially saturated fat and cholesterol, but are also relatively high in plant foods that contain dietary fiber and other components.

(3) Phytosterols (plant sterols) are structurally similar to cholesterol. Although there are many different phytosterols found in plants, the phytosterols most abundant in the diet are beta (β)-sitosterol, campesterol, and stigmasterol. Phytosterols usually have a double bond at the 5 position of the core ring structure. Phytosterols that have been saturated to remove the double bond in the ring structure are sometimes referred to as "stanols." This regulation uses the term phytosterol as inclusive of both sterol and stanol forms.

(4) Scientific evidence demonstrates that diets that include phytosterols may reduce the risk of CHD.

(b) *Significance of the relationship between diets that include phytosterols and the risk of CHD.* (1) CHD is a major public health concern in the United States. It accounts for more deaths than any other disease or group of diseases. Early management of risk factors for CHD is a major public health goal that can assist in reducing risk of CHD. High blood total and LDL cholesterol are major modifiable risk factors in the development of CHD.

(2) The scientific evidence establishes that including phytosterols in the diet helps to lower blood total and LDL cholesterol levels.

(c) *Requirements*—(1) *General.* All requirements set forth in § 101.14 shall be met, except § 101.14(a)(4), as specified in paragraph (c)(2)(iii)(C) of this section, for disqualifying levels of total fat in vegetable oil spreads resembling margarine, dressings for salad, and liquid vegetable oils and § 101.14(e)(6), as specified in paragraph (c)(2)(iii)(D) of this section, for minimum nutrient contribution requirements with respect to vegetable oil spreads resembling margarine, dressings for salad, and liquid vegetable oils.

(2) *Specific requirements*—(i) *Nature of the claim.* A health claim associating diets that include phytosterols with reduced risk of heart disease may be made on the label or labeling of a food described in paragraph (c)(2)(iii) of this section provided that:

(A) The claim states that phytosterols should be consumed as part of a diet low in saturated fat and cholesterol;

(B) The claim states that diets that include phytosterols "may" or "might" reduce the risk of heart disease;

(C) In specifying the disease, the claim uses the following terms: "heart disease" or "coronary heart disease";

(D) In specifying the substance, the claim accurately uses the term "phytosterols," "plant sterols," "plant stanols," or "plant sterols and stanols," except that if the sole source of the plant sterols or stanols is vegetable oil, the claim may so specify, *e.g.,* "vegetable oil phytosterols" or "vegetable oil sterols and stanols";

(E) The claim does not attribute any degree of risk reduction for CHD to diets that include phytosterols;

(F) The claim does not imply that consumption of diets that include phytosterols is the only recognized means of achieving a reduced risk of CHD;

(G) The claim specifies the daily dietary intake of phytosterols that is necessary to reduce the risk of CHD and the contribution one serving of the product makes to the specified daily dietary intake level. The daily dietary intake level of phytosterols that has been associated with reduced risk of CHD is 2 grams (g) per day, based on the nonesterified weight of phytosterols; and

(H) The claim specifies that the daily dietary intake of phytosterols should be consumed with meals or snacks.

(ii) *Nature of the substance.* (A) The substance may be derived from either vegetable oils or from tall oils and shall contain at least 80 percent beta-sitosterol, campesterol, stigmasterol, sitostanol, and/or campestanol (combined weight). For conventional foods, the substance may be esterified with food-grade fatty acids; for dietary supplements, the substance must be esterified with food-grade fatty acids.

(B) The Food and Drug Administration (FDA) will measure phytosterols by the Association of Official Analytical Chemists (AOAC) Official Method 994.10, "Cholesterol in Foods," as modified for assaying phytosterols by Sorenson and Sullivan (*Journal of AOAC International,* Vol. 89, No. 1, 2006). These methods are incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies may be obtained from the Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, or at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202–741–6030, or go to *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*

(iii) *Nature of the food eligible to bear the claim.* (A) The food product shall contain at least 0.5 g of phytosterols, based on the nonesterified weight of phytosterols that comply with paragraph (c)(2)(ii) of this section per reference amount customarily consumed;

(B) If the food product is a dietary supplement, the phytosterols shall be esterified with food-grade fatty acids;

(C) If the food product is a conventional food, the use of the phytosterols in such food has been submitted to FDA in a generally recognized as safe (GRAS) notification, to which the agency had no further questions, and the conditions of use are consistent with the eligibility requirements for the health claim;

(D) The food shall meet the nutrient content requirements in § 101.62 for a "low saturated fat" and "low cholesterol" food;

(E) The food shall meet the limit for total fat in § 101.14(a)(4), except that, if the label of the food bears a disclosure statement that complies with § 101.13(h), vegetable oil spreads resembling margarine and dressings for salad are not required to meet the limit for total fat per 50 g and liquid vegetable oils are not required to meet the limit for total fat per reference amount customarily consumed, per label serving size, and per 50 g; and

(F) The food shall meet the minimum nutrient contribution requirement in § 101.14(e)(6) unless it is a liquid vegetable oil or dressing for salad. The minimum nutrient contribution requirement for vegetable oil spreads

resembling margarine may be met by added vitamin A.

(d) *Optional information.* (1) The claim may state that the development of heart disease depends on many factors and may identify one or more of the following risk factors for heart disease about which there is general scientific agreement: A family history of CHD, elevated blood total and LDL cholesterol, excess body weight, high blood pressure, cigarette smoking, diabetes, and physical inactivity. The claim may also provide additional information about the benefits of exercise and management of body weight to help lower the risk of heart disease.

(2) The claim may state that the relationship between intake of diets that include phytosterols and reduced risk of heart disease is through the intermediate link of "blood cholesterol" or "blood total and LDL cholesterol."

(3) The claim may include information from paragraphs (a) and (b) of this section, which summarize the relationship between diets that include phytosterols and the risk of CHD and the significance of the relationship.

(4) The claim may include information from the following paragraph on the relationship between saturated fat and cholesterol in the diet and the risk of CHD: The scientific evidence establishes that diets high in saturated fat and cholesterol are associated with increased levels of blood total and LDL cholesterol and, thus, with increased risk of CHD. Intakes of saturated fat exceed recommended levels in the diets of many people in the United States. One of the major public health recommendations relative to CHD risk is to consume less than 10 percent of calories from saturated fat and keep total fat intake between 20 to 35 percent of calories. Recommended daily cholesterol intakes are 300 mg or less per day. Scientific evidence demonstrates that diets low in saturated fat and cholesterol are associated with lower blood total and LDL cholesterol levels.

(5) The claim may state that diets that include phytosterols and are low in saturated fat and cholesterol are consistent with "Dietary Guidelines for Americans." U.S. Department of Agriculture (USDA) and Department of Health and Human Services (DHHS), Government Printing Office (GPO).

(6) The claim may state that individuals with elevated blood total and LDL cholesterol should consult their physicians for medical advice and treatment. If the claim defines high or normal blood total and LDL cholesterol levels, then the claim shall state that individuals with high blood cholesterol should consult their physicians for medical advice and treatment.

(7) The claim may include information on the number of people in the United States who have heart disease. The sources of this information shall be identified, and it shall be current information from the National Center for Health Statistics, the National Institutes for Health, or "Dietary Guidelines for Americans," U.S. Department of Agriculture (USDA) and Department of Health and Human Services (DHHS), Government Printing Office (GPO).

(e) *Model health claims.* The following model health claims may be used in food labeling to describe the relationship between diets that include phytosterols and reduced risk of heart disease:

(1) Foods containing at least 0.5 g per serving of phytosterols [plant sterols, plant stanols, or plant sterols and stanols] eaten with meals or snacks for a daily total intake of 2 g as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease. A serving of [name of the food] supplies____g of phytosterols [plant sterols, plant stanols, or plant sterols and stanols].

(2) Diets low in saturated fat and cholesterol that include 2 g per day of phytosterols [plant sterols, plant stanols, or plant sterols and stanols] eaten with meals or snacks may reduce the risk of heart disease. A serving of [name of food] supplies____g of [phytosterols plant sterols, plant stanols, or plant sterols and stanols].

Dated: November 24, 2010.

**Leslie Kux,**

*Acting Assistant Commissioner for Policy.*

## Tables 1 and 2 to Preamble

**Note:** These tables will not appear in the Code of Federal Regulations.

TABLE 1—RANDOMIZED CLINICAL TRIALS OF PHYTOSTEROLS IN CONVENTIONAL FOODS AND TOTAL AND LDL CHOLESTEROL CONCENTRATION

| Study | Design | Population | Intervention | Diet | Results |
|---|---|---|---|---|---|
| AbuMweis *et al.,* 2006 (Ref. 38) | Randomized single-blind, placebo-controlled, crossover trial; five 29–d test periods, separated by 2–4 wk washout periods | Healthy adults 38 enrolled, 30 completed<br>Mean age ± sd<br>59 ± 10 y<br>n = 30/phase<br>Inclusion criteria: LDL–C >100 mg/dL, BMI 22–34, age 40–85 y, no chronic disease or lipid-lowering $R_X$<br>USA | One serving/d test margarine, eaten with breakfast. PS dose: 22 mg/kg body wgt (about 1.7 g PS/d) [1]<br>C = margarine w/o added PS<br>$I_1$ = ~1.7 g PS/d as nonesterified plant sterols in PS-enriched margarine<br>$I_2$ = ~1.7 g PS/d as plant sterol esters (sunflower oil fatty acids) in PS-enriched margarine<br>$I_3$ = ~1.7 g PS/d as plant sterol esters (fish oil n–3 LC PUFA) in PS-enriched margarine<br>$I_4$ = ~1.7 g PS/d as nonesterified plant sterols fish oil | Controlled diet; all food and beverage prepared/provided by study; American diet w/ 30% energy from fat | *Total-C* (mg/dL) Baseline: 228<br>After 4-wk test period:<br>C 222<br>$I_1$ 219<br>$I_2$ 220<br>$I_3$ 224<br>$I_4$ 223<br>*LDL–C* (mg/dL) Baseline: 147<br>After 4-wk test period:<br>C 141<br>$I_1$ 139<br>$I_2$ 139<br>$I_3$ 145<br>$I_4$ 143<br>No significant changes of *Total-C or LDL–C* compared to control |

TABLE 1—RANDOMIZED CLINICAL TRIALS OF PHYTOSTEROLS IN CONVENTIONAL FOODS AND TOTAL AND LDL CHOLESTEROL CONCENTRATION—Continued

| Study | Design | Population | Intervention | Diet | Results |
|---|---|---|---|---|---|
| Doornbos *et al.,* 2006 (Ref. 43) | Randomized double-blind, placebo-controlled, parallel trial with 5 groups; 4-wk run-in followed by 4-wk test period | Mildly hypercholesterolemic adults<br>191 randomized, 184 Included in analysis<br>Mean age ± sd<br>57 ± 2 y<br>n = 33(C)<br>n = 38 ($I_1$)<br>n = 38 ($I_2$)<br>n = 39 ($I_3$)<br>n = 36 ($I_4$)<br>Inclusion criteria: BMI 18–32 kg/m$^2$; total-C 193–309 mg/dL TG < 355 mg/dL<br>The Netherlands | Single serving bottled yogurt drink (100 g) consumed with a meal, or while fasting<br>C = drink w/o added PS<br>$I_1$ = 3.2 g PS/d in low-fat yogurt (0.1 g dairy fat, 2.2 g fat in the stanol/sterol ester) w/meal<br>$I_2$ = 3.2 g PS/d in low-fat yogurt (0.1 g dairy fat, 2.2 g fat in the stanol/sterol ester) w/o meal<br>$I_3$ = 2.8 g tall oil PS/d in regular-fat yogurt (1.5 g dairy fat, 2.1 g fat in the stanol/sterol ester) w/meal<br>$I_4$ = 2.8 g PS/d in regular-fat yogurt (1.5 g dairy fat, 2.1 g fat in the stanol/sterol ester) w/o meal | Habitual diet ..... | *Total-C* (mg/dL) Baseline: 234<br>*Total-C* % change compared to control:<br>$I_1$ ↓ 7.0%*<br>$I_2$ ↓ 4.1%*<br>$I_3$ ↓ 6.5%*<br>$I_4$ ↓ 4.7%*<br>*p < 0.05<br>*LDL–C* (mg/dL) Baseline: 155<br>*LDL–C* % change compared to control:<br>$I_1$ ↓ 9.5%*<br>$I_2$ ↓ 5.1%*<br>$I_3$ ↓ 9.3%*<br>$I_4$ ↓ 6.9%*<br>*p < 0.05 |
| Jauhiainen *et al.,* 2006 (Ref. 89). | Randomized double-blind, placebo-controlled parallel trial, 1-wk run-in, 5-wk test period | Mildly hypercholesterolemic adults<br>67 enrolled, 67 completed<br>n = 34 (C)<br>n = 33 (I)<br>Age range 25–65 y<br>Inclusion criteria: Total-C 193–251 mg/dL, TG < 266 mg/dL<br>Finland | 50 g/d hard cheese divided into 2 portions consumed with two major meals<br>C = cheese w/o added phytosterols<br>I = 2.0 g PS/d as plant stanol ester in PS-enriched hard cheese | Habitual diets ..... | *Total-C* (mg/dL) Baseline:<br>C 224<br>I 218<br>*Total-C* % change compared to placebo:<br>I ↓ 5.7% (p < 0.05)<br>*LDL–C* (mg/dL) Baseline:<br>C 139<br>I 138<br>*LDL–C* % change compared to control: I ↓ 10.1% (p < 0.05) |
| Korpela *et al*., 2006 (Ref. 37). | Randomized double-blind, placebo-controlled, parallel trial; 3-wk run-in, 6-wk test period | Mildly hypercholesterolemic adults. 170 enrolled, 164 completed<br>n = 82/group<br>Mean age ± sd<br>57 ± 8 y (C)<br>58 ± 9 y (I)<br>Inclusion criteria: Total-C 193–329 mg/dL, TG < 354 mg/dL<br>Finland | 150 g low-fat yogurt, 50 g low-fat hard cheese, and 50 g low-fat fresh cheese<br>C = yogurt and cheese w/out added PS<br>I= 1.65–2.0 g PS/d as nonesterified sterol/stanol in enriched yogurt and cheeses | Habitual diets plus low-fat yogurt and low-fat hard/fresh cheese | *Total-C* (mg/dL) Baseline:<br>C 247<br>I 247<br>% change compared to control: I ↓ 6.5% (p < 0.05)<br>*LDL–C* (mg/dL) Baseline:<br>C 155<br>I 159<br>% change compared to control: I ↓ 11.0% (p < 0.05) |
| Jakulj *et al.,* 2005 (Ref. 90). | Randomized double-blind, crossover design for PS component, and open-label $R_X$ tmt; 2x2 factorial trial. 2-wk run-in followed by four consecutive 4-wk test periods | Healthy moderately hypercholesterolemic adults 40 enrolled, 39 Included in analyses<br>Mean age ± sd<br>55.5 ± 7.9 y<br>n = 39<br>Inclusion criteria: plasma LDL–C 135–193 mg/dL; TG < 355 mg/dL<br>The Netherlands | 25 g/d test margarine on sandwiches or mixed with food in a hot meal<br>C = spread w/o added PS<br>$I_1$ = 2.0 g PS/d as plant sterol on PS-enriched spread. Information not provided as to whether nonesterified or esterified<br>$I_2$ = Ezetimibe<br>$I_3$ = Ezetimibe + PS-enriched spread | Habitual diets ..... | *Total-C* (mg/dL) Baseline: 261<br>At end of 4 wk test period:<br>C 249<br>$I_1$ 235<br>$I_2$ 208<br>$I_3$ 204<br>*Total-C* % change compared to control:<br>$I_1$ ↓ 5.2%*<br>$I_2$ ↓ 15.7%*<br>$I_3$ ↓ 17.2%*<br>*p < 0.05<br>*LDL–C* (mg/dL) Baseline: 174<br>At end of 4-wk:<br>C 157<br>$I_1$ 148<br>$I_2$ 121<br>$I_3$ 116<br>% change compared to control:<br>$I_1$ ↓ 5.1%*<br>$I_2$ ↓ 20.9%*<br>$I_3$ ↓ 23.8%*<br>*p < 0.05 |

TABLE 1—RANDOMIZED CLINICAL TRIALS OF PHYTOSTEROLS IN CONVENTIONAL FOODS AND TOTAL AND LDL CHOLESTEROL CONCENTRATION—Continued

| Study | Design | Population | Intervention | Diet | Results |
|---|---|---|---|---|---|
| Clifton *et al.* 2004 (Ref. 88). | Randomized single-blind, placebo-controlled, incomplete crossover trial; four consecutive 3-wk test periods, no washout periods | Mildly hypercholesterolemic adults 63 enrolled, 58 completed<br>n = 58 (C)<br>n = 36 ($I_1$)<br>n = 40 ($I_2$)<br>n = 58 ($I_3$)<br>n = 40 ($I_4$)<br>Mean age 54 y<br>Inclusion criteria: BMI < 31, no $R_X$ that affect lipids, total-C 193–290 mg/dL<br>Australia | One serving/d each 4 of test foods (bread, milk, cereal, and yoghurt) consumed with meals<br>C = test foods w/o added PS<br>$I_1$ = 1.6 g/d PS as soy sterol esters in 2 slices of PS-enriched bread<br>$I_2$ = 1.6 g/d PS as soy sterol esters in 500 ml of 2% PS-enriched milk<br>$I_3$ = 1.6 g/d PS as soy sterol esters in 45 g of PS-enriched cereal<br>$I_4$ = 1.6 g/d PS as soy sterol esters 200g of PS-enriched yogurt | Habitual diets supplemented by one serving daily of yoghurt, low-fat milk, bread, and muesli-type cereal. No changes in reported intakes of energy, fat, CHO, or protein across treatment periods or between centers | *Total-C* (mg/dL) Baseline: 241<br>% change compared to placebo:<br>$I_1$ ↓ 5.6%*<br>$I_2$ ↓ 8.5%*<br>$I_3$ ↓ 3.2%*<br>$I_4$ ↓ 6.3%*<br>*p < 0.05<br>*LDL–C* (mg/dL) Baseline: 156<br>% change compared to control:<br>$I_1$ ↓ 10.4%*<br>$I_2$ ↓ 13.2%*<br>$I_3$ ↓ 6.0%*<br>$I_4$ ↓ 10.4%*<br>*p < 0.05 |
| Devaraj *et al.,* 2004 (Ref. 33). | Randomized double-blind, parallel trial with 2 groups; 2-wk run-in period followed by 8-wk test period | Healthy mildly hypercholesterolemic adults<br>75 enrolled; 72 completed<br>Mean age ± sd<br>44 ± 13 y (C)<br>41 ± 13 y (I)<br>n = 36/group<br>Inclusion criteria: LDL–C >100 mg/dL; no $R_x$ that affect lipids, no smoking, no $H_X$ of CVD<br>USA | 2 servings/d of test orange juice, with meals.<br>C = orange juice w/o added PS<br>I=2 g PS/d as nonesterified sterol in PS-enriched orange juice | Habitual diets. No other orange juice, citrus fruit, or PS-enriched margarine allowed. 3-day diet records at beginning and end of study | *Total-C* (mg/dL) Baseline:<br>C 209<br>I 207<br>*Total-C* % change compared to control:<br>I ↓ 5.3% (p < 0.05)<br>*LDL–C* (mg/dL) Baseline:<br>C 140<br>I 137<br>*LDL–C* % change compared to control: I ↓ 7.3% (p < 0.05) |
| Thomsen *et al.,* 2004 (Ref. 26). | Randomized double-blind, crossover trial, with three consecutive 4-wk periods; no run-in or wash-our periods | Mildly hypercholesterolemic adults<br>81 subjects Randomized 69 completed<br>Mean age ± sd<br>60 ± 5 y<br>n = 69<br>Inclusion criteria: no $R_X$ that affect lipids, total-C 217–325 mg/dL, TG < 310 mg/dL<br>Denmark | 2 servings/d of 1.2%-fat test milk w/meals<br>C = milk w/o added PS<br>$I_1$ = 1.2 g PS/day as nonesterified plant sterols in PS-enriched milk<br>$I_2$ = 1.6 g PS/day as nonesterified plant sterols in PS-enriched milk | Habitual Danish diet with limits on certain fatty foods; *e.g.,* 20 g/d cheese, 2 portions of crustaceans and mollusks per wk | *Total-C* (mg/dL) Baseline: 271<br>*Total-C* % change relative to control:<br>$I_1$ ↓ 4.73%*<br>$I_2$ ↓ 7.05%*<br>* p < 0.0001<br>*LDL–C* (mg/dL) Baseline: 169<br>LDL–C % change relative to control:<br>$I_1$ ↓ 7.1%*<br>$I_2$ ↓ 9.6%*<br>* p < 0.0001 |
| Cleghorn *et al.,* 2003 (Ref. 91). | Randomized double-blind, placebo-controlled, crossover trial; 3-wk run-in period, 3-wk test period | Mildly hypercholesterolemic adults;<br>58 subjects enrolled, 53 completed<br>Mean age ± sd<br>46.7 ± 10.5 y<br>n = 53<br>Inclusion criteria: total-C 193–290 mg/dL, TG < 266 mg/dL; no cholesterol-lowing $R_X$<br>New Zealand | Test butter (20 g/d) or test margarine (25 g/d)<br>B = Butter w/o added PS<br>M = margarine w/o added PS<br>I = 2 g PS/d PS as plant sterol esters in PS-enriched margarine | Self-selected low-fat diets. Test substance (butter or margarine) added to low-fat diet | *Total-C* (mg/dL)<br>At end of 3 wk test period:<br>B 235<br>M 227<br>I 215<br>*Total-C* % change relative to control: I ↓ 5.45% (p < 0.05)<br>*LDL–C* (mg/dL)<br>At end of 3 wk test period:<br>B 154<br>M 145<br>I 135<br>*LDL–C* % change compared to control: I ↓ 7.2% (p < 0.01) |

TABLE 1—RANDOMIZED CLINICAL TRIALS OF PHYTOSTEROLS IN CONVENTIONAL FOODS AND TOTAL AND LDL CHOLESTEROL CONCENTRATION—Continued

| Study | Design | Population | Intervention | Diet | Results |
|---|---|---|---|---|---|
| Homma *et al.,* 2003 (Ref. 82). | Randomized double-blind, placebo-controlled, parallel trial, 4-wk test period, and 4-wk post-trial follow-up period | Healthy adult Japanese<br>105 enrolled, 104 completed<br>Mean age ± sd<br>46 ± 14 y (P)<br>47 ± 13 y ($I_1$)<br>49 ± 12 y ($I_2$)<br>n = 33–34/group<br>Inclusion criteria: age >20 y, total-C 209–278 mg/dL, TG < 345 mg/dL<br>Japan | 2 or 3 servings/d of low-fat test spread, eaten w/meals.<br>C = spread w/o added PS, 3 servings/d<br>$I_1$ = 2 g PS/d as plant stanol esters in PS-enriched spread, 2 servings/d<br>$I_2$ = 3 g PS/d as stanol esters in PS-enriched spread, 3 servings/d | Habitual Japanese diet. Diets were assessed with 2 day diet analysis at start and end of trial | *Total-C* (mg/dL) Baseline:<br>C 238<br>$I_1$ 235<br>$I_2$ 232<br>*Total-C* % change compared to control:<br>$I_1$ ↓ 5.7%*<br>$I_2$ ↓ 4.9%*<br>*p < 0.001<br>*LDL–C* (mg/dL) Baseline:<br>C 157<br>$I_1$ 153<br>$I_2$ 153<br>*LDL–C* % change compared to control:<br>$I_1$ ↓ 8.9%*<br>$I_2$ ↓ 6.6%*<br>*p < 0.001 |
| Ishiwata *et al.,* 2002 (Same subjects as Homma *et al.,* 2003) (Ref. 92). | Randomized double-blind, placebo-controlled, parallel trial, 4-wk test period, and 4-wk post-trial follow-up period | *See* Homma *et al.* 2003<br>n = 30–31/group<br>Analysis stratified by apolipoprotein E phenotype | 2 or 3 servings/d of low-fat test spread, eaten w/meals<br>C = spread w/o added PS, 3 servings/d<br>$I_1$ = 2 g PS/d as plant stanol esters in PS-enriched spread, 2 servings/d<br>$I_2$ = 3 g PS/d as stanol esters in PS-enriched spread, 3 servings/d | Habitual Japanese diet | *Total-C* (mg/dL) Baseline:<br>C $ApoE_3$ 236<br>C $ApoE_4$ 241<br>$I_1$ $ApoE_3$ 237<br>$I_1$ $ApoE_4$ 231<br>$I_2$ $ApoE_3$ 234<br>$I_2$ $ApoE_4$ 233<br>*Total-C* % change compared to control:<br>$I_1$ $ApoE_3$ ↓ 7.1%*<br>$I_1$ $ApoE_4$ ↓ 6.3%*<br>$I_2$ $ApoE_3$ ↓ 5.9%*<br>$I_2$ $ApoE_4$ ↓ 4.7%<br>* p < 0.05<br>*LDL–C* (mg/dL) Baseline:<br>C $ApoE_3$ 153<br>C $ApoE_4$ 161<br>$I_1$ $ApoE_3$ 155<br>$I_1$ $ApoE_4$ 148<br>$I_2$ $ApoE_3$ 155<br>$I_2$ $ApoE_4$ 151<br>*LDL–C* % change compared to control:<br>$I_1$ $ApoE_3$ ↓ 9.2%*<br>$I_1$ $ApoE_4$ ↓ 11.0%*<br>$I_2$ $ApoE_3$ ↓ 8.7%*<br>$I_2$ $ApoE_4$ ↓ 6.4%<br>* p < 0.01 |
| Jones *et al.,* 2003 (Ref. 34). | Randomized double-blind, crossover trial; three 3-wk controlled feeding test periods separated by 4-wk washout periods | Mildly hypercholesterolemic adults<br>15 enrolled, 15 completed<br>age range 22–68 y<br>n = 15<br>Inclusion criteria: BMI 22–32 kg/m$^2$, LDL–C 126–232 mg/dL, HDL < 31 mg/dL, TG < 355 mg/dL<br>Canada | 3 servings/d of nonfat or low fat test beverage consumed w/meals<br>C = nonfat beverage w/o added PS<br>$I_1$ = 1.8 g PS/d as nonesterified plant tall oil sterol/stanol in PS-enriched nonfat beverage<br>$I_2$ = 1.8 g PS/d as nonesterified plant tall oil sterol/stanol in PS-enriched low fat beverage | Typical American diet. Controlled intake; all food/beverage prepared/provided by study | *Total-C* (mg/dL) Baseline:<br>C 237<br>$I_1$ 242<br>$I_2$ 229<br>*Total-C* % change at 3 wk:<br>C ↓ 8.5%<br>$I_1$ ↓ 11.6%<br>$I_2$ ↓ 10.1%<br>no significant differences between control and PS periods<br>*LDL–C* (mg/dL) Baseline:<br>C 155<br>$I_1$ 160<br>$I_2$ 150<br>*LDL–C* % change at 3 wk:<br>C ↓ 5.0%<br>$I_1$ ↓ 10.4%<br>$I_2$ ↓ 8.5%<br>no significant differences between P and PS periods |

TABLE 1—RANDOMIZED CLINICAL TRIALS OF PHYTOSTEROLS IN CONVENTIONAL FOODS AND TOTAL AND LDL CHOLESTEROL CONCENTRATION—Continued

| Study | Design | Population | Intervention | Diet | Results |
|---|---|---|---|---|---|
| Naumann *et al.,* 2003 (Ref. 42). | Randomized double-blind, placebo-controlled, crossover trial; three consecutive 3-wk test periods | Healthy adults, 44 enrolled, 42 completed<br>Mean age ± sd<br>32 ± 14 y F<br>37 ± 16 y M<br>n = 42<br>Inclusion criteria: BP < 160/95, BMI < 30, stable body wgt, age 18–65 y, Total-C < 309 mg/dL, TG < 355 mg/dL<br>The Netherlands | 1 serving/d of test margarine<br>C = margarine w/o added PS<br>$I_1$ = 2 g PS/d as phytosterol ester, 1:1 sterol/stanol ester ratio in PS-enriched margarine<br>$I_2$ = 2 g PS/d as phytosterol ester, 3:1 sterol/stanol ester ratio in PS-enriched margarine | Habitual diets; food frequency questionnaires assessed diet at end of each period. No margarine was allowed other than the provided test margarine. Study provided sunflower oil shortening (w/o added plant sterols and stanols) to control unintended plant sterol and stanol intake | *Total-C* (mg/dL) At end of 3 wk:<br>C 173<br>$I_1$ 167<br>$I_2$ 168<br>*Total-C* % difference compared to control:<br>$I_1$ ↓ 3.4%*<br>$I_2$ ↓ 2.7%*<br>*p < 0.05<br>*LDL–C* (mg/dL)<br>At end of 3 wk<br>C 109<br>$I_1$ 102<br>$I_2$ 102<br>*LDL–C* % difference compared to control 3 wk:<br>$I_1$ ↓ 6.0%*<br>$I_2$ ↓ 6.7%*<br>*p < 0.05 |
| Quílez *et al.,* 2003 (Ref. 93). | Randomized double-blind, placebo-controlled, parallel trial; 2 groups, 8 wk test period | Healthy subjects, 61 enrolled, 57 competed<br>Mean age ± sd<br>30.9 ± 7.2 y (C)<br>31.0 ± 6.7 y (I)<br>n = 29 (C)<br>n = 28 (I)<br>Inclusion criteria: BMI < 40, no $R_X$ or diet that affect blood lipids, total-C < 240 mg/dL, global CV risk < 20% (Eur Soc for Atherosclerosis criteria), TG < 200 mg/dL, consumers of bakery products<br>Spain | 2 test bakery products/d (1 muffin, 1 croissant) eaten at any time of day<br>C = bakery products w/o added PS<br>I = 3.2 g PS/d as soy sterol esters; divided between PS-enriched croissant and muffin | Habitual diets with test foods replacing usual bakery product consumption | *Total-C* (mg/dL) Baseline:<br>C 162<br>I 167<br>*Total-C* % change compared to control: I ↓ 8.9% (p < 0.001)<br>*Total-C* (mg/dL) Baseline:<br>C 93<br>I 97<br>*Total-C* % change compared to control: I ↓ 14.6% (p < 0.001) |
| Seki *et al.,* 2003 (Ref. 54) | Randomized double-blind, parallel trial with 2 groups; 2-wk run-in period followed by 12-wk test period | Healthy mildly hypercholesterolemic males<br>61 enrolled, 60 completed<br>Mean age ± sd<br>39.4 ± 1.4 y<br>n = 28 (C)<br>n = 32 (I)<br>Inclusion criteria: healthy; total-C < 280 mg/dL, TG < 400 mg/dL<br>Japan | 3 slices test bread/d<br>C = bread made with veg oil w/o added PS<br>I = 0.45 g PS/d as plant sterol esters in PS-enriched veg oil baked into bread | Habitual diets; diets assessed with three 3-d diet records | *Total-C* (mg/dL) Baseline:<br>C 190<br>I 194<br>*Total-C* % change compared to control: I ↓ 3%<br>*LDL–C* (mg/dL) Baseline:<br>C 115<br>I 116<br>*LDL–C* % change compared to control: I ↓ 2.1%<br>No significant treatment effects |
| Spilburg *et al.,* 2003 (Ref. 27). | Randomized double-blind, parallel trial, with 6-wk run-in period followed by 4-wk test period | Moderately hypercholesterolemic adults<br>26 randomized, 24 completed<br>Mean age ± sd<br>50.6 ± 10 y<br>Inclusion criteria: LDL–C 80–210 mg/dL, TG < 300; no illness; no $R_X$ except for oral contraceptives, hormone replacement, anti-hypertensives, anti-depressants & analgesics<br>USA | Powdered lemonade-flavored fat-free test beverage, 3 servings/d<br>P = beverage w/added lecithin, w/o added PS<br>I = 1.9 g PS/d as lecithin emulsified soy nonesterified stanol in PS-enriched beverage | American Heart Association Step I diet; diet counseling to maintain weight if needed | *Total-C* (mg/dL) Baseline:<br>C 200<br>I 224<br>% change compared to control: I ↓ 10.1% (p < 0.05)<br>*LDL–C* (mg/dL)<br>C 128<br>I 148<br>% change compared to control: I ↓ 14.3% (p < 0.05) |

TABLE 1—RANDOMIZED CLINICAL TRIALS OF PHYTOSTEROLS IN CONVENTIONAL FOODS AND TOTAL AND LDL CHOLESTEROL CONCENTRATION—Continued

| Study | Design | Population | Intervention | Diet | Results |
|---|---|---|---|---|---|
| De Graaf *et al.,* 2002 (Ref. 32). | Randomized double-blind, parallel trial; 4 wk run-in period; 4-wk test period | Mildly hypercholesterolemic adults<br>70 randomized, 62 completed<br>Mean age<br>57.8 y (C)<br>56.2 y (I)<br>n = 31/group<br>Inclusion criteria: age 21–75 y; total-C 213–310 mg/dL, LDL–C ≥135 mg/dL; TG < 354 mg/dL; BMI < 35<br>The Netherlands | 3 servings/d of test chocolate/d (10.5 g each), eaten with meals<br>C = chocolate w/o added PS<br>I = 1.8 g PS/day as nonesterified tall oil sterols/stanols in PS-enriched chocolate | Self-selected Step I diet; supplemented w/three servings/d of chocolate | *Total-C* (mg/dL)<br>C 257<br>I 261<br>*Total-C*% change compared to control: I ↓ 6.4% ($p < 0.05$)<br>*LDL–C* (mg/dL)<br>C 177<br>I 182<br>*LDL–C*% change compared to control: I ↓ 11.1 ($p < 0.05$) |
| Geelen *et al.,* 2002 (Ref. 94). | Randomized double-blind, crossover trial, with 2 consecutive 3-wk test periods | Healthy adults with known apolipoprotein E phenotype 31 $ApoE_4$ subjects; 57 $ApoE_3$ subjects n = 88; Mean age 25.4 y<br>Inclusion criteria: age ≥18 y; no prescribed diets; no lipid-lowering $R_X$; total-C ≤310 mg/dL; TG < 266 mg/dL<br>The Netherlands | One tub (35 g) test margarine/d consumed in place of usual margarine<br>C = margarine w/o added PS<br>I = 3.2 g PS/d as vegetable oil sterol esters in PS-enriched margarine | Habitual diets; random 24-h recall diet surveys conducted during test | *Total-C* (mg/dL) Baseline:<br>E3/4 & E4/4 201<br>E3/3 178<br>*Total-C*% change compared to control: I ↓ 7% ($p < 0.05$)<br>*LDL–C*% change compared to control: I ↓ 11% ($P<0.05$) |
| Judd *et al.,* 2002 (Ref. 95). | Randomized double-blind, crossover trial; two consecutive 3-wk intervention periods, no wash out | Healthy adults, normal or slightly elevated total-C<br>58 enrolled, 53 completed<br>Mean age ± sd<br>47.1 ± 1.5 y<br>n = 53<br>Inclusion criteria: age 25–65 y; HDL >25 mg/dl (men) or >35 mg/dL (women), TG < 300 mg/dL<br>USA | Two servings/d of test salad dressing (Ranch or Italian), eaten w/meals<br>$C_1$ = Ranch dressing w/o added PS<br>$I_1$ = 2.2 g PS/d as soy sterol esters in PS-enriched Ranch dressing<br>$C_2$ = Italian dressing w/o added PS<br>$I_2$ = 2.2 g PS/d as soy sterol esters in PS-enriched Italian dressing | Typical American diet; Controlled diet provided by study and eaten on site | Type of salad dressing did not affect plasma lipids so data was combined<br>*Total-C* (mg/dL) baseline: 214<br>*Total-C*% change compared to control: I ↓ 7.0% ($p < 0.0001$)<br>*LDL–C* (mg/dL) Baseline: 141<br>LDL–C% change compared to control: I ↓ 9.2% ($p < 0.0001$) |
| Matvienko *et al,* 2002 (Ref. 60). | Randomized double-blind, placebo-controlled, parallel trial; single 4-wk test period | Hypercholesterolemic white males. 50% of subjects w/family $H_X$ of premature CVD & hyperlipidemia<br>36 enrolled, 34 completed<br>Mean age ± sd<br>22.2±3.9 y (C)<br>23.6±3.9 y (I)<br>n = 17/group<br>Inclusion criteria: total-C >197 mg/dL, LDL-total-C >130 mg/dL<br>USA | One serving/d (112 g) of cooked lean ground beef eaten at lunch<br>C = ground beef w/o added PS<br>I = 2.7 g PS/d as soy sterols, partially esterified, in PS-enriched beef | Habitual diets w/limits on eggs (2–3 eggs/wk), and no red meat other than that in the test meal. Diets assessed by interviewer administered questionnaires | *Total-C* (mg/dL) Baseline:<br>C 224<br>I 228<br>*Total-C*% change compared to control: I ↓ 8.4% ($p < 0.001$)<br>*LDL–C* (mg/dL) Baseline:<br>C 153<br>I 159<br>*LDL–C*% change compared to control: I ↓ 13.3% ($p < 0.001$) |
| Mensink *et al.,* 2002 (Ref. 86). | Randomized double-blind, placebo-controlled, parallel trial; 3-wk run-in followed by 4-wk test period | Mildly hypercholesterolemic adults<br>69 randomized, 60 completed<br>Mean age ± sd<br>36 ± 14 y<br>n = 30/group<br>Inclusion criteria: no diets that affects lipids, no CAD $H_X$, BMI < 30, total-C < 251 mg/dL<br>The Netherlands | 3 servings/d of test yogurt, eaten w/meals<br>C = yogurt w/o added PS<br>I = 3 g PS/d as plant stanol esters in PS-enriched yogurt | Habitual diets supplemented with 3 servings/day test yogurt. Low erucic acid rapeseed oil margarine and shortening provided to standardize fatty acid intake. Diet questionnaires to assess diet | *Total-C* (mg/dL) Baseline:<br>C 184<br>I 193<br>% change compared to control: I ↓ 8.7% ($p < 0.001$)<br>*LDL–C* (mg/dL) Baseline:<br>C 111<br>I 113<br>% change compared to control: I ↓ 13.7% ($p < 0.001$) |

TABLE 1—RANDOMIZED CLINICAL TRIALS OF PHYTOSTEROLS IN CONVENTIONAL FOODS AND TOTAL AND LDL CHOLESTEROL CONCENTRATION—Continued

| Study | Design | Population | Intervention | Diet | Results |
|---|---|---|---|---|---|
| Mussner *et al.,* 2002 (Ref. 96). | Randomized double-blind, crossover trial, with 2 consecutive 3-wk test periods | Mildly hypercholesterolemic adults<br>63 enrolled, 62 completed<br>Mean age ± sd<br>42 ± 11 y<br>n = 62<br>Inclusion criteria: BMI < 30, total-C 200–300 mg/dL, LDL–C 130–200 mg/dL; TG < 160 mg/dL<br>Germany | Two servings/d (10 g each) of test margarine, consumed in morning and evening, replacing usual margarine<br>C = margarine w/o added PS<br>I = 1.82 g PS/d as plant sterol esters in PS-enriched margarine | Habitual diets; 3-day dietary recalls (at beginning and end of study) to assess diets | *Total-C* (mg/dL) Baseline: 233<br>*Total-C*% change compared to control: I ↓ 3.8% ($p < 0.05$)<br>*LDL–C* (mg/dL) Baseline: 152<br>*LDL–C*% change compared to control: I ↓ 6.5% ($p < 0.05$) |
| Noakes *et al.,* 2002 (Ref. 41). | Randomized double-blind, crossover trial; three consecutive 3-wk test periods, no wash-out period; 1-wk run-in<br>Study 1 | Hypercholesterolemic adults<br>52 enrolled, 46 completed<br>Mean age ± sd<br>55 ± 9.7 y M<br>58 ± 7.3 y F<br>n = 46<br>Inclusion criteria: age 20–75 y; BMI < 31, no $R_X$ that affect lipids, total-C 209–329 mg/dL, TG < 400 mg/dL<br>The Netherlands | 3 servings/d of reduced fat test spread replacing usual margarine, consumed w/meals<br>C = spread w/o added PS<br>$I_1$ = 2.3 g PS/d as plant sterol esters in PS-enriched spread<br>$I_2$ = 2.5 g PS/d as plant stanol esters in PS-enriched spread | Usual low saturated fat diet; w/≥5 servings/d of fruit and vegetables, ≥1 of which was high in carotenoids | *Total-C* (mg/dL) After 3-wk intervention:<br>C 244<br>$I_1$ 229<br>$I_2$ 226<br>*Total-C*% change compared to control:<br>$I_1$ ↓ 6.0%*<br>$I_2$ ↓ 7.3%*<br>*$p < 0.001$<br>*LDL–C* (mg/dL) After 3-wk intervention:<br>C 166<br>$I_1$ 153<br>$I_2$ 150<br>*LDL–C*% change compared to control:<br>$I_1$ ↓ 7.7%*<br>$I_2$ ↓ 9.5%*<br>*$p < 0.001$<br>No significant difference between $I_1$ and $I_2$ |
| | Randomized double-blind, crossover trial; two consecutive 3-wk test periods, no wash-out period; 1-wk run-in<br>Study 2 | Hypercholesterolemic adults<br>40 enrolled, 35 completed<br>n = 35<br>Inclusion criteria: BMI < 31, no $R_X$ that affect lipids, total-C 209–329 mg/dL, TG < 400 mg/dL<br>The Netherlands | 3 servings/d of reduced fat test spread replacing usual margarine, consumed w/meals<br>C = spread w/o added PS<br>$I_3$ = 2 g PS/d as plant sterol esters in PS-enriched spread | Diet same as in Study #1 | *Total-C* (mg/dL) After 3-wk intervention:<br>C 233<br>$I_3$ 218<br>*Total-C*% change compared to control: $I_3$ ↓ 6.6%*<br>*LDL–C* (mg/dL) After 3-wk intervention:<br>C 161<br>$I_3$ 145<br>LDL–C% change compared to control: $I_3$ ↓ 9.6%*<br>*$p < 0.001$ |
| Ntanios *et al.,* 2002 (Ref. 97). | Double-blind, placebo-controlled, crossover trial. 1-wk run-in; Two consecutive 3-wk test periods w/o wash-out period | Healthy adult Japanese, 53 enrolled, 53 completed<br>Mean age ± sd<br>45.1 ± 10.4 y<br>n = 53<br>Inclusion criteria: age 24–67 y; BMI 19–30, healthy, normal diet, no $H_X$ of CVD or ↑ total-C<br>Japan | Two servings/d low-fat test spread consumed w/meals<br>C = spread w/o added PS<br>I = 1.8 g PS/d as plant sterol esters in PS-enriched spread | Habitual Japanese diet. Diets assessed with food frequency questionnaire during run-in period | *Total-C* (mg/dL) After 3 wks of intervention:<br>C 213<br>I 201<br>Total-C% change compared to control: I ↓ 5.8% ($p < 0.01$)<br>*LDL–C* (mg/dL) After 3 wks of intervention<br>C 119<br>I 109<br>*LDL–C*% change compared to control: I ↓ 9.1% ($p < 0.001$) |

TABLE 1—RANDOMIZED CLINICAL TRIALS OF PHYTOSTEROLS IN CONVENTIONAL FOODS AND TOTAL AND LDL CHOLESTEROL CONCENTRATION—Continued

| Study | Design | Population | Intervention | Diet | Results |
|---|---|---|---|---|---|
| Simons *et al.,* 2002 (Ref. 98). | Multicenter, randomized double-blind, placebo-controlled, parallel 2 X 2 factorial trial with 4-wk test period | Hypercholesterolemic adults, some using statin drugs<br>154 enrolled, 152 completed<br>Mean age ± sd<br>60 ± 9 y ($I_1$)<br>58 ± 10 y ($I_2$)<br>58 ± 11 y ($I_3$)<br>62 ± 11 y ($I_4$)<br>n = 37–29/group<br>Inclusion criteria: LDL–C ≥97 mg/dL, TG < 400 mg/dL, age >18 y<br>Australia | Two servings/d of test margarine, consumed w/meals. Drug intervention: 400 µg/day cerivastatin, or placebo tablet<br>$I_1$ = tablet + margarine<br>$I_2$ = placebo tablet + 2 g PS/d as plant sterol esters in PS-enriched margarine<br>$I_3$ = statin + placebo margarine<br>$I_4$ = statin + 2 g PS/d as plant sterol esters in PS-enriched margarine | American Heart Association Step I diet; closely supervised by a nutritionist | *Total-C* (mg/dL) Baseline:<br>$I_1$ 295<br>$I_2$ 297<br>$I_3$ 282<br>$I_4$ 298<br>*Total-C*% change at 4 wk relative to baseline:<br>$I_1$ ↑2.2%<br>$I_2$ ↓ 5.3%<br>$I_3$ ↓ 23.2%<br>$I_4$ ↓ 28.9%<br>Main effect of PS-enriched margarine: ↓ 6.7% (p < 0.0001)<br>*LDL–C* (mg/dL) Baseline:<br>$I_1$ 210<br>$I_2$ 209<br>$I_3$ 195<br>$I_4$ 209<br>*LDL–C*% change at 4 wk compared to baseline:<br>$I_1$ ↑2%<br>$I_2$ ↓ 8.2%<br>$I_3$ ↓ 32.4%<br>$I_4$ ↓ 38.5%<br>Main effect of PS-enriched margarine: ↓ 8.1% (p < 0.0001) |
| Tammi *et al.,* 2002 (Ref. 99). | Randomized double-blind, crossover trial, with two 3 month test periods separated by a 6-wk wash out period | Healthy children (age 6 y) enrolled in Finnish STRIP* study<br>81 enrolled, 79 completed<br>n = 35 F<br>n = 44 M<br>*Special Turku Coronary Risk Factor Project; subjects enrolled as infants; study diet aim was 1:1:1 ratio of PUFA:MUFA:sat fats, cholesterol < 200 mg/d | 20 g/d test margarine replaced similar amount of usual dietary fat<br>C = margarine w/o added PS<br>I = 1.6 g PS/d as plant stanol esters in PS-enriched margarine | Continuation of STRIP study diet (low sat fat, low cholesterol) that the subjects had followed for several years | *Total-C* (mg/dL) Baseline:<br>158 (boys)<br>176 (girls)<br>*Total-C*% change at 3-mo compared to control<br>$I_{boys}$ ↓ 6.4%*<br>$I_{girls}$ ↓ 4.4%*<br>*p < 0.05<br>*LDL–C* (mg/dL) Baseline:<br>98 (boys)<br>123 (girls)<br>*LDL–C*% change at 3-mo compared to control:<br>$I_{boys}$ ↓ 9.1%*<br>$I_{girls}$ ↓ 5.8%*<br>*p < 0.05 |
| Temme *et al.,* 2002 (Ref. 100). | Randomized double-blind, crossover trial; no run-in period; two consecutive 4-wk test periods | Healthy adults, 42 enrolled, 42 completed<br>Mean age ± sd<br>55 ± 9 y<br>n = 42<br>Inclusion criteria: BMI < 30, no $R_X$ or prescribed diet that affect lipids<br>Report states 70% of Belgium adult population is mildly hypercholesterolemic<br>Belgium | 3 portions/d of test margarine eaten w/meals replaced habitual margarine use<br>C = spread w/o added PS<br>I = 2.1 g PS/d as plant sterol esters in PS-enriched spread | Habitual diet ..... | *Total-C* (mg/dL) After 4 wk test period:<br>C 248<br>I 231<br>*Total-C*% change compared to control: I ↓ 6.9%*<br>*LDL–C* (mg/dL) After 4 wk test period:<br>C 166<br>I 150<br>*LDL–C* % change compared to control: I ↓ 9.6%*<br>*p < 0.05 |

TABLE 1—RANDOMIZED CLINICAL TRIALS OF PHYTOSTEROLS IN CONVENTIONAL FOODS AND TOTAL AND LDL CHOLESTEROL CONCENTRATION—Continued

| Study | Design | Population | Intervention | Diet | Results |
|---|---|---|---|---|---|
| Vanstone *et al.,* 2002 (Ref. 22). | Randomized double-blind, crossover trial; no run-in period; four 3-wk controlled test periods separated by 4-wk washout periods | Primary familial hyperlipidemia adults<br>16 enrolled, 15 completed<br>Mean age ± sd<br>47.8 ± 1.9 y<br>n = 15<br>Inclusion criteria: age 35–58 y; Total-C 201–348 mg/dL, and TG < 310 mg/dL<br>Canada | 3 portions/d test butter eaten w/meals<br>C = butter w/cornstarch added to mimic appearance of PS-enriched butter<br>$I_1$ =1.8 g PS/d as nonesterified soy sterols in PS-enriched butter<br>$I_2$ = 1.8 g PS/d as nonesterified soy stanols in PS-enriched butter<br>$I_3$ = 1.8 g PS/d as 50/50 mix of nonesterified soy sterols/stanols in PS-enriched butter | Controlled feeding of typical American diet, all food and beverage prepared/provided by study, 2 or more meals/d eaten onsite | *Total-C* (mg/dL) At end of 3 wk test period:<br>C 238<br>$I_1$ 214<br>$I_2$ 215<br>$I_3$ 216<br>*Total-C* % change compared to control:<br>$I_1$ ↓ 7.8%*<br>$I_2$ ↓ 11.9%*<br>$I_3$ ↓ 13.1%*<br>*LDL–C* (mg/dL) At end of three wk test period:<br>C 155<br>$I_1$ 139<br>$I_2$ 139<br>$I_3$ 137<br>*LDL–C* % change at 3 wk relative to placebo:<br>$I_1$↓11.3*<br>$I_2$↓13.4*<br>$I_3$↓16.0*<br>*p < 0.05<br>No significant difference between $I_1$, $I_2$ and $I_3$ |
| Christiansen *et al.,* 2001 (Ref. 24). | Randomized double-blind, parallel design; three arm, 6-wk run-in, 6-month test period | Hypercholesterolemic adults<br>155 enrolled, 134 completed<br>Mean age 50.7 y<br>n = about 45/group<br>Inclusion criteria: total-C ≥ 227 mg/dL, TG < 266 mg/dL<br>Finland | 2 servings/d of test spread (rapeseed oil margarine) in place of usual dietary fat<br>C = spread w/o added PS<br>$I_1$ = 1.5g PS/d as microcrystalline wood-derived (tall oil) nonesterified sterol/stanols in PS-enriched spread<br>$I_2$ = 3 g PS/d as microcrystalline wood-derived (tall oil) nonesterified sterol/stanols in PS-enriched spread | Habitual Finnish diet; 7-day food diaries "were kept by half of subjects." | *Total-C* (mg/dL) Baseline: 257<br>*Total-C* % change compared to control:<br>$I_1$ ↓ 9%*<br>$I_2$ ↓ 8.3%*<br>*p=0.001<br>*LDL–C* (mg/dL) Baseline: 166<br>*LDL–C* % change compared to control:<br>$I_1$ ↓ 11.3%*<br>$I_2$ ↓ 10.6%*<br>*p=0.002 |
| Davidson *et al.,* 2001 (Ref. 55). | Randomized double-blind, parallel trial; four arm, 8-wk test period | Healthy adults<br>84 randomized 77 completed<br>Mean Age 46 y<br>n = 19 (C)<br>n = 19 ($I_1$)<br>n = 18 ($I_2$)<br>n = 21 ($I_3$)<br>Inclusion criteria: total-C < 300 mg/dL, TG < 350 mg/dL, BMI < 35<br>USA | 2 servings/d of reduced-fat test spread, and 1 serving/d of reduced-fat test salad dressing<br>C = spread + salad dressing<br>$I_1$ = 3 g PS/d as sterol esters in PS-enriched spread; placebo salad dressing<br>$I_2$ = 6 g PS/d as sterol esters in PS-enriched salad dressing; placebo spread<br>$I_3$ = 9 g PS/d as sterol esters in PS-enriched spread + PS-enriched salad dressing | Habitual diet supplemented w/3 servings/d of test foods. 3-day diet records collected at wk 0, 4, and 8 | *Total-C* (mg/dL) Baseline: 205<br>*Total-C* % change compared to control:<br>$I_1$ ↓ 3.9%<br>$I_2$ ↓ 0.9%<br>$I_3$ ↓ 4.6%<br>*LDL–C* (mg/dL) Baseline: 130<br>*LDL–C* % change compared to control:<br>C ↓ 1.3%<br>$I_1$ ↓ 3.7%<br>$I_2$ ↓ 1.5%<br>$I_3$ ↓ 7.7%<br>No significant treatment effects on total-C or LDL–C |

TABLE 1—RANDOMIZED CLINICAL TRIALS OF PHYTOSTEROLS IN CONVENTIONAL FOODS AND TOTAL AND LDL CHOLESTEROL CONCENTRATION—Continued

| Study | Design | Population | Intervention | Diet | Results |
|---|---|---|---|---|---|
| Maki *et al.,* 2001 (Ref. 101). | Randomized double-blind, placebo-controlled, parallel trial, 4-wk run-in; 5-wk test period | Hypercholesterolemic adults<br>224 enrolled, 192 included in analysis<br>n = 83 (C)<br>n = 75 ($I_1$)<br>n = 35 ($I_2$)<br>Mean age ± sd<br>57.5 ± 10.8 y (C)<br>58.7 ± 10.6 y ($I_1$)<br>60.4 ± 9.7 y ($I_2$)<br>Inclusion criteria: no $R_X$ that affect lipids, BMI < 35, LDL–C 130–200 mg/dL, TG < 350 mg/dL, BMI < 35<br>USA | 2 servings/d of reduced-fat test spread eaten w/meals<br>C = spread with w/o added PS<br>$I_1$ = 1.1 g PS/d as soy sterol esters in PS-enriched spread<br>$I_2$ = 2.2 g PS/d as soy sterol esters in PS-enriched spread | National Cholesterol Education Program Step I, supplemented w/reduced-fat test spread | *Total-C* (mg/dL) Baseline: 238<br>*Total-C* % change compared to control:<br>$I_1$ ↓ 5.2%*<br>$I_2$ – 6.6%*<br>*p < 0.001<br>*LDL–C* (mg/dL) Baseline: 158<br>*LDL–C* % change compared to control:<br>$I_1$ ↓ 7.6%*<br>$I_2$ ↓ 8.1%*<br>*p < 0.001 |
| Nestel *et al.,* 2001 (Ref. 35). | Randomized single-blinded, crossover trial; 2-wk run-in, three 4-wk test periods w/o wash-out period<br>Study 1 | Hypercholesterolemic adults<br>22 enrolled, 22 completed<br>Mean age ± sd<br>60 ± 9 y<br>n = 22<br>Inclusion criteria: Total-C >213 mg/dL, TG < 266 mg/dL<br>Australia | 3 servings/d of test foods (low-fat wheat cereal, low-fat bread, spread), one serving eaten w/each meal<br>C = test foods, w/o added phytosterols<br>$I_1$ = 2.4 g PS/d as soy sterol esters in PS-enriched foods<br>$I_2$ = 2.4 g PS/d as nonesterified soy stanols in PS-enriched foods | Habitual low sat fat, low cholesterol diet prescribed for cholesterol control; diet assessed by 3-day FFQ during run-in phase | Median *Total-C* (mg/dL) at 4 wk:<br>C 271<br>$I_1$ 247*<br>$I_2$ 261*<br>*p < 0.001 compared to control<br>Median *LDL–C* (mg/dL) at 4 wk:<br>C 184<br>$I_1$ 159*<br>$I_2$ 169*<br>*p < 0.05 compared to control<br>$I_1$ significantly lower than $I_2$ |
| | Randomized single-blinded, crossover trial; 2-wk run-in followed by two 4-wk test periods w/o wash-out period<br>Study 2 | Hypercholesterolemic adults (all Study 1 participants)<br>15 enrolled, 15 completed<br>Australia | 1 serving/d of test dairy spread (butter + margarine blend) eaten w/a meal<br>C = spread w/o added PS<br>$I_3$ = 2.4 g PS/d as soy sterol esters in PS-enriched dairy spread | Habitual low sat fat, low cholesterol diet prescribed for cholesterol control | *Total-C* (mg/dL) Baseline: 257<br>*Total-C* % change compared to control: $I_3$ ↓ 9.8%*<br>*p < 0.001<br>*LDL–C* (mg/dL) Baseline: 178<br>*LDL–C* % change compared to control: $I_3$ ↓ 13.0%*<br>*p = 0.05 |
| Tikkanen 2001 (Ref. 25) .. | Double-blind, placebo-controlled, parallel trial, two arms; 2-wk run-in period w/placebo foods, 3 consecutive 5-wk periods. PS dose doubled w/each successive test period | Hypercholesterolemic adults<br>78 enrolled, 71 completed<br>Mean age ± sd<br>54 ± 11 y (C)<br>57 ± 8 y (I)<br>n = 35 (C)<br>n = 36 (I)<br>Inclusion criteria: age 25–75 y; no familial ↑total-C, no $H_X$ of CAD previous 3 mos, no $H_X$ of revascularization previous 4 mo, no $R_X$ that affect lipids, total-C 232–310 mg/dL; TG < 355 mg/dL<br>Finland | 3 servings/d of test foods/d (bread, meat, jam)<br>C = test foods w/o added PS<br>I=1.25 g PS/d for 5 wk, then 2.5 g PS/d for wks 6–10, then 5 g PS/d for wks 11–15. PS as nonesterified wood-derived sterol/stanol mixture in PS-enriched bread, meats, and jam | Subjects received individual dietary advice and kept 3-d food diaries 5 times during the study | *Total-C* (mg/dL) Baseline:<br>C 253<br>I 263<br>*Total-C* % change compared to control:<br>I $wk_5$ ↓ 4.4%<br>I $wk_{10}$ ↓ 6.2%<br>I $wk_{15}$ ↓ 5.5%<br>Significant difference between P and I by repeated measures ANOVA p < 0.05<br>*LDL–C* (mg/dL) Baseline:<br>C 166<br>I 173<br>*LDL–C* % change compared to control:<br>I $wk_5$ ↓ 5.4%<br>I $wk_{10}$ ↓ 7.9%<br>I $wk_{15}$ ↓ 8.9%<br>Significant difference between C and I by repeated measures ANOVA p < 0.05 |

TABLE 1—RANDOMIZED CLINICAL TRIALS OF PHYTOSTEROLS IN CONVENTIONAL FOODS AND TOTAL AND LDL CHOLESTEROL CONCENTRATION—Continued

| Study | Design | Population | Intervention | Diet | Results |
|---|---|---|---|---|---|
| Blair *et al.,* 2000 (Ref. 102). | Randomized double-blind, placebo-controlled, parallel trial, two arms; 8-wk test period with additional 6-wk follow-up | Hypercholesterolemic adults on statin $R_X$<br>167 randomized, 141 completed<br>Mean age ± sd<br>56 ± 10 y<br>n = 72 (C)<br>n = 69 (I)<br>Inclusion criteria: age ≥20 y; LDL–C ≥130 mg/dL, TG ≤350 mg/dL, stable statin dose for >90d<br>USA | 3 servings/d of test margarine in place of usual margarine consumptions<br>C = margarine w/o added PS<br>I = 3.0g PS/d as stanol esters in PS-enriched margarine | Habitual diet. Diets assessed by 24-hr recalls | *Total-C* (mg/dL) Baseline: 231<br>*Total-C* % change compared to control: I ↓ 7% (p < 0.0001)<br>*LDL–C* (mg/dL) Baseline: 147<br>*LDL–C* % change compared to control: I ↓ 9.6% (p < 0.0001) |
| Hallikainen *et al.,* 2000B (Ref. 39). | Randomized double-blind, crossover trial; 2-wk run-in period; three consecutive 4-wk test periods | Mildly hypercholesterolemic adults<br>42 enrolled, 34 completed<br>Mean age ± sd<br>48.8 ± 8.1 y<br>n = 34<br>Inclusion criteria: age 30–65 y, Total-C 186–271 mg/dL, TG < 220 mg/dL<br>Finland | 2–3 portions/d of test margarines eaten with meals<br>C = margarine w/o added PS<br>$I_1$ = 2 g PS/d as plant stanol ester in PS-enriched margarine<br>$I_2$ = 2 g PS/d as plant sterol ester in PS-enriched margarine | Step I diet. Diet was assessed with 4-day food records at the end of each period | *Total-C* (mg/dL) At end of 4 wk:<br>C 236<br>$I_1$ 213<br>$I_2$ 218<br>*Total-C* % change compared to control:<br>$I_1$ ↓ 9.2%*<br>$I_2$ ↓ 7.3%*<br>*p < 0.001<br>*LDL–C* (mg/dL) At end of 4 wk:<br>C 162<br>$I_1$ 141<br>$I_2$ 145<br>*LDL–C* % change compared to control:<br>$I_1$ ↓ 12.7%*<br>$I_2$ ↓ 10.4%*<br>*p < 0.001<br>$I_1$ and $I_2$ not significantly different |
| Hallikainen *et al.,* 2000a (Ref. 53). | Randomized single-blind crossover trial; 1-wk run-in period, five 3-wk test periods | Hypercholsterolemic adults<br>22 entolled, 22 completed<br>Mean age 50.5 ± 11.7<br>n = 22<br>Inclusion criteria: Total-C 194–329 mg/dL<br>Finland | 2–3 portions of test margarine w/meals<br>C = margarine w/out added PS<br>$I_1$ = 0.8 g PS/d as plant stanol esters<br>$I_2$ = 1.6 g/d PS/d as plant stanol esters<br>$I_3$ = 2.4 g PS/d as plant stanol esters<br>$I_4$ = 3.2 g PD/d as plant stanol esters | Subjects consumed a standardized background diet | *Total-C* (mg/dL) Baseline: 266 ± 50 mg/dL0<br>*Total-C* % change compared to control:<br>$I_1$ ↓ 2.8%<br>$I_2$ ↓ 6.8%*<br>$I_3$ ↓ 10.3%*<br>$I_4$ ↓ 11.3%*<br>*LDL–C* % change compared to control:<br>$I_1$ ↓ 1.7%<br>$I_2$ ↓ 5.6%<br>$I_3$ ↓ 9.7%*<br>$I_4$ ↓ 10.4%*<br>*p < 0.05 |
| Jones *et al.,* 2000 (Ref. 40). | Randomized double-blind, crossover trial; no run-in period; three 3-wk controlled feeding test periods separated by 5-wk washout periods | Hyperlipidemic males<br>18 enrolled, 15 included in analyses<br>n = 15<br>Inclusion criteria: Age 37–61 y; Total-C 232–387 mg/dL, TG < 266 mg/dL<br>Canada | 3 servings/d of test margarine, eaten with meals<br>C = margarine w/o added PS<br>$I_1$ = 1.84 g PS/d as plant sterol esters in PS-enriched margarine<br>$I_2$ = 1.84 g PS/d as plant stanol esters in PS-enriched margarine | Controlled diet formulated to meet Canadian Recommended Nutrient Intakes. All food and beverage prepared/provided by study; at least 2 meals/d eaten onsite | *Total-C* (mg/dL) Baseline:<br>C 250<br>$I_1$ 247<br>$I_2$ 246<br>*Total-C* % change compared to control:<br>$I_1$ ↓ 9.1%*<br>$I_2$ ↓ 5.5%<br>*p < 0.02<br>*LDL–C* (mg/dL) Baseline:<br>C 172<br>$I_1$ 166<br>$I_2$ 168<br>*LDL–C* % change compared to control:<br>$I_1$ ↓ 13.2%*<br>$I_2$ ↓ 6.4%* *<br>*p < 0.02<br>$I_1$ significantly lower than $I_2$ |

TABLE 1—RANDOMIZED CLINICAL TRIALS OF PHYTOSTEROLS IN CONVENTIONAL FOODS AND TOTAL AND LDL CHOLESTEROL CONCENTRATION—Continued

| Study | Design | Population | Intervention | Diet | Results |
|---|---|---|---|---|---|
| Plat *et al.* 2000 (Ref. 87) | Randomized double-blind, placebo-controlled, crossover trial. Three consecutive 4-wk test periods, no washout periods | Healthy, normal or mildly hypercholesterolemic subjects<br>40 enrolled, 39 completed<br>Mean age ± sd<br>31 ± 14 y<br>n = 39<br>Inclusion criteria: age 18–65 y; Total-C < 250 mg/dL; TG < 266; BMI < 30, BP < 160/95, no $R_X$ or diet that affect lipids, no $H_X$ of CVD<br>The Netherlands | One serving/d of test margarine and 3 servings/d of test shortening (in cookies/cakes) with each meals<br>C = margarine & shortening w/o added PS<br>$I_1$ = 2.5 g PS/d as stanol ester in PS-enriched margarine eaten w/ lunch<br>$I_2$ = 2.5 g PS/d as stanol ester in PS-enriched margarine and PS-enriched shortening divided over 3 servings w/meals | Habitual diets supplemented w/test margarine and test cookies/cake. PS-free shortening was provided to subjects for baking and cooking | *Total-C* (mg/dL)<br>At end of 4 wk:<br>C 194<br>$I_1$ 182<br>$I_2$ 181<br>*Total-C* % change compared to control:<br>$I_1$ ↓ 6.4%*<br>$I_2$ ↓ 6.6%*<br>*p < 0.001<br>*LDL–C* (mg/dL) At end of 4 wk<br>C 118<br>$I_1$ 106<br>$I_2$ 106<br>*LDL–C* % change compared to control:<br>$I_1$ ↓ 9.9%*<br>$I_2$ ↓ 10.2%*<br>*p < 0.001 |
| Vissers *et al.,* 2000 (Ref. 36). | Double-blind, crossover trial; no run-in period; three consecutive 3-wk test periods | Normal adults<br>60 enrolled, 60 completed<br>age range=18–59 y<br>n = 60<br>Inclusion criteria: age >17 y; no $R_X$ or prescribed diet that affect lipids, Total-C < 290 mg/dL, TG < 204 mg/dL<br>The Netherlands | Test margarine, divided over multiple portions, eaten with meals in place of usual margarine<br>C = margarine without added PS<br>$I_1$ = 2.1 g PS/d as rice bran nonesterified oil sterols in PS-enriched margarine (~1 g/d of 4-desmethylsterols)<br>$I_2$ = sheanut oil triterpenes in margarine | Habitual diets. Diet assessed each period with 24-h diet recall | *Total-C* (mg/dL) At end of 3 wks:<br>C 164<br>$I_1$ 157<br>$I_2$ 162<br>*Total-C* % change compared to control:<br>$I_1$ ↓ 4.5%*<br>$I_2$ ↓ 1.2%<br>*p < 0.05<br>*LDL–C* (mg/dL) At end of 3 wks:<br>C 91<br>$I_1$ 84<br>$I_2$ 89<br>*LDL–C* % change compared to control:<br>$I_1$ ↓ 8.5%*<br>$I_2$ ↓ 3.0%<br>*p < 0.05 |
| Andersson *et al.,* 1999 (Ref. 103). | Randomized double blind controlled parallel trial; 4-wk run-in period, three 8-wk test periods | Moderately hypercholesterolemic adults<br>Age ± sd<br>55.1 ± 7.9 y<br>n = 21 (C)<br>n = 19 (I)<br>Inclusion criteria: Total-C < 330 mg/dL, BMI >30<br>Sweden | 25 g/d margarine provided as 3 single servings<br>C = margarine w/o added PS<br>$I_1$ = 2 g PS/d as plant stanol esters in PS-enriched margarine | Consumed a test diet ..... | *Total-C* % change compared to baseline<br>C ↓ 8.0%<br>$I_1$ ↓ 15%*<br>*p = 0.0035<br>*LDL–C* % change compared to baseline<br>C ↓ 12%<br>$I_1$ ↓ 19%*<br>*p = 0.0158 |
| Ayesh *et al.,* 1999 (Ref. 104). | Randomized placebo-controlled parallel trial; 21 to 28 d run-in, 21–28 d test period | Healthy adults<br>24 enrolled, 21 completed<br>Age 30–40 y<br>n = 11 (C)<br>n =10 (I)<br>Inclusion criteria: Total-C 158–255 mg/dL<br>United Kingdom | 40 g/d margarine consumed at breakfast and dinner<br>C = margarine w/o added PS<br>I = 8.6 g PS/d as plant sterol esters in PS-enriched margarine | Typical British diet, breakfast and dinner consumed under supervision | *Total-C* % change compared to control:<br>I ↓ 18%*<br>*LDL–C* % change compared to control:<br>I ↓ 23%*<br>*p < 0.0001 |
| Gylling and Miettinen, 1999 (Ref. 105). | Randomized double-blind crossover trial; 1-wk run-in period; two 5 wk test periods | Moderately hypercholesterolemic, postmenopausal women; 24 enrolled<br>Age 50–55 y<br>n = 21 butter period<br>Inclusion criteria: Total-C between 213 and 310 mg/dL<br>Finland | 25 g/d butter<br>C = butter w/out added PS<br>I = 2.4 g PS/d as wood sitostanol ester in PS-enriched butter | Subjects were advised to replace 25 g of their normal dietary fat with butter | *Total-C* % change compared to control:<br>I ↓ 8%*<br>*LDL–C* % change compared to control:<br>I ↓ 12%*<br>*p < 0.05 |

TABLE 1—RANDOMIZED CLINICAL TRIALS OF PHYTOSTEROLS IN CONVENTIONAL FOODS AND TOTAL AND LDL CHOLESTEROL CONCENTRATION—Continued

| Study | Design | Population | Intervention | Diet | Results |
|---|---|---|---|---|---|
| Hendriks *et al.,* 1999 (Ref. 51). | Randomized, double-blind, crossover trial; no run-in period, four test periods of 3.5 wks | Normocholesterolemic and mildly cholesterolemic adults, 100 enrolled, 80 per test period<br>Age 19–58 y<br>n = 80<br>Inclusion criteria: Total-C < 290 mg/dL<br>The Netherlands | 25 g/d butter or spread consumed at lunch or dinner<br>$C_1$ = butter w/out added PS<br>$C_2$ = spread w/out added PS<br>$I_1$ = 0.8 g PS/d as plant sterol esters in PS-enriched spreads<br>$I_2$ = 1.6 g PS/d as plant sterol esters in PS-enriched spreads<br>$I_3$ = 3.2 g PS/d as plant sterol esters in PS-enriched spreads | Habitual diets. Spreads replace an equivalent amount of spreads habitually used | *Total-C* (mg/dL) Baseline: 197 mg/dL<br>*Total-C* % change compared to $C_2$<br>$I_1$ ↓ 4.9%*<br>$I_2$ ↓ 5.9%*<br>$I_3$ ↓ 6.8%*<br>*LDL–C* % change compared to $C_2$<br>$I_1$ ↓ 6.7%*<br>$I_2$ ↓ 8.5%*<br>$I_3$ ↓ 9.9%*<br>*p < 0.0001 |
| Jones *et al.,* 1999 (Ref. 21). | Randomized double-blind, placebo-controlled, parallel trial with 2 groups; No run-in period; 30-d test period; 20-d follow-up after test period | Hypercholsterolemic adults, 32 enrolled, 32 completed<br>Age 25–60 y<br>n = 16 (C)<br>n = 16 (I)<br>Inclusion criteria: Total-C 252–387 mg/dL<br>Canada | 30 g/d test margarine consumed with 3 meals<br>C = margarine w/o added PS<br>I = 1.7 g PS/d sistostanol-containing phytosterols (20% sitostanol, remaining plant sterols are sitosterol, campesterol) as nonesterified tall oil | Controlled feeding regimen; a prudent fixed North American diet formulated to meet Canadian recommended nutrient intakes | *Total-C* (mg/dL) Baseline:<br>C 263<br>I 260<br>*LDL–C* % change compared to control: I ↓ 15.5% (p < 0.05) |
| Nguyen *et al.,* 1999 (Ref. 106). | Multicenter randomized, double-blind, placebo-controlled parallel trial; 4-wk run-in period, 8-wk test period | Mildly hypercholesterolemic adults<br>Age ± sd<br>51.3 ± 12.0 to 54.5 ± 11.3 y<br>n = 76 (C)<br>n = 71 ($I_1$)<br>n = 77 ($I_2$)<br>Inclusion criteria: 20 y, Total-C 200 and 280 mg/dL<br>USA | 24 g/d U.S. vegetable oil spread (three 8 g servings/d)<br>C = U.S. vegetable oil spread w/out added PS<br>$I_1$ = 3 g PS/d as stanol esters in U.S. vegetable oil spread<br>$I_2$ = 2 g PS/d as stanol esters in U.S. vegetable oil spread | Usual dietary habits maintained | *Total-C* % change compared to control:<br>$I_1$ ↓ 6.4*<br>$I_2$ ↓ 4.1*<br>*p < 0.001<br>*LDL–C* % change compared to control:<br>$I_1$ ↓ 10.1*<br>$I_2$ ↓ 4.1*<br>*p < 0.02 |
| Sierksma *et al.,* 1999 (Ref. 29). | Balanced, double-blind crossover trial; 1-wk run-in, 3-wk test period | Healthy adults, 78 enrolled, 76 completed<br>Age 18–62 y<br>n = 75<br>Inclusion criteria: < Total-C < 309 mg/dL<br>The Netherlands | 25 g/d Flora spread, with meals<br>C = Flora spread w/o added PS<br>$I_1$ = 0.8 g PS/d as nonesterified sterols in PS-enriched Flora spread<br>$I_2$ = 3.3 g PS/d as esterified sterols in PS-enriched Flora spread | Habitual diets. Phytosterol-containing spread replaced all or part of habitual spread or butter used for spreading | *Total-C* (mg/dL) Baseline: 310 mg/dL<br>*Total-C* (mg/dL)<br>C 196<br>$I_1$ 188*<br>$I_2$ 194<br>*LDL–C* (mg/dL)<br>C 122<br>$I_1$ 114*<br>$I_2$ 119<br>*Total-C* % change compared to control:<br>$I_1$ ↓ 3.8%*<br>*LDL–C* % change compared to control:<br>$I_1$ ↓ 6.0%*<br>*p < 0.05 |
| Westrate and Meijer, 1998 (Ref. 31). | Balanced, Randomized double-blind crossover trial; 5-d run-in, four test periods of 3.5 wks | Normocholesterolemic and mildly hypercholesterolemic adults, 100 enrolled, 95 completed<br>Mean age ± sd<br>45 ± 12.8 y<br>n = 95<br>Inclusion criteria: Total-C < 310 mg/dL<br>The Netherlands | 30 g/d margarine consumed at lunch and dinner<br>C = Flora spread w/o added PS<br>$I_1$ = 2.7 g PS/d as plant stanol esters (2.7 g/d<br>$I_2$ = 3.0 g PS/d as soybean sterol esters<br>$I_3$ = 1.6 g PS/d as rice bran nonesterified sterols<br>$I_4$ = 2.9 g PS/day as sheanut nonesterified sterols<br>Stanol source: wood | Test margarine replaced margarines habitually used | *Total-C* (mg/dL) Baseline: 207<br>*Total-C* % change compared to control:<br>$I_1$ ↓ 7.3%*<br>$I_2$ ↓ 8.3%*<br>$I_3$ ↓ 1.1%<br>$I_4$ ↓ 0.7%<br>*LDL–C* % change compared to control:<br>$I_1$ ↓ 13%*<br>$I_2$ ↓ 13%*<br>$I_3$ ↓ 1.5%<br>$I_4$ ↓ 0.9%<br>*p < 0.05 |

TABLE 1—RANDOMIZED CLINICAL TRIALS OF PHYTOSTEROLS IN CONVENTIONAL FOODS AND TOTAL AND LDL CHOLESTEROL CONCENTRATION—Continued

| Study | Design | Population | Intervention | Diet | Results |
|---|---|---|---|---|---|
| Niinikoski *et al.,* 1997 (Ref. 107). | Randomized double-blind, placebo-controlled parallel trial; no run-in period, 5-wk test period | Normocholesterolemic adults, 24 enrolled<br>Age 24–52 y<br>n = 12 (C)<br>n = 12 (I)<br>Inclusion criteria: not provided<br>Finland | 24 g margarine consumed in 3 portions<br>C = margarine w/out added PS<br>I = 3 g PS/day as esterified sitostanol | Habitual diet. Replace normal dietary fat with test rapeseed oil margarine | *Total-C* (mg/dL) Baseline: 197<br>*Total C* % compared to control<br>C ↓ 11<br>I ↓ 31*<br>*p < 0.05 |
| Pelletier *et al.,* 1995 (Ref. 30). | Randomized, crossover trial; 1-wk run-in, two test periods of 4 wks | Normolipidemic men<br>Mean age ± sd<br>22.7 ± 2.6 y<br>n = 12<br>Inclusion criteria: light smokers and normal physical activity<br>France | 50 g/d butter as part of a normal diet<br>C =butter w/out added PS<br>I = 0.74 g PS/d as soybean nonesterified sterols | Controlled but normal diet | *Total-C* % change compared to control:<br>I ↓ 10%*<br>*LDL–C* % change compared to control:<br>I ↓ 15%*<br>*p < 0.05 |
| Miettinen *et al.,* 1994 (Ref. 28). | Randomized double-blind, placebo-controlled parallel trial; 6-wk run-in, 9-wk test period | Hypercholesterolemic adults, 31 enrolled<br>Mean age ± sd<br>45 ± 3 y<br>n = 31<br>Inclusion criteria: Total-C >232 mg/dL<br>Finland | 50 g rapeseed oil mayonnaise, with meals<br>C = mayonnaise w/out added PS<br>$I_1$ = 0.7 g PS/d as nonesterified sitosterol in mayonnaise<br>$I_2$ = 0.7 g PS/d as nonesterified sitostanol in mayonnaise<br>$I_3$ = 0.8 g PS/d as sitostanol ester in mayonnaise | Habitual diets. Advised to replace 50 g of typical daily fat with mayonnaise containing rapeseed oil | *Total-C* % change compared to control:<br>$I_1$ ↓ 7.7%<br>$I_2$ ↓ 0.4%<br>$I_3$ ↓ 7.4%*<br>*LDL–C* % change compared to control:<br>$I_1$ ↓ 7.0%<br>$I_2$ ↓ 1.2%<br>$I_3$ ↓ 7.7%*<br>*p < 0.05 |
| Blomqvist *et al.,* 1993 Vanhanen *et al.,* 1993 (Ref. 108). | Randomized double-blind placebo controlled parallel trial; 4-wk run-in, 6-wk test period | Hypercholesterolemic adults, 37 enrolled<br>Mean age ± sd<br>43–48 ± 2 y<br>n = 33 (C)<br>n =34 (I)<br>Inclusion criteria: Total-C >232 mg/dL<br>Finland | 50 g rapeseed oil mayonnaise, with meals<br>C = mayonnaise w/out added PS<br>I = 3.4 g PS/d as sitosterol ester in mayonniase | Habitual diets. Advised to replace 50 g of daily fat intake with 50 of mayonnaise containing rapeseed oil | *Total-C* % change compared to control:<br>C ↓ 2.7<br>I ↓ 17.0*<br>*LDL–C* % change compared to control:<br>C ↓ 1.5<br>I ↓ 14.3*<br>*p < 0.051 |

[1] Weight represents nonesterified sterols or stanols.

TABLE 2—RANDOMIZED CLINICAL TRIALS OF PHYTOSTEROLS IN SUPPLEMENTS AND TOTAL AND LDL CHOLESTEROL CONCENTRATION

| Study | Design | Population | Intervention | Diet | Results |
|---|---|---|---|---|---|
| **Nonesterified Phytosterols** | | | | | |
| Denke 1995 (Ref. 65) ..... | Non-random, non-blinded, 3 sequential 3-mos trial periods separated by 3-mos washout periods. | Moderately hypercholesterolemic males.<br>33 enrolled, 33 completed<br>Age range 31–70 y<br>Subjects' characteristics: mean LDL–C with Step I diet 175 mg/dL, TG < 250 mg/dL, mean BMI 26.2<br>USA | (1) Gelatin capsules containing tall oil sitostanol suspended in safflower oil; 3 doses/d of 4 capsules (total 12 capsules/d) taken with meals. (2) Cholestyramine supplied in flavored bars.<br>$I_1$ = 3 g/d sitostanol[1]<br>$I_2$ = cholestyramine<br>$I_3$ = sitostanol + cholestyramine | Step I diet (control) during intervention and washout periods. | *Total-C* (mg/dL) Baseline: 239<br>*Total-C* % change compared to Step I diet:<br>$I_1$ ↓ 0.5%<br>$I_2$ ↓ 7.1%*<br>$I_3$ ↓ 8.9%*<br>*LDL–C* (mg/dL) Baseline: 175<br>*LDL–C* % change from Sep 1 diet:<br>$I_1$ ↓ 1.8%<br>$I_2$ ↓ 12.6%*<br>$I_3$ ↓ 14.8%*<br>*p < 0.001 compared to preceding and subsequent washout periods. |

TABLE 2—RANDOMIZED CLINICAL TRIALS OF PHYTOSTEROLS IN SUPPLEMENTS AND TOTAL AND LDL CHOLESTEROL CONCENTRATION—Continued

| Study | Design | Population | Intervention | Diet | Results |
|---|---|---|---|---|---|
| McPherson *et al.,* 2005 (Ref. 66). | Randomized, double blind, placebo-controlled, parallel design; four arms; 6-wk trial period. | Healthy adults 52 enrolled, 52 completed.<br>Mean age ± sd 46.5 ± 8.1 y (tablets)<br>50.7 ± 12.5 y (capsules)<br>tablet trial<br>n = 13 ($I_T$)<br>n = 12 ($P_T$)<br>n = 27 (capsule trial)<br>Inclusion criteria: LDL–C 70–190 mg/dL, TG < 300 mg/dL<br>USA | Dietary supplement of rapidly disintegrating tablets or slowly disintegrating capsules, twice/d with meals.<br>$C_T$ = lecithin-containing tablets w/o PS.<br>$C_C$ = lecithin-containing capsules w/o PS.<br>$I_T$ = 1.26 g PS/d as spray-dried plant stanol/lecithin emulsion in tablets.<br>$I_C$ = 1.26 g PS/d as spray-dried plant stanol/lecithin emulsion in gelatin capsules. | AHA heart healthy diet ... | *Total-C* (mg/dL) Baseline:<br>$C_T$ 195<br>$I_T$ 186<br>$C_C$ 198<br>$I_C$ 203<br>*Total-C* % change compared to control:<br>$I_T$ ↓ 4.8%<br>$I_C$ ↓ 1.9%<br>No significant differences between $I_T$ and $I_C$ and control<br>*LDL–C* (mg/dL) Baseline:<br>$C_T$ 121<br>$I_T$ 117<br>$C_C$ 123<br>$I_C$ 235<br>*LDL–C* % change relative to placebo:<br>$I_T$ ↓ 10.4%*<br>$I_C$ ↓ 2.5%<br>* $p < 0.05$ compared to placebo |
| Goldberg *et al.,* 2006 (Ref. 67). | Randomized double-blind, placebo-controlled, parallel trial, 1-wk run-in, 6-wk test period. | Hyperlipidemic adults taking statins 26 enrolled, 26 completed..<br>age range 40–78 y<br>n = 13/group<br>Inclusion criteria: Stable statin dose, LDL–C >100 mg/dL, TG < 300 mg/dL<br>USA | Soy stanols as a tableted stanol/lecithin emulsion. 225 mg PS/tablet; 4 tablets twice a day before meals. Starch replaced stanol/lecithin complex in placebo tablets.<br>C = placebo tablet<br>I = 1.8 g PS/d as stanol/lecithin emulsion in tablets | American Heart Association Heart Healthy Diet. | *Total-C* (mg/dL) Baseline:<br>C 197<br>I 193<br>*Total-C* % change compared to control:<br>I ↓ 5.7% ($p < 0.05$)<br>*LDL–C* (mg/dL) Baseline:<br>C 119<br>I 112<br>*LDL–C* % change compared to placebo:<br>I ↓ 9.1% ($p < 0.05$) |
| **Esterified Phytosterols** | | | | | |
| Woodgate *et al.,* 2006 (Ref. 64). | Randomized, double-blind, placebo-controlled trial with 2 groups; 4-wk test period. | Hyperchoelsterolemic adults, 30 enrolled, 29 completed.<br>Age 33–70 y<br>Inclusion criteria: no diabetes, no cholesterol lowering Rx, no prior myocardial infarction or heart surgery | Total of 6 softgel (glyceron) capsules with breakfast and dinner.<br>C = corn oil<br>I = 1.6 g PS/d as stanol esters | Habitual diets | *Total-C* (mg/dL) Baseline:<br>C 266<br>I 267<br>*Total-C* % change compared to control<br>I ↓ 8% ($p < 0.05$)<br>*LDL–C* (mg/dL) Baseline:<br>C 207<br>I 201<br>*LDL–C* % change compared to control<br>I ↓ 9% ($p < 0.05$) |
| Acuff *et al.,* 2007 (Ref. 62). | Randomized, double-blind, placebo-controlled, sequential trial; two 4-wk test periods separated by 2-wk washout period. | Hypercholesterolemic adults, 20 enrolled, 16 completed.<br>Mean age ± sd<br>51 ± 13 y<br>Inclusion criteria: hyperlipidemia, BMI < 30, no lipid lowering $R_X$, no diseases requiring tmt, no hypertension<br>USA | 2 dietary supplement capsules/d, one capsule w/lunch, second capsule w/dinner.<br>C = soy oil capsules.<br>I = 0.8 g PS/d as plant sterol esters divided between 2 capsules | Habitual diets, diets not monitored. | *Total-C* (mg/dL) Baseline: 256<br>After 4 wk test period:<br>C 242<br>I 230<br>*Total-C* % change compared to control:<br>I ↓ 4.7% (not significant)<br>*LDL–C* (mg/dL) Baseline: 177<br>After 4 wk test period:<br>C 169<br>I 163<br>*LDL–C* % change compared to control:<br>I ↓ 3.5% ($p < 0.05$) |

TABLE 2—RANDOMIZED CLINICAL TRIALS OF PHYTOSTEROLS IN SUPPLEMENTS AND TOTAL AND LDL CHOLESTEROL CONCENTRATION—Continued

| Study | Design | Population | Intervention | Diet | Results |
|---|---|---|---|---|---|
| Earnest *et al.,* 2007 (Ref. 63). | Randomized double-blind, placebo-controlled, parallel trial with 2 groups; 12-wk test period. | Mildly hypercholesterolemic adults.<br>54 enrolled, 54 completed<br>Age 20–70 y<br>Inclusion criteria: LDL–C ≥130 mg/dL<br>USA | 4 dietary supplement capsules/d; 2 capsules w/each of 2 meals.<br>C = capsule w/o PS<br>I = 2.6 g PS/d as plant sterol esters divided among 4 capsules | Habitual diets, diets not monitored. | *Total-C* (mg/dL) Baseline:<br>C 232<br>I 243<br>After 4 wk test period:<br>C 237<br>I 234<br>*Total-C* % change compared to control:<br>I ↓ 6.0% ($p < 0.05$)<br>*LDL–C* (mg/dL) Baseline:<br>P 155<br>I 165<br>After 4 wk test period:<br>P 161<br>I 157<br>*LDL–C* % change compared to control:<br>I ↓ 9.2% ($p < 0.05$) |
| Rader and Nguyen, 2000 (Ref. 61). | Randomized, double-blind, placebo-controlled, parallel trial, two arm. 3-wk trial period. | Hypercholesterolemic adults; 160 enrolled, 156 completed.<br>n = 156<br>Inclusion criteria: Total-C 220–300 mg/dL; TG ≤350 mg/dL; good health<br>USA | 3 dietary supplement test capsules/d with meals.<br>C = placebo capsules w/o PS<br>I = 1 g PS/d as plant stanol esters divided over 3 capsules | Habitual diets | *Total-C* (mg/dL) Baseline:<br>P 245<br>I 248<br>*Total-C* % change compared to control:<br>I ↓ 3.0% ($p < 0.05$)<br>*LDL–C* (mg/dL) Baseline:<br>C 154<br>I 155<br>*LDL–C* % change compared to control:<br>I ↓ 5.2% ($p < 0.05$) |

[1] Weight represents nonesterified sterols or stanols.
Abbreviations Used in table:
C control group/period
I intervention group/period
BMI body mass index
Total-C serum total cholesterol
LDL–C serum low density lipoprotein cholesterol
wk week
y years
PS phytosterols (mixture of sterols and stanols)
mg/dL milligrams per deciliter
g gram
g/d grams per day
w/ with
w/o without
TG serum triglycerides
tmt treatment
mos months
CAD coronary artery disease
CVD cardiovascular disease
Rx prescription drugs
Hx history
Sd standard deviation
d day
RSO Rape seed oil

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