

U. S. Food and Drug Administration  
Center for Food Safety & Applied Nutrition  
Office of Premarket Approval

## Agency Response Letter GRAS Notice No. GRN 000039

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Washington, DC 20204

April 24, 2000

Judith A. Weinstein  
Novartis Consumer Health, Inc.  
560 Morris Avenue  
Building F  
Summit, NJ 07901-1312

Re: GRAS Notice No. GRN 000039

Dear Ms. Weinstein:

The Food and Drug Administration (FDA) is responding to the notice, dated January 28, 2000, that you submitted in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received your notice on January 28, 2000 and designated it as GRAS Notice No. GRN 000039.

The subject of your notice is tall oil phytosterols. The notice informs FDA of the view of Novartis Consumer Health, Inc. (Novartis) that tall oil phytosterols are GRAS, through scientific procedures, for use as a nutrient in vegetable oil spread to reduce the absorption of cholesterol from the gastrointestinal tract at a level up to 12% free phytosterols.

### **Identity, method of manufacture, and specifications**

Your notice describes the manufacturing process for tall oil phytosterols, which are extracted from tall oil soap (a by-product of the pulping process used for coniferous trees in North America and Europe) using organic solvents. The extracted phytosterols are subjected to a complexation-washing process that removes the bulk of the organic material, and the crude phytosterols are then dissolved in alcohol and crystallized. The resulting product, tall oil phytosterols, is predominantly a mixture of four phytosterols (i.e., sitosterol, sitostanol, campesterol, and campestanol). Your notice includes food grade specifications for tall oil phytosterols.

**Dietary exposure**

According to your notice, the major components of tall oil phytosterols already are present in other vegetable oil based spreads that have a similar intended use.<sup>(1)</sup> For this reason, you assert that the ingredient tall oil phytosterols provides an additional choice for consumers seeking to maintain a healthy cholesterol level through the consumption of vegetable oil spread. Thus, the intended use of tall oil phytosterols is a substitutional use that would not increase dietary exposure to its main components.

**Report of Novartis' "GRAS Panel"**

The notice includes the findings of a panel of individuals (Novartis' GRAS panel) who evaluated the data and information that are the basis for Novartis' GRAS determination. Novartis considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food.

In its report, Novartis' GRAS panel compares the composition of tall oil phytosterols to that of the two related ingredients, i.e., vegetable oil sterol esters and plant stanol esters. This comparison includes the levels of the major component phytosterols and phytostanols, the levels of minor phytosterol-like components, and the chemical form of the phytosterols and phytostanols (i.e., whether they are esterified). Novartis' GRAS panel finds that the composition of tall oil phytosterols is intermediate between that of vegetable oil sterol esters and plant stanol esters, and notes that the ester forms that are present in vegetable oil sterol esters and plant stanol esters are rapidly de-esterified *in vivo*.

Novartis' GRAS panel also considers that the level of use of tall oil phytosterols in vegetable oil-based spreads is similar to that of the phytosterol and phytostanol components of vegetable oil sterol esters and plant stanol esters. Novartis' GRAS panel further considers that the intended use of tall oil phytosterols as a nutrient in vegetable oil spread to reduce the absorption of cholesterol from the gastrointestinal tract is similar to that of vegetable oil sterol esters and plant stanol esters.

Given the similarities between the composition, level of use, and intended use of tall oil phytosterols compared to that of the related substances, vegetable oil sterol esters and plant stanol esters, Novartis' GRAS Panel concludes that the intended use of tall oil phytosterols does not raise safety questions. In addition, Novartis' GRAS panel asserts that the potential that the use of tall oil phytosterols would have adverse nutritional effects (i.e., on the uptake of fat-soluble vitamins) has been addressed and adequately resolved in the course of the determinations that vegetable oil sterol esters and plant stanol esters are GRAS.

Novartis' GRAS panel concludes that tall oil phytosterols are GRAS, through scientific procedures, when used in vegetable oil-based spreads to help maintain a healthy cholesterol level, provided that the tall oil phytosterols meet the specifications cited in its report and are used in accordance with current good manufacturing practice in an amount not to exceed 12% phytosterol plus phytostanol in the finished product.

**Data and information that Novartis describes to support its GRAS determination**

Your notice describes a series of studies conducted with free phytosterols, vegetable oil sterol esters, plant stanol esters, or tall oil phytosterols. In general, you rely on published studies conducted with free phytosterols, vegetable oil sterol esters, or plant stanol esters to determine that the major components of tall oil phytosterols are GRAS. To corroborate this determination, you describe unpublished studies conducted with tall oil phytosterols.

**Conclusions**

Based on the information provided by Novartis, as well as other information available to FDA, the agency has no questions at this time regarding Novartis' conclusion that tall oil phytosterols are GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of tall oil phytosterols. As always, it is the continuing responsibility of Novartis to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter, as well as a copy of the information in your notice that conforms to the information in proposed 21 CFR 170.36(c)(1), is available for public review and copying on the Office of Premarket Approval's homepage on the World Wide Web.

Sincerely,  
/s/  
Alan M. Rulis, Ph.D.  
Director  
Office of Premarket  
Approval  
Center for Food Safety  
and Applied Nutrition

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<sup>(1)</sup>In a submission dated January 11, 1999, Lipton informed FDA of its view that vegetable oil sterol esters are GRAS for use in vegetable oil spreads at levels up to 20% to supplement the nutritive value of the spread, and to help structure the fat phase and reduce the fat and water content of the spread. According to Lipton, the use of vegetable oil sterol esters in vegetable oil-based spreads was intended to help maintain healthy cholesterol levels as part of a diet low in saturated fat and cholesterol.

In a submission dated February 18, 1999, McNeil Consumer Healthcare informed FDA of its view that plant stanol esters are GRAS for use as a nutrient in spread at a level of 1.7 grams of plant stanol esters per serving of spread. According to McNeil, the use of plant stanol esters was intended as a nutrient in food to reduce the absorption of cholesterol from the gastrointestinal tract.

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