

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

## Agency Response Letter GRAS Notice No. GRN 000061

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Washington, DC 20204

April 18, 2001

Mark W. Empie, Ph.D.  
Vice President Regulatory and Scientific Affairs  
Archer Daniels Midland Company  
1001 North Brush College Road  
Decatur, IL 62521

Re: GRAS Notice No. GRN 000061

Dear Dr. Empie:

The Food and Drug Administration (FDA) is responding to the notice, dated November 22, 2000, that you submitted on behalf of Archer Daniels Midland (ADM) 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)). FDA received the notice on November 27, 2000 and designated it as GRAS Notice No. GRN 000061. In a letter of February 28, 2001, you provided additional clarifying information.

The subjects of the notice are plant sterols and plant sterol esters. The notice informs FDA of the view of ADM that plant sterols are GRAS, through scientific procedures, for use as an ingredient<sup>(1)</sup> in vegetable oil spreads, dressings for salad, health drinks, health bars, and yogurt-type products at a level of 1 gram per serving, and as a raw material in the manufacture of plant sterol esters for use as an ingredient in the same foods at a level of 1.65 grams (i.e., 1 gram sterol equivalent) per serving. Because evaluation that a use of a food ingredient is safe is a time-dependent judgment, ADM commits to provide production and sale data, for the purpose of monitoring usage of plant sterols and plant sterol esters, if FDA requests such data in the future.

The main sterol components of the ingredients plant sterols and plant sterol esters are beta-sitosterol, campesterol, and stigmasterol. ADM describes the manufacturing processes for plant sterols and plant sterol esters, in which the plant sterols are esterified with vegetable oil fatty acids. The sterols are derived from oil seeds such as corn, palm, soy, rape and sunflower. The fatty acids are preferentially

derived from soy, sunflower, safflower, and canola; but corn, peanut, cottonseed and palm may also be used as sources. ADM's notice includes food grade specifications for plant sterols and plant sterol esters, including a specification for lead of less than 0.1 parts per million.

ADM intends to provide to its customers plant sterols and plant sterol esters for incorporation into spreads, dressings for salad, yogurt-type products, health drinks, and health bars. ADM estimates that a total daily consumption of plant sterols for an individual who would consume all the listed products and conventional food sources of plant sterols (i.e., 0.25 grams of phytosterols per day) would be up to 5.5 grams at the mean level and up to 10.6 grams at the 90th percentile level.

ADM considers that the ingredients plant sterols and plant sterol esters are similar to the ingredient vegetable oil sterol esters, which is marketed by Lipton and which FDA previously evaluated for use in vegetable oil based spreads (Ref. 1). In ADM's view, Lipton's submission of January 11, 1999, presents a thorough evaluation of the available literature. This literature was evaluated by a panel of individuals (Lipton's GRAS panel) whom Lipton considered qualified by scientific training and experience to evaluate the safety of substances added to food. ADM notes that several relevant studies that were not publicly available at the time of Lipton's submission have now been published. Because the publicly available information draws on studies that included both sterol esters and free sterols, ADM concludes that this literature supports the safety of both of its ingredients.<sup>(2)</sup>

ADM notes that Lipton's GRAS panel set an acceptable daily intake (ADI) for vegetable oil sterol esters of 130 milligrams/kilogram/day (as the free phytosterol), equivalent to 9.1 grams per day for a 70 kg person. ADM discusses the rationale that Lipton's GRAS panel used to set this ADI.

ADM notes that its own estimated daily intake (i.e., 10.6 grams per day at the 90th percentile level) exceeds the ADI set by Lipton's GRAS panel by 16 percent. ADM discusses the rationale for its own conclusion that dietary exposure to plant sterols and plant sterol esters from ADM's proposed uses remains within a safe range. To a large extent, ADM relies on consumers' previous exposure to a drug product (i.e., *Cytellin*) marketed by Eli Lilly as a treatment for hypercholesterolemia during the 1950's to 1980's. The primary component of *Cytellin* (beta-sitosterol) was the same as the primary component of plant sterols. More than 1800 people participated in clinical studies conducted with *Cytellin* to assess effects on blood cholesterol levels, with no reported adverse effects. Individuals who used the marketed drug typically consumed dosages ranging from 9 to 30 grams per day. More recently, plant sterols as the esters have been the subject of additional studies and there has been general consumption in the United States. For all of these reasons, ADM considers that the ADI set by Lipton's GRAS panel is a conservative number.

Based on the information provided by ADM, as well as other information available to FDA, the agency has no questions at this time regarding ADM's conclusion that the ingredients plant sterols and plant sterol esters 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 plant sterols or plant sterols esters. As always, it is the continuing responsibility of ADM 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 Internet (at <http://www.cfsan.fda.gov/~lrd/foodadd.html>).

Sincerely,

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

### References

1. Letter dated April 30, 1999, from Alan Rulis of FDA to Daniel R. Dwyer.
2. Letter dated May 17, 1999, from Alan Rulis of FDA to Vivian A. Chester and Edward B. Nelson.
3. Letter dated April 24, 2000, from Alan Rulis of FDA to Judith A. Weinstein.
4. Letter dated November 27, 2000, from Alan Rulis of FDA to Steven D. McCurry.
5. Letter dated December 20, 2000, from Alan Rulis of FDA to Maury M. Bandurraga.

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<sup>(1)</sup>In describing the intended use of plant sterols and plant sterol esters, ADM asserts that plant sterols contribute nutritive value. ADM's assertion raises an issue under section 403(r) of the Federal Food, Drug, and Cosmetic Act, which lays out the statutory framework for a health claim. Under 21 CFR 101.14(b)(3)(i), the substance that is the subject of a health claim must contribute taste, aroma, or nutritive value, or any other technical effect listed in 21 CFR 170.3(o), to the food and must retain that attribute when consumed at the levels that are necessary to justify a claim. Whether plant sterols and plant sterol esters contribute nutritive value within the meaning of 21 CFR 101.14(b)(3)(i) is the purview of the Office of Nutritional Products, Labeling, and Dietary Supplements (ONPLDS) in FDA's Center for Food Safety and Applied Nutrition. The Office of Premarket Approval neither consulted with ONPLDS on this labeling issue nor evaluated the information in ADM's notice to determine whether it would support ADM's view that plant sterols and plant sterol esters contribute nutritive value.

<sup>(2)</sup>FDA has evaluated the data and information supporting the safety of similar ingredients when consumed in vegetable oil based spread and additional product categories, including dressings for salads, bars, yogurt, or vegetable oils for home use applications such as baking, frying, and salad dressings (Refs. 2-5).

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