APPENDIX A

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GRAS status of Phytosterols at a Level Necessary to Justify the Proposed Health Claim

A. *Introduction*

Pursuant to 21 CFR 101.70(f), this section provides information on how phytosterols comply with the requirements of 21 CFR 101.14(b)(3)(ii), in that the proposed use of the substance at levels necessary to justify the health claim is generally recognized as safe (GRAS).

Since 1999, phytosterols have been determined to be GRAS for use in most foods that might be the subject of the phytosterol health claim, at levels generally ranging from 0.4 g to 1.0 g per serving, with some higher levels. A list of publicly available prior safety evaluations is provided at the end of this section (paragraph G).

The health claim proposed by this petition would be used to describe a product that contains 2.0 g phytosterols or more per RACC or per serving. For purposes of this petition, Unilever determined that phytosterols are GRAS for use at 2.0 g per serving in a beverage analogous to a yogurt "smoothie" that is intended to be entirely consumed in one serving of approximately 100 mL (the "proposed beverage").

B. *Acceptable Daily Intake of Phytosterols*

On January 11, 1999, Unilever (under the name of its Lipton business unit) submitted a GRAS notification to FDA for phytosterols. That notification established an acceptable daily intake (ADI) of 130 mg/kg (or 9.1 g for a 70 kg adult) (as the free, unesterified plant sterol) based on the highest no-observed adverse effect level in a rat subchronic study.

For purposes of this petition, Unilever reevaluated this ADI by conducting a literature review and considering in detail studies published since 1999 that bear on the safety of phytosterols. Unilever concluded that the previous ADI is still appropriate because no credible reports have appeared in the scientific literature since the original GRAS determination to suggest any new adverse effects or that effects are seen at lower levels. Further, food and dietary supplement products containing phytosterols have been marketed in the United States since 1999 and no reports of adverse reactions to such products have been reported.

In 2001, Archer Daniels Midland Co. (ADM) submitted GRAS notification GRN No. 61, which referred to proposed uses of phytosterols with an estimated daily intake (EDI) of 10.6 grams per day at the 90th percentile level, exceeding our ADI by 16 percent. ADM concluded that this proposed use was GRAS and that our ADI was conservative. FDA did not disagree with this GRAS determination. Thus, there is precedent for a conclusion that use of phytosterols that somewhat exceeds the ADI of 130 mg/kg is GRAS.

C. *Estimated Daily Intake from the Proposed Use of Phytosterols*

Unilever analyzed the potential consumption of phytosterols from the proposed beverage. Drinks that are somewhat similar but do not contain phytosterols (such as yogurt smoothies) are marketed in the United States, but have not been marketed for a sufficient time to enable standard consumption data to be compiled for all relevant population groups. Moreover, such data would not necessarily provide an accurate prediction of consumption of a product that is labeled with the proposed health claim.

Products labeled with the health claim would have an intended use that includes reduction of cholesterol and the risk of heart disease, and would be labeled with a recommendation that consumption of phytosterols be at least 2.0 g total per day when eaten once a day. Thus, the most likely use of this product is by adults who will use the product once a day. The resulting intake of 2.0 g phytosterols per day would be well below the ADI.

If intake is estimated based on current consumption of yogurt drinks by adults, use of the proposed beverage would result in consumption of approximately 328 mg phytosterols per day. Although the available data do not suggest that this product would be consumed at higher levels, it is possible that an adult might consume three 100 mL servings per day (which would be approximately equal to one 12 fl. oz. bottled drink), providing a total of 6 g phytosterols. Such use would result in phytosterol intake below the ADI.

It is also possible that, although the proposed beverage would not be intended for use by children, it might be inadvertently consumed by children. Children are theoretically the most sensitive subpopulation (although adverse effects from phytosterols have not been seen in young animals in a multigeneration study). Based on sales and other survey data it appears reasonable to estimate that routine consumption by children is less than one yogurt drink per day and it would be unlikely for a child to consume more than one such drink per day. Infrequent, acute consumption by children might occur – for example, at a level analogous to that of flavored milk drinks, as high as three 100 mL servings a day.

Such infrequent use could result in daily intake of 6 g phytosterols (on the days when consumption occurs), with an EDI as follows:

$$6000 \text{ mg/d} \div 35 \text{ kg body weight} = 170 \text{ mg/kg/d}$$

Older children (or adults with lower than normal body weight) might, on a sporadic basis, consume up to four 100 mL servings per day. Mean body weights for female children (ages 6 through 12 years) and female teenagers (ages 13 through 19 years, considered to have the lowest body weight of any group of persons that might drink four 100 mL servings) were obtained from National Health and Nutrition Examination Survey (NHANES) 1999-2002 data. The intake for a teenage female under these circumstances would be:

$$8000 \text{ mg/d} \div 62 \text{ kg body weight} = 130 \text{ mg/kg/d}$$

These EDIs are at or above the ADI of 130 mg/kg. Therefore, Unilever assessed whether occasional, temporary excursions over the ADI, such as these, could be adverse for children. Exposures above the ADI are reported in the literature with no reports of adverse effects. Based on data from the medical and scientific literature, Unilever concluded that no adverse effects would result from such infrequent acute intake of phytosterols by children (or by adults with lower than normal body weight).

D. *Current Use of Phytosterols*

Unilever currently markets phytosterols in vegetable oil spreads in the United States. In 2005, Unilever received no complaints from consumers about possible adverse effects from these products. Phytosterol-containing products are also marketed by other companies in the United States; no complaints about those products are known to have been publicly reported as of January 2006.

Because the health claim requested by this petition would include a recommendation that consumption of phytosterols be at least 2.0 g total per day when eaten once a day, this proposed use of phytosterols is expected to substitute for approximately two servings of other phytosterol-containing products (most of which would contain from 0.4 to 1.0 of phytosterols per serving). Thus, this proposed use is not anticipated to result in increased consumption of phytosterols.

E. *Labeling*

The proposed product will be labeled with the health claim requested by this petition, which will include a recommendation that consumption of phytosterols be at least 2.0 g total per day when eaten once a day. Although phytosterol-containing products are safe for use by children and pregnant and nursing women, such products may not be good nutritional choices for these subpopulations, and therefore the product will be labeled with a statement such as "Not recommended for use by children or women who are pregnant or nursing." These labeling statements will provide information to help consumers assure that their use of the product is nutritionally appropriate.

F. *Conclusion*

Using generally available and accepted scientific data, information, methods, and principles, there is reasonable certainty that phytosterols, meeting appropriate specifications and produced by current good manufacturing practice, will not be harmful when used at 2.0 g per serving in the proposed beverage. In reaching this conclusion, Unilever relied on the advice of a qualified, independent scientific expert that conducted a review of the scientific literature and analyzed consumption data, and also considered prior GRAS determinations for phytosterols that have not been questioned by FDA. Unilever also relied on the critical evaluation of this information by a panel of independent experts qualified by scientific training and experience to evaluate the safety of substances added to food. This panel concluded that the proposed use of phytosterols is safe

and GRAS, and that other qualified experts would concur with this opinion. Accordingly, Unilever concludes that the proposed use of phytosterols is GRAS based on scientific procedures within the meaning of 21 CFR 170.30.[1]

Based on this conclusion, the petitioner has satisfied the requirement of 21 CFR 101.14(b)(3)(ii) to demonstrate that the use of phytosterols at the levels necessary to justify the proposed health claim is safe and lawful.

G. *Summary of Previous GRAS Determinations for Phytosterols*

- *Letter of January 11, 1999 from Lipton to FDA*: vegetable oil sterol esters are GRAS in vegetable oil spreads at levels up to 20% (ADI = 130 mg/kg/day expressed as free phytosterols). (Amended by letter of September 24, 1999 regarding dressings for salad.)

- *Letter of February 18, 1999 from McNeil Consumer Healthcare to FDA*: plant stanol esters are GRAS in spread at a level of 1.7 grams of plant stanol esters per serving.

- *GRAS Notification by Novartis Consumer Health (GRN No. 39)*: tall oil phytosterols are GRAS in vegetable oil spreads at levels up to 12% free phytosterols.

- *GRAS Notification by Cargill Inc. (GRN No. 48)*: vegetable oil phytosterol esters are GRAS in vegetable oil spreads, dressings for salads, bars, and yogurt.

- *GRAS Notification by the Procter & Gamble Co. (GRN No. 53)*: phytosterol esters are GRAS in vegetable oil up to 13.3% for home use applications.

- *GRAS Notification by ADM (GRN No. 61)*: plant sterols are GRAS in vegetable oil spreads, dressings for salad, health drinks, health bars, and yogurt-type products at a level of 1 g per serving. ADM stated that its estimated daily intake (i.e., 10.6 grams per day at the 90th percentile level) exceeded the ADI set by Lipton (9.1 grams per day) by 16 percent, and that this level is safe.

- *GRAS Notification by Teriaka Ltd. (GRN No. 112)*: phytosterols are GRAS in margarine and vegetable-based spreads; yogurt and yogurt-like products; milk-based juice beverages; ice cream and non-standardized ice cream products; cream cheese and cream cheese-like products; snack bars (health bars); salad dressing, mayonnaise, French dressing, and dressings for salads; and white breads, white rolls and buns, and comparable non-standardized white bread products.

- *GRAS Notification by ADM (GRN No. 176)*: phytosterols are GRAS in various foods including margarines and vegetable oil spreads, dressings for salads, beverages, snack bars, dairy analogs (including soy milk, ice cream and cream substitutes), cheese and cream, baked foods, ready-to-eat breakfast cereals, mayonnaise, pasta and noodles,

[1] A copy of the detailed basis for this GRAS determination is available upon request.

sauces, salty snacks, processed soups, puddings, yogurt, confections, and vegetarian meat analogs at a level up to 0.4 g sterol equivalents per serving and in fruit/vegetable juices at a level up to 1 g sterol equivalents per serving.

- *GRAS Notification by Heart Blend Foods (GRN No. 177)*: plant sterol esters are GRAS in ground roasted coffee at 1.0 g per serving.

- *GRAS Notification by Michael Foods (GRN No. 181)*: phytosterols are GRAS in egg substitutes and related products at levels up to 1.1 g per serving.