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GRAS Notice Review

August 15, 2011

Dr. Mary Ditto
Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Dear Dr. Ditto:

Re: GRAS Notification for Vegetable Oil and Tall Oil Derived Phytosterol and Phytosterol Ester Formulations (CoroWise™ Phytosterols)

In accordance with proposed 21 CFR §170.36 [Notice of a claim for exemption based on a Generally Recognized as Safe (GRAS) determination] published in the *Federal Register* [62 FR 18938 (17 April 1997)], I am submitting in triplicate, as the notifier [Cargill Incorporated, 15407 McGinty Road West, Wayzata, MN, 55391 USA], a Notice of the determination, on the basis of scientific procedures, that phytosterols derived from vegetable and tall oils, both free and esterified with common dietary fatty acids, produced by Cargill Incorporated, as defined in the enclosed documents, is GRAS under specific conditions of use as a food ingredient, and therefore, is exempt from the premarket approval requirements of the *Federal, Food, Drug and Cosmetic Act*. Information setting forth the basis for the GRAS determination, which includes detailed information on the notified substance, information on self-limiting levels of use, and a summary of the basis for the GRAS determination, as well as a consensus opinion of an independent panel of experts in support of the safety of vegetable oil and tall oil derived phytosterol and phytosterol ester formulations (CoroWise™ Phytosterols) under the intended conditions of use, also are enclosed for review by the agency.

Should you have any questions or concerns regarding this GRAS Notice, please do not hesitate to contact me at any point during the review process so that we may provide a response in a timely manner.

Sincerely,

(b) (6)

Kristen Dammann, Ph.D., R.D.
Cargill Incorporated

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Generally Recognized as Safe (GRAS) Exemption Claim for Vegetable Oil and Tall Oil Derived Phytosterol and Phytosterol Ester Formulations (CoroWise™ Phytosterols)

Submitted to:

Office of Food Additive Safety (HFS-200)
Center for Food Safety & Applied Nutrition (CFSAN)
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD
USA 20740-3835

Submitted by:

Cargill Incorporated
15407 McGinty Road West
Wayzata, MN
55391

August 11, 2011

Generally Recognized as Safe (GRAS) Exemption Claim for Vegetable Oil and Tall Oil Derived Phytosterol and Phytosterol Ester Formulations (CoroWise™ Phytosterols)

Table of Contents

Page

I GRAS EXEMPTION CLAIM 3
- I.A Claim of Exemption from the Requirement for Premarket Approval Pursuant to Proposed 21 CFR §170.36(c)(1) [62 FR 18938 (17 April 1997) (U.S. FDA, 1997)] 3
- I.B Name and Address of Notifier 3
- I.C Common Name of the Notified Substance 3
- I.D Conditions of Intended Use in Food 4
  - I.D.1 Intended Uses of Phytosterols/Phytosterol Esters and Levels of Use 4
  - I.D.2 Estimated Consumption of Phytosterols Based upon Intended Uses 6
- I.E Basis for the GRAS Determination 7
- I.F Availability of Information 8

II. DETAILED INFORMATION ABOUT THE SOURCE AND IDENTITY OF THE SUBSTANCE 8
- II.A Source and Identity 8
- II.B Method of Manufacture 11
- II.C Specifications and Analytical Data 13
- II.D Additional Compositional Characterization 14
  - II.D.1 Impurities 14
  - II.D.2 Cargill's CoroWise™ Product Formulations 15
  - II.D.3 CoroWise™ Formulations – Product Specifications and Analytical Data 17
- II.E Stability 19
  - II.E.1 Shelf Life 20

III. SELF-LIMITING LEVELS OF USE 20

IV. BASIS FOR GRAS DETERMINATION 20
- IV.A Documentation to Support the Safety of Phytosterols 20
- IV.B Natural Occurrence and Background Dietary Consumption of Phytosterols 21
- IV.C Current Regulatory Status 21
  - IV.C.1 United States 21
  - IV.C.2 Canada 23
  - IV.C.3 European Union 23
  - IV.C.4 Australia and New Zealand 24

000004

IV.C.5 Regulatory Status Summary 25
IV.D Summary of Safety Information and Basis for GRAS Conclusion 26

V. REFERENCES 30

APPENDICES

Appendix A Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS) Status of Vegetable Oil and Tall Oil Derived Phytosterol and Phytosterol Ester Formulations (CoroWise™ Phytosterols)

List of Figures and Tables

Figure II.A-1 Empirical and Structural Formula and Molecular Weight 10
Figure II.B-1 Flow Diagram - Vegetable Oil Phytosterol Manufacturing 11
Figure II.B-2 Flow Diagram - Tall Oil Phytosterol Manufacturing 12

Table I.D.1-1 Summary of the Individual Proposed Food-Uses and Use-Levels for Phytosterols/Phytosterol Esters in the U.S. 4
Table II.C-1 Vegetable Oil and Tall Oil Phytosterol Specifications 14
Table II.C-2 Vegetable Oil and Tall Oil Phytosterol Ester Specifications 14
Table II.D.1-1 Vegetable Oil and Tall Oil Phytosterols – Impurities 15
Table II.D.1-2 Vegetable Oil Phytosterols – Residual Solvents 15
Table II.D.2-1 Cargill Product Formulations 16
Table II.D.2-2 Formulation Ingredients and Processing-Aids Used in Production of Cargill's CoroWise™ Products 17
Table II.D.3-1 Cargill Product Formulations – Specification and Analytical Data 17
Table IV.C.1-1 Current U.S. Food and Drug Administration Notified GRAS Uses of Phytosterols 22
Table IV.C.3-1 Current Commission Decisions Permitting Use of Phytosterols/ Phytostanols in Food 24
Table IV.C.4-1 Food Standard Code Permitting Use of Phytosterols/Phytostanols in Food 25

000005

I GRAS EXEMPTION CLAIM

I.A Claim of Exemption from the Requirement for Premarket Approval Pursuant to Proposed 21 CFR §170.36(c)(1) [62 FR 18938 (17 April 1997) (U.S. FDA, 1997)]

Vegetable oil and tall oil derived phytosterol and phytosterol ester formulations (CoroWise™ Phytosterols) have been determined to be Generally Recognized as Safe (GRAS) by Cargill Incorporated (Cargill) for use in conventional foodstuffs, consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act*. This determination is based on scientific procedures as described in the following sections. Therefore, the use of phytosterols derived from vegetable and tall oils, both free and esterified with common dietary fatty acids in foods as described below is exempt from the requirement of premarket approval.

Signed,

(b) (6) [redacted]

08-11-2011
Date

I.B Name and Address of Notifier

Kristen Dammann, Ph.D., R.D.
Cargill Incorporated
15407 McGinty Road West
Wayzata, MN
55391

I.C Common Name of the Notified Substance

The common names of the notified substance are:

Plant sterols/stanols
Plant sterol/stanol esters
Phytosterols/phytostanols
Phytosterol/phytostanol esters

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The major free phytosterols and phytostanols present in vegetable oil and tall oil derived ingredients are listed below. In some formulations these compounds will be esterified to vegetable oil fatty acids.

Sitosterol
Sitostanol
Campesterol
Campestanol
Stigmasterol
Brassicasterol

Example of esterified form: Campesterol stearate

I.D Conditions of Intended Use in Food

I.D.1 Intended Uses of Phytosterols/Phytosterol Esters and Levels of Use

Cargill intends to market phytosterols/phytostanols derived from vegetable and tall oils, both free and esterified with common dietary fatty acids, as ingredients for use in conventional foodstuffs at 0.5 or 1.0 g/serving. These use levels are consistent with the proposed revised health claims for plant sterol/stanol esters (U.S. FDA, 2010; 75 FR 76526). The individual proposed food-uses and maximum use-levels for the individual components of phytosterols are summarized in Table I.D.1-1

Table I.D.1-1 Summary of the Individual Proposed Food-Uses and Use-Levels for Phytosterols/Phytosterol Esters in the U.S.

Food Category	Proposed Food-Uses	Serving Size* (g or mL)	Phytosterols Level (g/serving)	Use-Level (%)
Alcoholic Beverages	Wine	240	0.5	0.21
Baked Goods and Baking Mixes	Bagels and English Muffins	55	0.5	0.91
	Biscuits	55	0.5	0.91
	Bread (whole grain and dietary fiber bread)[1]	50	0.5	1.00
	Breadcrumbs	30	0.5	1.67
	Cookies (low fat)	30 to 40	0.5	1.25 to 1.67
	Crackers	30	0.5	1.67
	French Toast, Pancakes, and Waffles	85 to 110	0.5	0.45 to 0.59
	Muffins	55	0.5	0.91
	Pizza Crusts	55	0.5	0.91
	Tortillas	55	0.5	0.91
Beverages and Beverage Bases	Cereal Beverages	240	1.0	0.42
	Non-Dairy Meal Replacement Beverages	240	1.0	0.42
Breakfast Cereals	Cooked Cereals	240	1.0	0.42

Table I.D.1-1 Summary of the Individual Proposed Food-Uses and Use-Levels for Phytosterols/Phytosterol Esters in the U.S.

Food Category	Proposed Food-Uses	Serving Size* (g or mL)	Phytosterols Level (g/serving)	Use-Level (%)
	RTE Breakfast Cereals (healthy adult cereals)	15 to 55	1.0	3.33 to 6.67
Cheeses	Cottage Cheese[1]	110	1.0	0.91
	Cream Cheese and Cheese Spreads[1]	30	0.5	1.67
	Natural Cheese[1]	30	0.5	1.67
	Processed Cheese[1]	30	0.5	1.67
Coffee and Tea	Coffee and Substitutes	240	0.5	0.21
	RTD Tea Beverages	240	1.0	0.42
Condiments and Relishes	Ketchup	15	0.5	3.33
Dairy Product Analogs	Cream Substitutes	15	1.0	6.67
	Imitation Milk (soy)	240	1.0	0.42
Egg Products	Egg Substitutes	50	1.0	2.00
Fats and Oils	Butter	15	1.0	6.67
	Margarine[1] and Margarine-like Spreads	15	1.0	6.67
	Mayonnaise[1] and Mayonnaise-Type Dressings	15	1.0	6.67
	Salad Dressings[1]	30	1.0	3.33
	Vegetable Oils (including olive oil)	15	1.0	6.67
Fish Products	Frozen Fish Dinners	85	0.5	0.59
Frozen Dairy Desserts and Mixes	Frozen Yogurt	120	0.5	0.42
	Ice Cream[1]	120 to 240	0.5	0.21 to 0.42
Grain Products and Pastas	Frozen Dinners	85	0.5	0.59
	Grain-Based Dishes (rice, barley, lentils)	140 to 195	0.5	0.26 to 0.36
	Health Bars (breakfast, granola, protein)	40	1.0	2.50
	Pasta and Noodles[1]	140	1.0	0.71
Gravies and Sauces	Sauces (including white, tomato, salsa, and vegetable-based sauces)	5 to 60	0.5	0.83 to 10.00
Hard Candy	Hard Candy and Mints	2	0.5	25.00
Herbs, Seeds, Spices, Seasonings, Blends, Extracts, and Flavorings	Spices[2]	1.25	1.0	80.00
Jams and Jellies	Jams, Jellies, and Preserves[1]	15	0.5	3.33
Milk, Whole, and Skim	Fluid Milk[1]	240	1.0	0.42
Milk Products	Dairy-Based Creamers[1]	15 to 30	1.0	3.33 to 6.67
	Flavored Milk Beverages	120 to 240	1.0	0.42 to 0.83
	Meal Replacement Beverages	240	1.0	0.42
	Sour Cream and Dips[1]	30	1.0	3.33

Table I.D.1-1 Summary of the Individual Proposed Food-Uses and Use-Levels for Phytosterols/Phytosterol Esters in the U.S.

Food Category	Proposed Food-Uses	Serving Size* (g or mL)	Phytosterols Level (g/serving)	Use-Level (%)
	Yogurt[1]	225	1.0	0.44
Nuts and Nut Products	Nut Butters	30	0.5	1.67
Processed Fruits and Fruit Juices	Dried Fruits	40	0.5	1.25
	Fruit Drinks and Ades	240	1.0	0.42
	Fruit Juices and Smoothies	240	1.0	0.42
	Fruit-Based Nectars	240	1.0	0.42
Processed Vegetables and Vegetable Juices	Vegetable Juices	240	1.0	0.42
Snack Foods	Savory Snacks (potato, popcorn, pretzel, corn, rice cakes)	30	1.0	3.33
Soft Candy	Chocolate Confectionary and Chewy Candies	40	0.5	1.25
Soups and Soup Mixes	Soups (vegetable and pasta-based)	245	0.5	0.20

RTD = ready-to-drink; RTE = ready-to-eat
[1] These food-uses represent non-standardized food products; however, in order to obtain a conservative intake estimate, surrogate codes for the standardized food products were chosen.
[2] Spices include caraway seeds, chili powder, chives, cinnamon, cloves, coriander, cumin seed, curry powder, dill seed, garlic powder, ginger (ground), mustard seed, nutmeg, onion (powder), paprika, pepper, sage, thyme, and turmeric.
* RACC – Reference Amounts Customarily Consumed Per Eating Occasion (21 CFR §101.12) (U.S. FDA, 2011a). When a range of values is reported for a proposed food-use, particular foods within that food-use may differ with respect to their RACC.

I.D.2 Estimated Consumption of Phytosterols Based upon Intended Uses

The consumption of phytosterols/phytosterol esters from the proposed food uses was estimated using the National Center for Health Statistics' (NCHS) 2003-2004 and 2005-2006 National Health and Nutrition Examination Surveys (NHANES) (CDC, 2006; USDA, 2009).

Approximately 97.2% of the total U.S. population was identified as potential consumers of phytosterols from proposed food-uses (16,224 actual users identified). A high percentage of users were identified in each of the individual population groups (99.9 to 100.0%), with the exception of the infant population group (75.7% users). As a result of the high percentage of users identified within all population groups, except for the infant population group, the intake estimates for the all-person and all-user categories were similar; therefore, only the all-user results are discussed in detail. Consumption of proposed food-uses by the total U.S. population resulted in an estimated mean all-user intake of phytosterols of 6.6 g/person/day (120 mg/kg body weight/day). The 90th percentile all-user intake of phytosterols from proposed food-uses by the total population was 11.0 g/person/day (244 mg/kg body weight/day).

The intake methodology used is generally considered to be "worst case" as a result of several conservative assumptions made in the consumption estimates. For example, it is often assumed that all food products within a food category contain the ingredient at the maximum specified level of use. In addition, it is well established that the length of a dietary survey affects the estimated consumption of individual users. Short-term surveys, such as the typical 2- or 3-day dietary surveys, overestimate the consumption of food products that are consumed relatively infrequently.

I.E Basis for the GRAS Determination

Pursuant to Title 21, Section 170.30 of the *Code of Federal Regulations* (CFR) (U.S. FDA, 2011b), phytosterols has been determined to be GRAS on the basis of scientific procedures. This GRAS determination is based on data generally available in the public domain pertaining to the safety of phytosterols/phytosterol esters, as discussed herein, the permitted uses of several comparable phytosterol/phytosterol ester formulations in the marketplaces of the United States (U.S.), the European Union (EU), Japan, Australia, and New Zealand, as well as a consensus among a panel of experts who are qualified by scientific training and experience to evaluate the safety of the phytosterol/phytosterol ester ingredients as components of food [see Appendix A, entitled "Expert Panel Consensus Report Regarding the Generally Recognized as Safe (GRAS) Status of Vegetable Oil and Tall Oil Derived Phytosterol and Phytosterol Ester Formulations (CoroWise™ Phytosterols)]".

At the request of Cargill, an Expert Panel ("the Expert Panel") of independent scientists, qualified by their relevant national and international experience and scientific training to evaluate the safety of food ingredients, was specially convened to conduct a critical and comprehensive evaluation of the available pertinent data and information, and to determine whether the intended uses of phytosterols derived from vegetable and tall oils, both free and esterified with common dietary fatty acids in foods is safe and suitable and would be GRAS based on scientific procedures.

The Panel consisted of the below-signed qualified scientific experts: Professor Joseph F. Borzelleca, Ph.D. (Virginia Commonwealth University School of Medicine), Professor John Doull, Ph.D., M.D. (University of Kansas Medical Center) and Professor Robert J. Nicolosi, Ph.D. (University of Massachusetts Lowell).

The Expert Panel convened on behalf of Cargill independently and collectively, and critically evaluated the data and information summarized herein and concluded that the intended uses in conventional foods described herein for phytosterols derived from vegetable and tall oils, both free and esterified with common dietary fatty acids, meeting appropriate food-grade specifications and manufactured according to current Good Manufacturing Practice (cGMP), are safe and suitable and GRAS based on scientific procedures. It also is the Expert Panel's

opinion that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion.

Phytosterols derived from vegetable and tall oils, both free and esterified with common dietary fatty acids are GRAS based on scientific procedures for its intended use as a food ingredient; therefore, it is excluded from the definition of a food additive, and thus, may be marketed and sold for its intended purpose in the U.S. without the promulgation of a food additive regulation under Title 21 of the CFR.

I.F Availability of Information

The data and information that serve as the basis for this GRAS Notification will be sent to the U.S. Food and Drug Administration (FDA) upon request, or will be available for review and copying at reasonable times at the offices of:

Cargill Incorporated
15407 McGinty Road West
Wayzata, MN
55391

Should FDA have any questions or additional information requests regarding this notification, Cargill will supply these data and information.

II. DETAILED INFORMATION ABOUT THE SOURCE AND IDENTITY OF THE SUBSTANCE

II.A Source and Identity

Phytosterols and phytostanols are naturally occurring compounds present in numerous types of plants. The phytosterols present in vegetable oil seeds are used as a source of vegetable oil phytosterols and those obtained from various species of coniferous trees are used as a source of tall oil phytosterols.

Common or Usual Name:

Plant sterols/stanols
Plant sterol/stanol esters
Phytosterols/phytostanols
Phytosterol/phytostanol esters

The major free phytosterols and phytostanols present in vegetable oil and tall oil derived ingredients are listed below. In some formulations these compounds will be esterified to vegetable oil fatty acids.

Sitosterol
Sitostanol
Campesterol
Campestanol
Stigmasterol
Brassicasterol

Example of esterified form: Campesterol stearate

Chemical Name(s)/Chemical Abstract Service (CAS) Number:

Since the products are not single compound ingredients, CAS numbers do not exist. However, chemical names and CAS numbers for the major phytosterol and phytostanol constituents are shown below. No CAS numbers for the esterified forms have been assigned.

Sitosterol: (3β)-Stigmast-5-en-3-ol	(CAS# 83-46-5)
Sitostanol: (3β, 5α)-Stigmastan-3-ol	(CAS# 83-45-4)
Campesterol: (3β)-Ergost-5-en-3-ol	(CAS# 474-62-4)
Campestanol: (3β, 5α)-Ergostan-3-ol	(CAS# 474-60-2)
Stigmasterol: (3β)-Stigmasta-5,22-dien-3-ol	(CAS# 83-48-7)
Brassicasterol: (3β)-Ergosta-5,22-dien-3-ol	(CAS# 474-67-9)

Trade Name(s): CoroWise™

Cargill intends to market the following vegetable oil derived and tall oil derived phytosterol products:

Vegetable Oil Phytosterols and Product Formulations

- CoroWise™ PS-100 (Vegetable Oil Phytosterols)
    - CoroWise™ FG-50 [Powdered (prill) Vegetable Oil Phytosterols]
    - CoroWise™ FP-100 (Powdered Vegetable Oil Phytosterols)
    - CoroWise™ FP-300 (Granular Vegetable Oil Phytosterols)
    - CoroWise™ FP-400 (Granular Vegetable Oil Phytosterols)
    - CoroWise™ PSD-100 (Pulp-Vegetable Oil Sterol Dispersion)
    - CoroWise™ ES-200 (Emulsified Vegetable Oil Phytosterols)

Vegetable Oil Phytosterol Esters and Product Formulations

- CoroWise™ SE-C100 (Vegetable Oil Phytosterol Esters)
    - CoroWise™ WDSE-33 (Water Dispersible Vegetable Oil Phytosterol Esters)

Tall Oil Phytosterols and Product Formulations

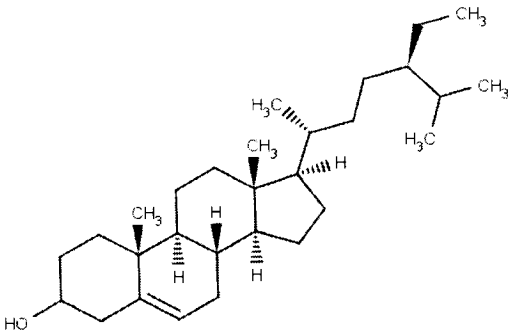
- CoroWise™ Tall Oil Phytosterols (not a commercial product until in a formulation)
    - CoroWise™ FP-100E (Powdered Tall Oil Phytosterols)

- CoroWise™ FP-300E (Granular Tall Oil Phytosterols)
- CoroWise™ PSD-100E (Pulp-Tall Oil Sterol Dispersion)
- CoroWise™ ES-101E (Emulsified Tall Oil Phytosterols)

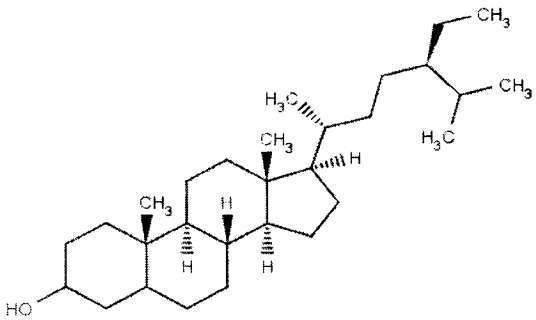
Tall Oil Phytosterol Esters and Functional Products

- CoroWise™ SE-C102E (Tall Oil Phytosterol Esters).

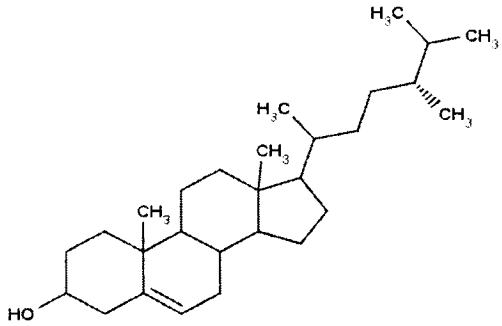
Figure II.A-1 Empirical and Structural Formula and Molecular Weight



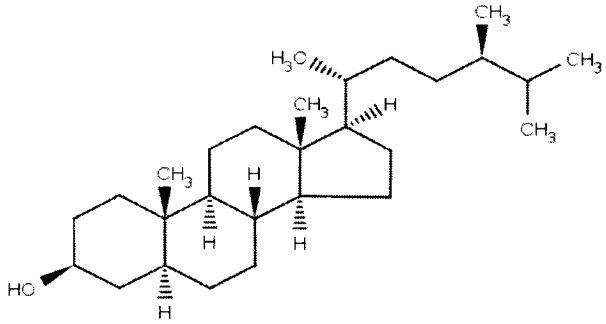
Sitosterol: $C_{29}H_{50}O$
MW = 414.71



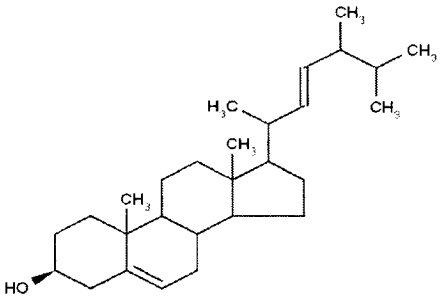
Sitostanol: $C_{29}H_{52}O$
MW = 416.73



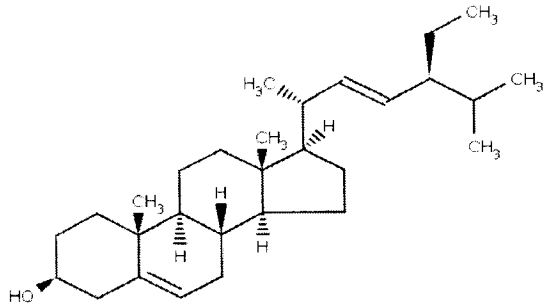
Campesterol: $C_{28}H_{48}O$
MW = 400.69



Campestanol: $C_{28}H_{50}O$
MW = 402.70



Brassicasterol: $C_{28}H_{46}O$
MW = 398.67



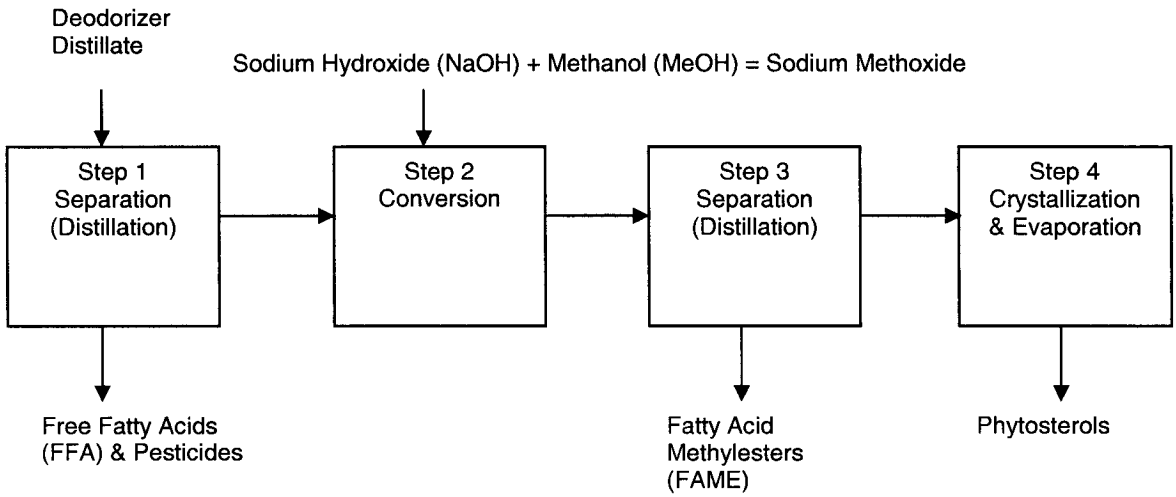
Stigmasterol: $C_{29}H_{48}O$
MW = 412.70

II.B Method of Manufacture

Vegetable Oil Phytosterols

Plant sterols can be extracted from vegetable oil deodorizer distillate, which is a by-product obtained during the vegetable oil refining process. The isolation of phytosterols from the deodorizer distillate raw material occurs at high temperatures and vacuums, and the first step is to remove the free fatty acids through a distillation process. The product then undergoes a transesterification reaction during which any residual neutral oils (tri, di, and monoglycerides) are converted to fatty acid methyl esters (FAME) (Figure II.B-1), which occurs under a high pressure reaction catalyzed by sodium methoxide. During this reaction, any sterol esters found in the raw material are converted to free sterols and FAME. Through the use of distillation, the FAME are removed, and the stream with a high concentration of sterols and tocopherol are isolated and processed using a solvent crystallization step that separates the sterols from the tocopherols. The sterols are than purified and packaged. All processing aids used in the manufacture of phytosterols/phytosterol esters are used in compliance with appropriate federal regulations.

Figure II.B-1 Flow Diagram - Vegetable Oil Phytosterol Manufacturing

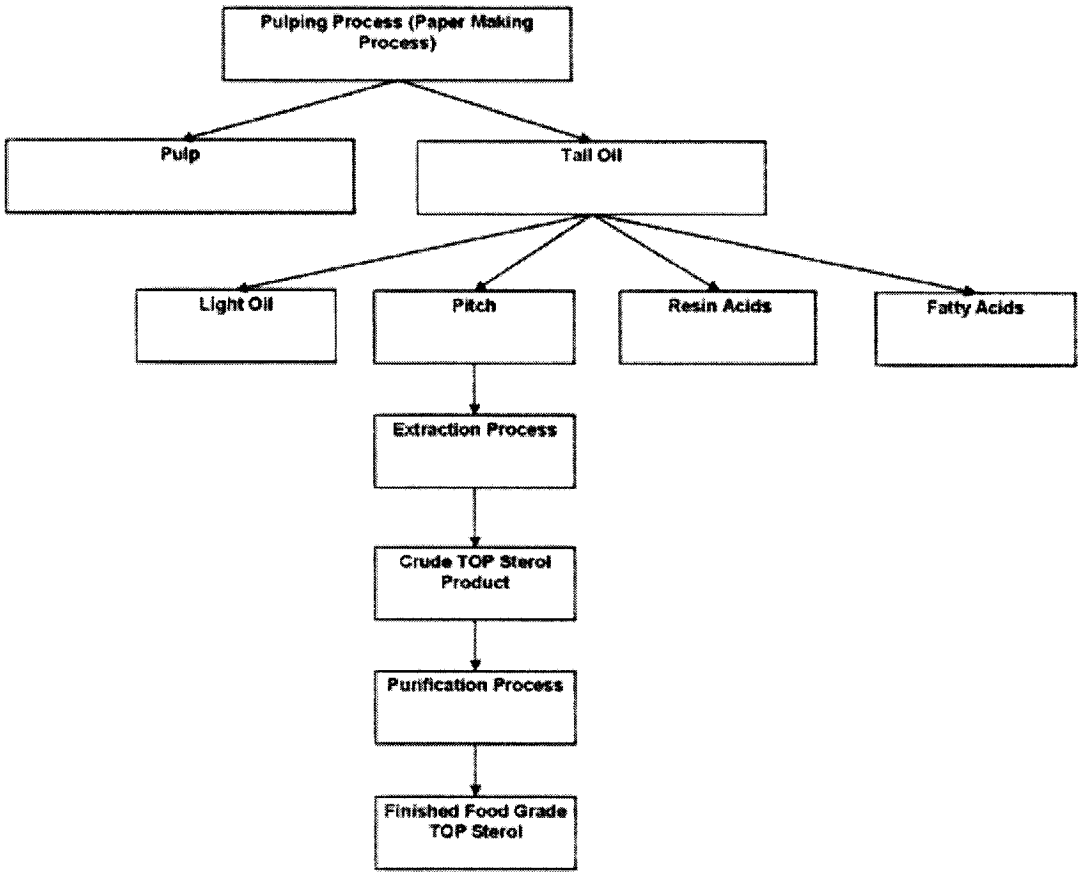


Tall Oil Phytosterols

Phytosterols are obtained from tall oil of pine trees (mainly *Pinus elliottii* and *Pinus taeda*), and are manufactured using the following process (see Figure II.B-2). First the tall oil pitch is saponified with caustic soda to obtain a mixture of free sterols and organic salts. The phytosterols are then concentrated using several steam evaporation stages to separate the sterols from the residual organic salts. The phytosterols are further concentrated by distillation to obtain a high sterol concentration fraction. The crude phytosterols are then crystallized using

a mixture of organic solvents, and the crystals recovered by filtration. In the final stage of the manufacturing process, the crystals are dried under vacuum to remove any remaining solvent and prilled to produce a pure (~99%) phytosterol product. Cargill sources food grade tall oil from various suppliers depending on market prices. The product is GRAS for use in the U.S., and complies with EC 2004/333/EC Annex 2 (Commission of the European Communities, 2004a).

Figure II.B-2 Flow Diagram - Tall Oil Phytosterol Manufacturing



Phytosterol Esters - CoroWise™ (SE-C100; SE-C102E)

Cargill's phytosterol ester products (CoroWise™ SE-C100 and SE-C102E) are produced by reacting vegetable oil or tall oil derived sterols with FAME in the presence of a catalyst (sodium methoxide). The fatty acids are typically obtained from soy, canola, sunflower, or other

vegetable oils (as desired in the finished product). Methanol is produced as a by-product of esterification; however, it is removed during processing[1].

In the first step, sterol and FAME are mixed in a reactor and dried under vacuum at an elevated temperature to remove water. The esterification reaction is initiated and catalyzed by the addition of sodium methoxide. The reaction is carried out at >100°C under varying degrees of vacuum. Under these conditions the majority of methanol that is liberated during the reaction is removed. When the reaction is complete, the product is cooled to <100°C and water is added to deactivate the catalyst, which is converted irreversibly to sodium hydroxide and methanol. The water contains most of the sodium hydroxide, methanol, and fatty acid soaps and is separated from the product stream by centrifugation.

After the reaction is complete and the catalyst removed, multiple adsorbents are used to remove trace components and color bodies. Silica (Trysil™) is used to remove any remaining traces of polar compounds (mainly sodium hydroxide and fatty acid soaps). Bleaching clay is then added to remove color bodies and to aid in filtration.

In the final processing step, excess FAME and minor impurities, as well as flavor and odor components are removed by vacuum steam stripping. The product is then filtered to remove any trace foreign material and packaged into drums or totes under nitrogen.

II.C Specifications and Analytical Data

Product specifications for the vegetable oil and tall oil phytosterols and vegetable oil and tall oil phytosterol esters used in the production of Cargill's CoroWise™ phytosterol products are shown in Tables II.C-1 and II.C-2 below. These products are of high purity ingredients that meet or exceed the phytosterol/stanol specifications recently established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA, 2008).

[1] The absence of methanol in the phytosterol ester products has been confirmed internally by Cargill, and all phytosterol/stanol ester products are absent methanol at a detection limit of 10 ppm.

Table II.C-1 Vegetable Oil and Tall Oil Phytosterol Specifications

Parameter	Cargill Specification		Method of Analysis
	Vegetable Oil Phytosterols	Tall Oil Phytosterols*	
Total Des-Methyl Sterols (%) (based on 9-16 peaks)	≥92	>99	Cargill Method QC_VE053
Moisture and Volatiles (%)	2.0 Max	3.0 Max	Cargill Method QC_VE072
Lead (ppm)	<0.1 ppm	<0.1 ppm	USP 28th ed, 2005, FCC 6th ed., 2008 (USP, 2005; FCC, 2008)
Sulphated Ash (%)	0.1 Max	0.1 Max	FCC, 6th ed., 2008 (FCC, 2008)

* Complies with EC 2004/333/EC Annex 2 (Commission of the European Communities, 2004a). Tall oil phytosterols are not a commercial product until they are processed into the functional product formulations as described in section 3.5. Product Specifications are located in Appendix A.

Table II.C-2 Vegetable Oil and Tall Oil Phytosterol Ester Specifications

Parameter	Cargill Specification		Method of Analysis
	Vegetable Oil Phytosterol Esters (SE-C100)	Tall Oil Phytosterol Esters (SE-C100E)	
Total Sterols (%)	≥97	≥97	Cargill Method QC_VE053
Phytosterol Esters (%)	≥91	≥91	
Free Phytosterols (%)	≤6	≤6	
Des-Methyl Sterols (%)	≥59	≥59	
Acyl-glycerides (%)	≤5	≤5	
Acidity (mg/kg)	≤0.2	≤0.2	Cargill Method QC_VE072
Lead (ppm)	≤0.1	≤0.1	USP28, FCC 6th ed., 2008 (USP, 2005; FCC, 2008)
Loss on drying (%)	≤0.1	≤0.1	FCC, 6th ed., 2008 (FCC, 2008)

Analyses of 2 to 5 non-consecutive Lots of vegetable oil and tall oil phytosterols, and their esters, confirm that the materials produced by the manufacturing processes are consistent and comply with the product specifications. The analytical data also demonstrate the absence of any chemical impurities or microbiological contamination.

II.D Additional Compositional Characterization

II.D.1 Impurities

Several additional Lots of vegetable oil and tall oil phytosterols were analyzed for additional parameters including sulphated ash, moisture, arsenic and lead, as outlined in Table II.D.1-1.

000017

Table II.D.1-1 Vegetable Oil and Tall Oil Phytosterols – Impurities

Analytical Parameter	Vegetable Oil Phytosterol Lot No.			Tall Oil Phytosterol Lot No.		
	P90309	P90310	P90311	C9M0218	C9M0119	C9M0120
Sulphated Ash (%)	0.02	0.01	0.02	0.03	0.05	0.04
Moisture (%)	0.20	0.18	0.19	0.12	0.17	0.15
Arsenic (ppm)	ND	ND	ND	ND	ND	ND
Lead (ppm)	ND	ND	ND	ND	ND	ND

ND = Not Detected (detection limit = 0.1 ppm).

Several additional Lots of vegetable oil phytosterols were analyzed for residual solvents such as ethanol and methanol which is the basis of the residual solvent specification of <1,000 ppm for ethanol and <40 ppm for methanol (Table II.D.1-2). In addition, vegetable oil phytosterol preparations sourced from soybean oil manufacturing distillates contain small amounts of long chain hydrocarbons primarily $C_{27}H_{56}$, $C_{29}H_{60}$ and $C_{31}H_{64}$ hydrocarbons at levels of 2 to 4%. Refined soybean oil also contains approximately 0.5% long chain hydrocarbons (Kuksis, 1964). Considering that the per capita consumption of refined soybean oil is 56.7 g/person/day (FAOSTAT, 2007), then individuals in the population are consuming 0.28 g/day of long chain hydrocarbons from this source and the additional material from consumption of phytosterols approximates this amount.

Table II.D.1-2 Vegetable Oil Phytosterols – Residual Solvents

Analytical Parameter	Manufacturing Lots		
	P101004	P101103	P100903
Methanol (ppm)	25	6	12
Ethanol (ppm)	511	440	467

II.D.2 Cargill's CoroWise™ Product Formulations

Most of the vegetable oil and tall oil phytosterol products described above are not used directly as food ingredients since the physicochemical properties of the products are not suitable for many food applications. Cargill has therefore developed several different product formulations produced from the base phytosterol and phytosterol ester products (*e.g.*, various pelletized and granular forms, and emulsions), each optimized for different food applications and country-specific regulatory requirements. A description of each product currently available in the U.S., European Community, Australia, or New Zealand market and its corresponding physico-chemical properties and intended food uses are described below in Table II.D.2-1. Food grade ingredients and processing aids used in the production of each CoroWise™ formulation is included in Table II.D.2-2. All ingredients and processing aids used in U.S. formulations will be

permitted for use in the production of food and used in accordance with applicable U.S. laws and regulations.

Table II.D.2-1 Cargill Product Formulations

Product Name	Product Description and Food Application
CoroWise ™ FG-50 Powdered (prilled) Vegetable Oil Phytosterols	CoroWise™ FG-50 phytosterols are a white, free flowing powder that can be used in dairy and soy milks, beverages, creamers, seasoning blends, baked goods, spreads and dressings.
CoroWise™ FP-100 Powdered Vegetable Oil Phytosterols	CoroWise™ FP-100 phytosterols are a fine powder with low fat solubility and hydrophobic properties. It can be incorporated into low fat foods, dietary supplements and beverages.
CoroWise™ FP-300 Granular Vegetable Oil Phytosterols	CoroWise™ FP-300 phytosterols are a white powder with low fat solubility and hydrophobic properties that can be used in low fat foods, dietary supplements and tableting.
CoroWise™ FP-400 Granular Vegetable Oil Phytosterols	CoroWise™ FP-400 phytosterols are a white powder with low fat solubility and hydrophobic properties that can be used in low fat foods, dietary supplements and tableting.
CoroWise™ ES-200 Emulsified Vegetable Oil Phytosterols	CoroWise™ ES-200 are an aqueous-dispersible form of phytosterols (plant sterols) that can be used in a variety of foods, including beverages, sauces, dry mixes, yogurts and smoothies, cereals, and other types of products.
CoroWise™ PSD-100 Pulp- Vegetable Oil Phytosterol Dispersion	CoroWise™ PSD-100 are a homogeneous dispersion of sterols and citrus pulp in water. They are ideal for beverages, especially juice or acidic-based beverages. Plant sterols are stable across a wide range of temperatures and pH levels.
CoroWise™ SE-C100 Vegetable Oil Phytosterol Esters	CoroWise™ SE-C100 phytosterol (plant sterols) esters, are a naturally sourced, fat soluble, hydrophobic food ingredient. Corowise™ SE-C100 phytosterol esters are a viscous, oily liquid, which becomes flowable upon heating to ~40°C or 100°F. Developed for use in spreads, dressings, beverages, and other food and dietary supplement products.
CoroWise™ Instant WDSE-33 Water Dispersable Vegetable Oil Phytosterol Esters	CoroWise™ Instant WDSE-33 phytosterols esters are a powder that is readily dispersible in water and other liquids. Corowise™ Instant WDSE-33 phytosterols esters are ideally suited for use in dry mixes, instant formulas, and liquid beverage systems.
CoroWise™ FP-100E Powdered Tall Oil Phytosterols	CoroWise™ FP-100E plant sterols are a fine white powder with low fat solubility and hydrophobic properties. Corowise™ FP-100E plant sterols can be incorporated into a variety of foods and beverages.
CoroWise™ FP-300E Granular Tall Oil Phytosterols	CoroWise™ FP-300E sterols are a white powder used in low fat foods, dietary supplements and tableting.
CoroWise™ PSD-100E Pulp – Tall Oil Phytosterol Dispersion	CoroWise™ PSD-100E plant sterols are a homogeneous dispersion of sterols and citrus pulp in water. Corowise™ PSD-100E plant sterols are ideal for beverages, especially juice or acidic based beverages.
CoroWise™ ES-101E – Emulsified Plant Sterols	CoroWise™ ES-101E emulsified plant sterols are in an aqueous-dispersible form that can be added to a variety of food and beverage products.
CoroWise™ SE-C102E Tall Oil Phytosterol Esters	CoroWise™ SE-C102E plant sterol esters are a viscous, oily liquid, which becomes flowable upon heating to ~40°C or 100°F. Plant sterol esters are a fat soluble, hydrophobic, ingredient developed for use in spreads, dressings, beverages and other food products.

000019

Table II.D.2-2 Formulation Ingredients and Processing-Aids Used in Production of Cargill's CoroWise™ Products

Product Name	Additional Formulation Ingredients and Processing-Aids Used in Production of CoroWise™ Phytosterol Products
CoroWise™ SE-C100 Vegetable Oil Phytosterol Esters	Natural Flavors, Ascorbic Acid, Citric Acid.
CoroWise™ PSD-100 Pulp-Tall Oil Sterol Dispersion	Water, Washed Pulp Solids.
CoroWise™ SE-C102E Tall Oil Phytosterol Esters	Natural Mixed Tocopherols, Ascorbic Acid.
CoroWise™ PSD-100E Pulp-Tall Oil Sterol Dispersion	Water, Washed Pulp Solids.
CoroWise™ ES-101E – Emulsified Plant Sterols	Corn syrup solids, sucrose esters
CoroWise™ ES200 Emulsified Phytosterols	Corn Syrup Solids, Polyglycerol Esters of Fatty Acids, Gum Acacia.
CoroWise™ Instant WDSE-33 Water Dispersable Vegetable Oil Phytosterol Esters	Corn Syrup Solids, Sodium Caseinate (milk), Dipotassium Phosphate, Distilled Monoglycerides, Diacetyl Tartaric Acid Ester of Monoglycerides*, Natural Flavors, Ascorbic Acid, and Citric Acid.

* Diacetyl tartaric acid ester of monoglycerides is used in the commercially available formulation in the U.S.

II.D.3 CoroWise™ Formulations – Product Specifications and Analytical Data

As shown below in Table II.D.3-1, suitable food grade product specifications have been developed for each CoroWise™ product. Associated batch analyses confirming compliance with the product specifications also are presented.

Table II.D.3-1 Cargill Product Formulations – Specification and Analytical Data

Product	Parameter	Specification	Lot No.		
			FG-CK101201	FG-CK100901	FG-CK100501
CoroWise™ FG-50	Total Des-Methyl Sterols (16 peaks)	>92%	94.4	94.0	95.7
	B-sitosterol		40.4	39.6	40.3
	Stigmasterol		18.1	17.8	19.1
	Campesterol		26.6	26.5	26.7
	Moisture and volatiles	<5%	0.2	0.3	0.3
	Particle size 50-150 µm	90%	N/A	N/A	N/A
			FP-LK80601	FP-LK80902	FP-LK90201
CoroWise™ FP-100	Total Des-Methyl Sterols (16 peaks)	>92%	96.1	96.6	96.0
	β-sitosterol		42.2	42.5	41.6
	Stigmasterol		19.4	19.4	19.2
	Campesterol		25.1	25.3	25.8
	Moisture	2.0% max.	0.2	0.5	0.4

Table II.D.3-1 Cargill Product Formulations – Specification and Analytical Data

Product	Parameter	Specification	Lot No.		
	Particle Size	25 µm max.	6.3	9.2	3.7
CoroWise™ FP-100E			TFP-LK80110	TFP-LK80111	TFP-LK80610
	Total Des-Methyl Sterols (16 peaks – dry basis)	>92%	100.5	100.5	100.1
	β-sitosterol		77.1	77.1	76.8
	Stigmasterol		0.9	0.9	0.8
	Campesterol		7.2	7.2	7.1
	Moisture and Volatiles	3.0% max.	0.1	0.1	1
	Particle Size	25 µm max.	9.1	6.6	5.8
CoroWise™ FP-300			FP3G-LK80520	FP3G-LK80620	FP3G-LK90323
	Total Des-Methyl Sterols (16 peaks)	>92%	95.8	95.7	95.3
	β-sitosterol		41.9	41.9	40.7
	Stigmasterol		19.4	19.2	19.8
	Campesterol		25.2	25.4	25.8
	Moisture and Volatiles	2.0% max.	0.4	0.2	0.1
	%through 30 sieve % through 100 sieve	>90 <15	99.8 1.3	99.6 0.8	99.8 1.1
CoroWise™ FP-300E			TFP3G-LK80760	TFP3G-LK80940	TFP3G-LK81243
	Total Des-Methyl Sterols (16 peaks)	>92%	99.9	99.9	99.6
	β-sitosterol		77.0	77.0	76.7
	Stigmasterol		0.6	0.6	0.6
	Campesterol		6.7	6.7	6.6
	Moisture and Volatiles	3.0%	0.5	0.9	NA
	%through 30 sieve % through 100 sieve	>90 <15	99.7 2.7	100 2.4	99.7 2.7
CoroWise™ SE-C100			SE-RK70101	SE-RK80205	SE-RK90101
	Phytosterol Esters	≥97	98.0	98.0	99.4
	Total Sterols (Esters + Free)	≥91	98.8	98.8	100.1
	Free Phytosterols	≤6	0.8	0.8	0.6
	Des-Methyl Sterols	≥59	60.5	60.5	61.2
	Acyl-glycerides	≤5	0	0	0
	Acidity (g KOH/kg)	≤0.2	0.2	0.2	0.2
	Lead (mg/kg)	≤0.1	<0.1	<0.1	<0.1
	Loss on drying	≤0.1	0	0.02	0.02

Table II.D.3-1 Cargill Product Formulations – Specification and Analytical Data

Product	Parameter	Specification	Lot No.		
CoroWise™ SE-C102E			TSSE-RK70803	TSSE-RK71103	TSSE-RK90103
	Total Sterols (Esters + Free)	91% min.	98.8	98.8	99.7
	Phytosterol Esters	97% min.	98.0	98.2	98.7
	Free Phytosterols	6% max.	0.8	0.6	1.0
	Des-Methyl Sterols	59% min.	60.5	60.4	61.3
	Acyl-glycerides	5% max.	0	0	0
	Acidity (g KOH/kg)	0.2 max.	0.2	0.2	0.2
	Lead (mg/kg)	0.1 max.	<0.1	<0.1	<0.1
	Loss on drying	0.1 max.	0	0	0.03
CoroWise™ PSD-100E			PSD100E-81215	PSD100E-81216	
	Total Sterols	9-11% w/w	10	9.8	
	Citrus Pulp	3-3.5% w/w	3.3	3.3	
	Moisture	85-87% w/w	86	86	
CoroWise™ ES-101E			TES-N110301	TES-N101001	TES-N100402
	Total Sterol	60% min.	66.5	66.9	64.3
	Moisture and Volatiles	3.0% max.	2.5	2.4	2.0
CoroWise™ ES-200			ES-NK70801	ES-NK80804	ES-NK90104
	Total Sterols	60% min.	66.7	65.0	62.9
	β-sitosterol		29.3	28.3	26.8
	Stigmasterol		14.1	13.1	12.4
	Campesterol		17.1	17.2	17
	Moisture and Volatiles	3.0% max.	1.1	2.4	2.6
CoroWise™ Instant WDSE-33			WD-NK71202	WD-NK80801	WD-NK90203
	Total Sterol Esters	33% w/w min.	34.2	34.8	35.8
	Moisture and Volatiles	6% w/w max.	2	1.8	1.6
	Total Aerobic Count	5000 CFU/g max.	TPC: 100 CFU/g	TPC: <100 CFU/g	TPC: 200 CFU/g
	Coliform	-	<10 CFU/g	<10CFU/g	<10CFU/g
	Salmonella	Negative per 375 g	Negative	Negative	Negative

NA = Not available

II.E Stability

The stability of phytosterols/phytosterol esters has been assessed at various temperatures, and the results are discussed below.

000022

II.E.1 Shelf Life

Three-year stability testing was performed on Cargill's phytosterol prills lots P20201, P20202, and P20203. The samples used in this study were packaged in a polyethylene liner that was goose-necked and zip-tied shut. The sample products were stored in a "long-term" stability chamber at 25°C and 60% relative humidity (RH) following International Conference Harmonization (ICH) guidelines for product stability at ambient conditions in zones 1 and 2 (ICH, 2003). Each lot of Cargill's phytosterol product remained within the product specifications for sterol purity at ≥88% over the 3-year period, and therefore Cargill's vegetable oil phytosterols are considered stable for 3 years.

Three (3) lots of tall oil phytosterols were tested for long-term stability. The products were stored in clear quart jars with plastic caps at ambient temperature and humidity for between 58 to 59 months. The tall oil phytosterols used in the manufacture of Cargill's CoroWise™ products are highly stable under these conditions and a shelf-life of at least 59 months was established for the product.

Finally, Cargill's phytosterol and phytosterol ester products are intended for use in a variety of different food applications, therefore the stability of these products under a variety of food applications representative of the various proposed food matrices and expected processing conditions were evaluated and confirmed to be stable. The analytical methodology used to analyze the phytosterol content during stability testing is a validated method (Cargill Method QC-VE053) and is of sufficient resolution to identify phytosterol oxidation. The presence of phytosterol oxides was considered during interpretation of all stability studies.

III. SELF-LIMITING LEVELS OF USE

The use of the vegetable oil and tall oil phytosterol ester products are self-limiting in the need to properly balance oil levels in food products such as to maintain flavor, and texture properties.

IV. BASIS FOR GRAS DETERMINATION

IV.A Documentation to Support the Safety of Phytosterols

The determination that phytosterols/phytosterol esters are GRAS is based on scientific procedures, and the information supporting the general recognition of the safety of the ingredient includes:

- data pertaining to the identity, intended use, and estimated intake of phytosterols/phytosterol esters;
- the natural occurrence of phytosterols in food and background dietary intakes;

000023

- animal and human toxicity/safety studies corroborating the safety of phytosterols; and
- the safety evaluations conducted by regulatory authorities in the U.S., Canada, the EU, and Australia, related to the addition of phytosterols to foods.

Moreover, these data were reviewed by a panel of experts, qualified by scientific training and experience to evaluate the safety of ingredients as components of food, who concluded that the intended uses of phytosterols/phytosterol esters are safe and suitable and would be GRAS based on scientific procedures. As the available information on the metabolic fate, toxicology studies in animals, and human studies have been extensively reviewed and evaluated by regulatory agencies (as described in Section IV.C), summaries of these data are provided in brief form in Section IV.D (Summary and Basis for GRAS).

IV.B Natural Occurrence and Background Dietary Consumption of Phytosterols

Phytosterols are naturally occurring compounds that are widespread in nature. As reported by Piironen and Lampi (2004), phytosterols are abundant in many foods that are widely consumed in the American diet. The most significant source of dietary phytosterols is expected to occur *via* the consumption of refined vegetable oils; corn and canola oil contain phytosterol concentrations as high as 7 and 9 g/kg. The consumption of a typical western diet has is reported to contain between 150 to 400 mg of phytosterols per day, and vegetarians are exposed to even higher levels with estimated average exposures of 500 mg per person per day (Ling and Jones, 1995). Thus, Americans have a long-history of apparent safe exposure to moderate levels of dietary phytosterols (between 250 to 500 mg) through the consumption of a normal diet.

IV.C Current Regulatory Status

IV.C.1 United States

In the United States, a variety of different vegetable oil and tall oil derived phytosterol ingredients are considered GRAS for use in a large variety of different food products. Typical use levels range from 0.6 to 1.1 g/serving, and the current estimated intake of phytosterols in the U.S. population under the combined food uses described in Table IV.C.1-1 below have been estimated to be as high as 12.1 g/person/day in 90th percentile users (GRN 250, 2009). Cargill has previously submitted a GRAS Notification for vegetable oil phytosterol esters (GRN 48; 2000) for a limited number of uses.

Table IV.C.1-1 Current U.S. Food and Drug Administration Notified GRAS Uses of Phytosterols

GRAS Notification No.	Product	Uses	Use Levels
GRN 335 (2010)	Pine tree phytosterol esters	Multiple food categories including margarine and vegetable based spreads, yogurt and yogurt-like products, milk based juice beverages, ice cream and non-standardized ice cream, cream cheese and cream cheese-like products, snack bars, salad dressing, standardized and non-standardized bread products, baked goods, beverages, dairy analogs, cheese and cream, breakfast cereal, mayonnaise, pasta and noodles, sauces, salty snacks, processed soups, puddings, confections, vegetarian meat analogs, fruit/vegetable juice, vegetable oils, egg products including egg whites and substitute egg products	Use levels the same as previously notified by other companies
GRN 250 (2009)	Plant sterols and stanols from pine trees	Multiple food categories including 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, salad dressings, standardized and non-standardized bread products, baked foods, beverages, dairy analogs, cheeses and cream, breakfast cereals, mayonnaise, pasta and noodles, sauces, salty snacks, processed soups, puddings, confections, vegetarian meat analogs, fruit/vegetable juices, vegetable oils, egg products, including egg whites and substitute egg products	Use levels the same as previously notified by other companies
GRN 206 (2006)	Phytosterol esters and diglycerides resulting from transesterification of vegetable oils/fats with soy phytosterols	Baked goods and baking mixes; fats and oils; frozen dairy desserts and mixes; gelatins, puddings, and fillings; grain products and pastas; gravies and sauces; hard candy; milk and milk products; soft candy, soups and soup mixes; and snack foods	0.6 g/serving
GRN 181 (2006)	Phytosterols	Egg products including egg whites and egg substitutes	1.1 g/serving
GRN 177 (2005)	Plant sterol esters	Ground coffee	1.0 g/serving
GRN 176 (2005)	Plant sterols and plant sterol esters from vegetable oils or sterols/stanols from tall oil	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, sauces, salty snacks, processed soups, puddings, yogurt, confections, vegetarian meat analogs at a level up to 0.4 gram (g) sterol equivalents per serving; in fruit/vegetable juices at a level up to 1 g sterol equivalents per serving; and in edible vegetable oils, including diacylglycerol oil as a replacement	Up to 4.0 g/100 g

000025

Table IV.C.1-1 Current U.S. Food and Drug Administration Notified GRAS Uses of Phytosterols

GRAS Notification No.	Product	Uses	Use Levels
GRN 112 (2003)	Phytosterols	Vegetable spread, yogurt, milk-based juice beverages, ice cream, cream cheese, snack bars, salad dressings, and white bread products	1.5 g/serving for yogurt, and 0.75 g/serving for all other food categories
GRN 61 (2001)	Plant sterols/Plant sterol esters	Vegetable oil spreads, dressings for salad, health drinks, health bars, yogurt-type products	1.0 g/serving
GRN 53 (2000)	Phytosterol esters	Vegetable oil for home use applications such as baking, frying, and salad dressings	Up to 13.3% by weight
GRN 48 (2000)	Vegetable oil phytosterol esters	Vegetable oil spread, dressings for salad, bars, and yogurt	Use levels the same as previously notified by other companies
GRN 39 (2000)	Tall oil phytosterols	Vegetable oil spreads	Up to 12% by weight

IV.C.2 Canada

In Canada, phytosterols are permitted as novel food ingredients (Health Canada, 2010). Total phytosterol consumption is restricted to 3 g/day from specific food categories where amounts per serving are restricted to 1 g/serving. Specific food uses include unstandardized spreads, mayonnaise, margarine, calorie-reduced margarine, salad dressings and unstandardized salad dressings, yogurt and yogurt drinks, and vegetable and fruit juice drinks.

IV.C.3 European Union

In the EU, there are several regulations authorizing the addition of phytosterols to a variety of foods. Food uses and use levels are shown in Table IV.C.3-1 below. The safety of phytosterol enriched foods was reviewed by the Scientific Committee on Food (SCF) who issued the following report titled "the long-term effects of the intake of elevated levels of phytosterols from multiple dietary sources, with particular attention to the effects on β-carotene". The SCF concluded that the consumption of 3 g of phytosterols per day was safe (SCF, 2002). However, the daily limits set out as per the European Commission regulations cited in Table IV.C.3-1, are actually 3 g/person/day per food category, meaning permitted daily intakes of phytosterols are higher than 3 g/day.

Estimated exposures to phytosterols in the European diet based on the current food uses have not been comprehensively assessed; however, a number of intake estimations for various population groups and phytosterol food uses have been published in the literature. For

example, intake estimations using foods commonly fortified with phytosterols in the European Union were evaluated by de Jong *et al.* (2004). The study was conducted using a sample of the Dutch population comprised of men and women aged 20 to 60, and assuming that all food products within a given food use were replaced with foods fortified with phytosterols. The authors estimated that the fortification of margarine, cheese, and yogurt with phytosterols, 3 commonly fortified foods, would result in theoretical maximum total phytosterol/stanol intakes of 5.1 g and 8.8 g per day for median and 90th percentile users. Exposures to fortification of margarine alone were estimated to result in exposures of 2.4 and 4.9 g per person for median and 90th percentile users. However, based on recent post-market surveillance data conducted for the use of phytosterol containing margarine, it is clear that these estimates significantly overestimate exposures: estimated intakes by regular consumers of phytosterol containing margarines was determined to be 1.44 g and 3.6 g per person for median and 90th percentile Dutch consumers (Lea and Hepburn, 2006).

Table IV.C.3-1 Current Commission Decisions Permitting Use of Phytosterols/ Phytostanols in Food

EC No.	Product	Uses	Use Levels
2004/333/EC 2004/334/EC 2004/336/EC 2004/845/EC 2006/58/EC 2006/59/EC 2007/343/EC 2008/36/EC	Phytosterols/ phytostanols extracted from plants*	Yellow fat spreads, excluding cooking and frying fats and spreads based on butter or other animal fat. Milk based products/beverages, milk type products, fermented milk type products, yogurt type products and cheese type products where milk fat and or protein has been partly or fully replaced by vegetable fat and/or protein. Rye Bread, soya drinks, spicy sauces and salad dressings, mayonnaise, and rice drinks.	Uses not to exceed 3 g per day/food category
2000/500/EC	Phytosterol esters	Yellow fat spreads.	8% w/w Sterols or 12% w/w of sterol esters

* Phytosterols/phytostanols extracted from plant sources other than vegetable oil must be free of contaminants, best assured by a purity of more than 99%.

**(Commission of the European Communities, 2000; 2004a-d; 2006a-b; 2007; 2008)

IV.C.4 Australia and New Zealand

In Australia and New Zealand vegetable oil phytosterol esters and non-esterified tall oil derived phytosterols are permitted for addition to a limited number of foods. Currently, edible oil spreads, breakfast cereals, milk, and yogurt may contain phytosterol products at various use levels. During their safety evaluation of the use of phytosterol ingredients in various foods, Food Standards Australia New Zealand (FSANZ) estimated the exposure to phytosterols in the diet under the permitted food uses, and at the maximum use levels (Table IV.C.4-1). Using worst-case scenario intake modeling the agency estimated that the intake of phytosterols from these uses would result in mean and 90th percentile intakes of 1.9 and 4.7 g/person among the

highest users (users aged 40 to 64) of phytosterol containing foods. Whole population (aged 15+) exposures were similar at 1.8 and 4.6 g/person per day in mean and 90th percentile users (FSANZ, 2004). In 2010 (FSANZ, 2010), FSANZ modified its position on phytosterols by recognizing that phytosterol and phytostanol and their fatty acid esters were equivalent from a safety and efficacy standpoint and recognized modified JECFA specifications in terms of solvent and des-methyl sterols levels (>95% purity).

Table IV.C.4-1 Food Standard Code Permitting Use of Phytosterols/Phytostanols in Food

Food Standard Code No.	Product	Uses*	Use Levels
Standard 1.5.1 Standard 2.4.2	Vegetable oil phytosterol esters and non-esterified tall oil phytosterols	Edible oil spreads	8% - tall oil phytosterols 13.7% - phytosterol esters
Standard 1.5.1	Vegetable oil phytosterol esters	Breakfast cereals	2.6 to 3.2%
Standard 1.5.1 Standard 2.5.1	Vegetable oil phytosterol esters and non-esterified tall oil phytosterols	Milk	5.2 to 6.4% phytosterol esters 3.2 to 4.0% tall oil phytosterols
Standard 1.5.1 Standard 2.5.3	Vegetable Oil phytosterol esters	Yogurt	1.3 to 1.6 g per serving

* Food uses also are subject to the conditions prescribed in standards 1.2.4 and 1.2.3.

IV.C.5 Regulatory Status Summary

Plant derived phytosterols and stanols are found in a large variety of foods, and therefore have a long history of consumption in the diet, and background consumption of naturally occurring phytosterols/stanols from the consumption of a typical western diet has been estimated to be 150 to 400 mg of phytosterols per day. The fortification of a variety of foods - margarine, spreads, yogurt and milk in particular - is currently permitted in the United States, the European Union, Australia, and New Zealand. Current exposure to phytosterols in the diet through the consumption of foods fortified with phytosterols has been estimated to result in daily exposures of between 5 to 12 g/person/day in "high" users of phytosterol containing products among various jurisdictions. Although these estimates are likely an overestimation of actual dietary exposures from the introduction of phytosterol containing foods to these markets, the widespread use of these products throughout the world provides strong support for a history of apparent safe use of phytosterols as food ingredients. The results of post-market surveillance studies conducted following the introduction of phytosterols to the European marketplace indicate that the use of these products were not associated with any unexpected health effects and further support the current history of apparent safe consumption of phytosterols/stanol fortified foods (Lea and Hepburn, 2006).

IV.D Summary of Safety Information and Basis for GRAS Conclusion

Cargill's CoroWise™ products are intended for use at levels providing 500 mg or 1 g phytosterols per serving in various foods in the following categories: alcoholic beverages; baked goods and baking mixes; beverages and beverage bases; breakfast cereals; cheeses; coffee and tea; condiments and relishes; dairy product analogs; egg products; fats and oils; fish products; frozen dairy desserts and mixes; grain products and pastas; gravies and sauces; hard candy; herbs, seeds, spices, seasonings, blends, extracts, and flavorings; jams and jellies; milk, whole and skim; milk products; nuts and nut products; processed fruits and fruit juices; processed vegetables and vegetable juices; snack foods; soft candy; and soups and soup mixes. Using NHANES consumption data, under the conditions of intended use of CoroWise™ products, the estimated mean and 90th percentile all-user phytosterol intakes were 6.6 and 11.0 g/person/day, respectively (120 and 244 mg/kg body weight/day on a body weight basis, respectively). Highest exposures on a body weight basis were estimated for infants. Intakes of phytosterols in infants aged 0 to 2 years were 390 and 654 mg/kg body weight for mean and 90th percentile exposures, respectively. Although young children are certainly expected to consume phytosterol containing products through the use of phytosterol-containing foods purchased by their parents, based on the standard overestimation that occurs from the use of dietary surveys in intake modeling combined with the targeted marketing of these products to adults seeking heart healthy foods, current intake estimates for children and infants are significantly overestimated. In addition, post marketing surveillance studies in Europe have indicated that most older adults consuming phytosterol containing food products do not have younger children in the household and therefore, this younger group of individuals will not be consuming what their parents consume.

In animals and humans phytosterols and phytostanols are poorly bioavailable due to their poor absorption in the gastrointestinal tract, which typically does not exceed 5% of dietary concentrations (Salen *et al.* 1989; Miettinen *et al.* 1990). Thus, systemic exposure to even high dietary quantities of these compounds is limited; unabsorbed dietary phytosterols/stanols are excreted unchanged in the feces.

A large number of traditional toxicology studies evaluating the subchronic, reproductive, developmental, teratogenic, and mutagenicity/genotoxicity of phytosterols and phytostanol were reviewed. Two studies reported adverse effects attributed to phytosterol administration. In one study a reduction in fat soluble vitamin absorption was reported (Turnbull *et al.*, 1999a), and in a second study, cardiomyopathy in high-dose males and reduction in weight gain in high-dose males and high-dose females was observed (Kim *et al.*, 2002); however, these effects were concluded not to be relevant to humans. The highest no-observed-adverse-effect level

(NOAEL) reported in the literature was therefore 4,200 mg of vegetable oil phytosterols/kg body weight/day, the highest dose tested[2].

Phytosterols and phytostanols are not mutagenic or genotoxic (Turnbull *et al.*, 1999b,c; Wolfreys and Hepburn, 2002; Paniagua-Pérez *et al.*, 2005). Studies investigating the addition of phytosterols to mammalian cell cultures at high concentrations, or the administration of large doses of phytosterols *via* parenteral routes have shown that phytosterols can exert estrogenic activity. However, based on observations from animal and human studies evaluating the estrogenic effects of orally administered phytosterols, there is no evidence to suggest that phytosterols induce physiological changes in humans or rodents indicative of estrogenic activity when consumed in the diet. All phytosterols currently on the market are manufactured using similar manufacturing practices, from food grade vegetable oil or tall oil sources. The test articles used in the available published toxicology studies were compositionally comparable to Cargill's phytosterol products and were, therefore, considered relevant to the safety evaluation of the company's products under the proposed food uses. In addition, although the majority of toxicity and safety studies have been conducted using esterified products, dietary phytosterol esters are rapidly hydrolyzed by pancreatic lipases in the small intestine to yield phytosterol/stanols in free form (Mattson *et al.*, 1977, 1982), and, therefore, these studies were considered applicable to the safety evaluation of exposure to non-esterified phytosterol ingredients. Under typical food uses and some manufacturing conditions, small amounts of phytosterol oxides are produced (ppm range); however, these compounds also have been shown to be poorly absorbed, non-toxic, and non-genotoxic in rodents at levels well in excess of the intended uses in humans (Lea *et al.*, 2004; Hovenkamp *et al.*, 2008; Koschutnig *et al.*, 2010).

The safety of repeat phytosterol/stanol consumption has been reported in a large number of human studies conducted in healthy subjects that have also been reviewed by various regulatory agencies. The daily consumption of up to 9.0 g of phytosterols (117 mg/kg body weight) from phytosterol enriched spreads and salad dressing over a 2-month period did not affect adverse event reporting, serum chemistry, hematology, and urinalysis measurements (Davidson *et al.* 2001). Similar absence of toxicity has been reported for the daily consumption of 1.6 g of phytosterols from phytosterol esters enriched spread over a one year period (Hendriks *et al.*, 2003)[3]. A number of additional clinical studies evaluating the effects of phytosterols on neurocognition, safety in pregnant and lactating women, and potential estrogenic effects were reviewed; no adverse effects were noted in these studies (Baker *et al.*, 1999; Turnbull *et al.*, 1999c; Laitinen *et al.*, 2009; Schiepers *et al.*, 2009; Tuomilehto *et al.*,

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[2]Although adverse effects relevant to humans were not observed in the study by Kim *et al.* (2002), who administered a higher dietary concentrations of phytosterol esters, the authors failed to report the phytosterol content of the test article, and therefore derivation of a NOAEL for exposure to phytosterols could not be determined.
[3] It was noted that the test spread contained 5.7 mg/kg of carotenoids.

2009). In studies conducted to evaluate the safety of Cytellin™, a drug containing phytosterols as the active ingredient marketed by Eli Lilly between the 1950s and the 1980s in the U.S. as treatment for hypercholesterolemia, no contraindications or adverse side effects were reported during repeated clinical investigations at doses of up to 30 g/day (Best *et al.*, 1955; Joyner and Kuo, 1955; Lesesne *et al.*, 1955; Farquhar *et al.*, 1956; Kuo, 1956; Duncan and Best, 1963). Similarly, studies in dogs receiving Cytellin™ at doses of 500 or 1,000 mg/kg body weight/day for 18 months, did not reveal any adverse effects. Cytellin™ contained phytosterols derived from tall oil, and was composed of approximately 80% sitosterol, 10% sitostanol, 7% campesterol, and 2% campestanol. Cargill's phytosterols are primarily composed of β-sitosterol (45%), campesterol (25%), and stigmasterol (25%).

In animal and human studies phytosterol consumption has been reported to decrease circulating levels of fat-soluble vitamins and carotenoids. The effect of phytosterols/stanols on circulating concentrations fat soluble vitamins and carotenoids in humans has been evaluated in a large number of clinical studies. However, based on the available evidence, it was concluded the effects of phytosterols/stanols on fat soluble vitamins and the carotenoids would be limited to β-carotene. The effect of repeat consumption of phytosterols/stanols fortified foods appears to be maximal at a dose of 3 g/person/day, and reductions up to 30% have been reported; typical reductions of between 15 to 20% were noted. Currently, the only nutritional function of β-carotene in the diet is as a source of provitamin A. Based on dietary survey data, the typical North American diet is expected to provide adequate quantities of vitamin A in accordance with IOM guidelines. In addition, it also was observed that even "low consumers" of dietary carotenoids have intakes of β-carotene in excess of 2,000 μg/day. Therefore, it was concluded that the effect of dietary phytosterols on carotenoid absorption is not expected to be of nutritional concern.

Other nutritional effects associated with phytosterol/stanol consumption are reductions in cholesterol absorption, an effect that is widely reported in the literature. Typical reductions in cholesterol associated with phytosterol consumption are between 10 to 15%, and maximal effects are noted with intakes of approximately 3 g/person/day. Although cholesterol is an important nutrient, mild to moderately elevated circulating levels of cholesterol is common and is a widely accepted risk factor for cardiovascular heart disease. Since individuals with mild to moderate elevations in plasma cholesterol are prevalent in the population, the introduction of phytosterols/stanols to the diet is expected to provide beneficial nutritional effects. In addition, reductions in cholesterol concentrations from consuming phytosterol fortified foods has been reported for a number of food matrices and optimal reductions are reported when these foods are consumed throughout the day. These observations suggest that the nutritional benefits of phytosterol administration will be achieved through the introduction of phytosterols to a number of food types. In contrast to the beneficial effects of phytosterols on cholesterol absorption, it has been suggested that elevated circulating phytosterol levels are involved in increasing

coronary heart disease (CHD) risk; however, to date, there is no conclusive evidence that dietary consumption of phytosterols is associated with an increased risk for CHD.

Finally, the Expert Panel convened on behalf of Cargill, independently and collectively, critically evaluated the data and information summarized above and concluded that the intended uses of vegetable oil and tall oil derived phytosterol and phytosterol ester formulations (CoroWise™ phytosterols), produced consistently with cGMP and meeting appropriate food-grade specifications described herein, are safe and suitable. Furthermore, the Expert Panel unanimously concluded that the intended uses of vegetable oil and tall oil derived phytosterol and phytosterol ester formulations (CoroWise™ phytosterols) are GRAS based on scientific procedures. It is also Cargill's opinion that other qualified and competent scientists reviewing the same publicly available toxicological and safety information would reach the same conclusion. This is supported by the fact that numerous regulatory agencies have reviewed the safety of adding phytosterols/phytosterol esters to foods, and concluded that they are safe for the various intended uses. Therefore, Cargill has concluded that vegetable oil and tall oil derived phytosterol and phytosterol ester formulations (CoroWise™ phytosterols) are GRAS under the intended conditions of use on the basis of scientific procedures; therefore, the ingredients are excluded from the definition of a food additive and thus may be marketed and sold for the uses designated above in the U.S. without the promulgation of a food additive regulation under Title 21 of the CFR.

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APPENDIX A

Appendix A

Expert Panel Consensus Statement Concerning the Generally Recognized as Safe (GRAS) Status of Vegetable Oil and Tall Oil Derived Phytosterol and Phytosterol Ester Formulations (CoroWise™ Phytosterols)"

EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF VEGETABLE OIL AND TALL OIL DERIVED PHYTOSTEROL AND PHYTOSTEROL ESTER FORMULATIONS (COROWISE™ PHYTOSTEROLS)

June 9, 2011

INTRODUCTION

At the request of Cargill Incorporated of Wayzata, MN (Cargill), an Expert Panel (the "Panel") of independent scientists, qualified by their relevant national and international experience and scientific training to evaluate the safety of food ingredients, was specially convened to conduct a critical and comprehensive evaluation of the available pertinent data and information, and determine whether, under the conditions of intended use, phytosterols derived from vegetable and tall oils, both free and esterified with common dietary fatty acids, as food ingredients for use in conventional foodstuffs would be Generally Recognized as Safe (GRAS), based on scientific procedures. The Panel consisted of the below-signed qualified scientific experts: Professor Joseph F. Borzelleca, Ph.D. (Virginia Commonwealth University School of Medicine), Professor John Doull, Ph.D., M.D. (University of Kansas Medical Center) and Professor Robert J. Nicolosi, Ph.D. (University of Massachusetts Lowell).

The Panel, independently and collectively, critically examined a comprehensive package of scientific information and data compiled from the literature and other published sources. This information was presented in a dossier [Documentation Supporting the Evaluation of Vegetable Oil and Tall Oil Derived Phytosterol and Phytosterol Ester Formulations (CoroWise™ Phytosterols) as Generally Recognized as Safe (GRAS) for Use as Food Ingredients] that was submitted by Cargill to the Panel. In addition, the Panel evaluated other information deemed appropriate or necessary, including data and information provided by Cargill. The data evaluated by the Panel included information pertaining to the method of manufacture and product specifications, analytical data, intended use level, consumption estimates, and a comprehensive assessment of the available scientific literature pertaining to the safety of phytosterols and phytosterol esters.

Following independent, critical evaluation of such data and information, the Panel unanimously concluded that under the conditions of intended use described herein, phytosterols derived from vegetable and tall oils, both free and esterified with common dietary fatty acids, meeting appropriate food-grade specifications, and manufactured in accordance with current Good

Manufacturing Practice (cGMP), are GRAS based on scientific procedures. A summary of the basis for the Panel's conclusion, excluding confidential data and information, is provided below.

SUMMARY AND BASIS FOR GRAS

Cargill intends to market phytosterols/phytostanols derived from vegetable and tall oils, both free and esterified with common dietary fatty acids, as an ingredient for use in conventional foodstuffs at 0.5 or 1.0 g/serving. The ingredients are already considered GRAS at use levels up to 0.4 g/serving for a lesser number of food categories (GRAS Notification 000048). The products that Cargill intend to market are phytosterols/phytostanols and phytosterol/phytostanol esters formulated with various physico-chemical functional attributes to meet customer-specific product characteristics (under the trade name CoroWise™).

Cargill's plant derived phytosterol/phytostanol and phytosterol/phytostanol ester products are manufactured using standard manufacturing practices in accordance with cGMP using suitable food grade ingredients and processing aids. CoroWise™ plant sterol ester products are produced by direct esterification of free plant sterols with food-grade fatty acids from various vegetable oils followed by purification of the raw sterol ester. Cargill has developed several different product formulations of its free and esterified phytosterol/phytostanol products (*e.g.*, various pelletized and granular forms, esterified forms and emulsions), each optimized for different food applications; these products are produced using various food grade ingredients, all of which are or will be adapted to include ingredients permitted for use as food ingredients. All reagents and processing aids used in the manufacture of the phytosterols/phytostanols and phytosterol/phytostanol esters are food-grade materials. The specifications for the phytosterol/phytostanol and phytosterol/phytostanol ester products are provided in Appendix A.

Numerous non-consecutive manufactured Lots of vegetable oil phytosterol/phytostanol and phytosterol/phytostanol ester products and tall oil phytosterol/phytostanol and phytosterol/phytostanol ester products were tested and met the proposed chemical specifications. Three lots each of vegetable oil phytosterols/phytostanols and tall oil phytosterols/phytostanols were tested and reported to be stable for 3 and 5 years, respectively, meeting all stability specifications. CoroWise™ phytosterols/phytostanols and phytosterol/phytostanol esters were also tested in various food matrices and were found to be suitable for proposed food uses.

The consumption of phytosterols/phytostanols and phytosterol/phytostanol esters from the proposed food uses was estimated using the National Center for Health Statistics' (NCHS) 2003-2004 and 2005-2006 National Health and Nutrition Examination Surveys (NHANES) (CDC, 2006; USDA, 2008). Consumption of proposed food-uses by the total U.S. population resulted in an estimated mean all-user intake of phytosterols/phytostanols of 6.6 g/person/day (120 mg/kg body weight/day). The 90th percentile all-user intake of phytosterols/phytostanols

from proposed food-uses by the total population was 11.0 g/person/day (244 mg/kg body weight/day). The list of proposed uses are found in Appendix B.

Plant derived phytosterols and stanols are found naturally in a large variety of foods, and therefore have a long history of consumption in the diet. Background consumption of naturally occurring phytosterols/stanols from the consumption of a typical western diet has been estimated to be 150 to 400 mg of phytosterols/phytostanols per day. Current exposure to phytosterols/phytostanols in the diet through the consumption of foods fortified with phytosterols/phytostanols or phytosterol/phytostanol esters has been estimated to result in daily exposures of between 5 to 12 g/person/day in "high" users of phytosterol containing products among various jurisdictions.

This type of intake methodology is generally considered to be "worst case" as a result of several conservative assumptions made in the consumption estimates. For example, it is often assumed that all food products within a food category contain the ingredient at the maximum specified level of use. In addition, it is well established that the length of a dietary survey affects the estimated consumption of individual users. Short-term surveys, such as the typical 2- or 3-day dietary surveys, overestimate the consumption of food products that are consumed relatively infrequently.

Post marketing surveillance studies in several European jurisdictions have demonstrated that the actual intakes of phytosterols/phytostanols is less than that determined from modeling exercises (SCF, 2002; Wolfs *et al.,* 2006; de Jong *et al.,* 2008; Hearty *et al.*, 2008).

The safety of phytosterols/phytostanols and phytosterol/phytostanol esters under the intended conditions of use is supported by the permitted uses of several comparable phytosterol/phytostanol formulations in the marketplaces of the United States, the European Union, Japan, Australia, and New Zealand, as well as supporting evidence from studies in animals and humans.

In animals and humans phytosterols and phytostanols are poorly bioavailable due to their poor absorption in the gastrointestinal tract, which typically does not exceed 5% of dietary concentrations. Thus, systemic exposure to even high dietary quantities of these compounds is limited; unabsorbed dietary phytosterols/stanols are excreted unchanged in the feces. A large number of traditional toxicology studies evaluating the subchronic, reproductive, developmental, teratogenic, and mutagenicity/genotoxicity of phytosterols and phytostanols were reviewed. Two studies reported adverse effects attributed to phytosterol administration. In one study a reduction in fat soluble vitamin absorption was reported (Turnbull *et al.,* 1999), and in a second study, cardiomyopathy in high-dose males and reduction in weight gain in high-dose males and high-dose females was observed (Kim *et al.*, 2002); however, these effects were concluded not to be relevant to humans considering the long safe human use of Cytellin™. The highest NOAEL reported in the literature was therefore 4,200 mg of vegetable oil phytosterols/kg body

weight/day, the highest dose tested[1]. Phytosterols and phytostanols are not mutagenic or genotoxic. Studies investigating the addition of phytosterols to mammalian cell cultures at high concentrations, or the administration of large doses of phytosterols *via* parenteral routes have shown that phytosterols can exert estrogenic activity. However, based on observations from animal and human studies evaluating the estrogenic effects of orally administered phytosterols, there is no evidence to suggest that phytosterols induce physiological changes in humans or rodents indicative of estrogenic activity when consumed in the diet.

All phytosterols currently on the market are manufactured using similar manufacturing practices, from food grade vegetable oil or tall oil sources. The test articles used in the available published toxicology studies were compositionally comparable to Cargill's phytosterol products and were, therefore, considered relevant to the safety evaluation of the company's products under the proposed food uses. In addition, although the majority of toxicity and safety studies have been conducted using esterified products, dietary phytosterol esters are rapidly hydrolyzed by pancreatic lipases in the small intestine to yield phytosterol/stanols in free form, and, therefore, these studies were considered applicable to the safety evaluation of exposure to non-esterified phytosterol ingredients. Under typical food uses and some manufacturing conditions, small amounts of phytosterol oxides are produced; however, these compounds also have been shown to be non-toxic and non-genotoxic in rodents at levels well in excess of the intended uses in humans. The safety of repeat phytosterol/stanol consumption has been reported in a large number of clinical studies conducted in healthy subjects. The daily consumption of up to 9.0 g of phytosterols (117 mg/kg body weight) from phytosterol enriched spreads and salad dressing over a 2-month period did not affect adverse event reporting, serum chemistry, hematology, and urinalysis measurements (Davidson *et al.*, 2001). Similar absence of toxicity has been reported for the daily consumption of 1.6 g of phytosterols from phytosterol esters enriched spread over a one year period (Hendriks *et al.*, 2003). A number of additional clinical studies evaluating the effects of phytosterols on neurocognition, safety in pregnant and lactating women, and potential estrogenic effects were reviewed; no adverse effects were noted in these studies.

Cytellin™, a drug containing phytosterols as the active ingredient was marketed by Eli Lilly between the 1950s and the 1980s in the United States as treatment for hypercholesterolemia. Cytellin™ contained phytosterols derived from tall oil, and was composed of approximately 80% sitosterol, 10% sitostanol, 7% campesterol, and 2% campestanol. Recommended therapeutic levels ranged from 9,000 to 30,000 mg per day. No contraindications or adverse side effects

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[1]Although adverse effects relevant to humans were not observed in the study by Kim *et al.* (2002), who administered a higher dietary concentrations of phytosterol esters, the authors failed to report the phytosterol content of the test article, and therefore derivation of a NOAEL for exposure to phytosterols could not be determined.

were reported during repeated clinical investigations of Cytellin™ (Best *et al.*, 1955; Joyner and Kuo, 1955; Lesesne *et al.*, 1955; Farquhar *et al.*, 1956; Kuo, 1956; Duncan and Best, 1963).

In animal studies conducted with high levels of phytosterols, phytosterols have been reported to decrease circulating levels of fat-soluble vitamins and carotenoids. The effect of phytosterols/stanols on circulating concentrations fat soluble vitamins and carotenoids in humans at significantly lower levels of consumption have also been evaluated in a large number of clinical studies. However, based on the available evidence, it was concluded the effects of phytosterols/stanols on fat soluble vitamins and the carotenoids would be limited to β-carotene. The effect of repeat consumption of phytosterols/stanols fortified foods appears to be maximal at a dose of 3 g/person/day, and reductions up to 30% have been reported; typical reductions of between 15 to 20% were noted. Currently, the only nutritional function of β-carotene in the diet is as a source of provitamin A. Based on dietary survey data, the typical North American diet is expected to provide adequate quantities of vitamin A in accordance with IOM guidelines. In addition, it also was observed that even "low consumers" of dietary carotenoids have intakes of β-carotene in excess of 2,000 μg/day. Therefore, it was concluded that the effect of dietary phytosterols on carotenoid absorption is not expected to be of nutritional concern.

Other nutritional effects associated with phytosterol/stanol consumption are reductions in cholesterol absorption, an effect that is widely reported in the literature. Typical reductions in cholesterol associated with phytosterol consumption are between 10 to 15%, and maximal effects are noted with intakes of approximately 3 g/person/day. Although cholesterol is an important nutrient, mild to moderately elevated circulating levels of cholesterol is common and is a widely accepted risk factor for cardiovascular heart disease. Since individuals with mild to moderate elevations in plasma cholesterol are prevalent in the population, the introduction of phytosterols/stanols to the diet is expected to provide beneficial nutritional effects. In addition, reductions in cholesterol concentrations from consuming phytosterol fortified foods have been reported for a number of food matrices and optimal reductions are reported when these foods are consumed throughout the day. These observations suggest that the nutritional benefits of phytosterol administration will be achieved through the introduction of phytosterols to a number of food types.

In contrast to the beneficial effects of phytosterols on cholesterol absorption, it has been suggested that elevated circulating phytosterol levels are involved in increasing CHD risk; however, to date, there is no conclusive evidence that dietary consumption of phytosterols is associated with an increased risk for CHD.

The intake of phytosterols and phytosterol esters from the proposed food uses would result in intakes by heavy (90th percentile) users that are comparable to estimated intakes by "high" users of already fortified foods (11 g/day compared to up to 12 g/day). Therefore, no adverse

effects would be expected from the intake of phytosterols derived from vegetable and tall oils, both free and esterified, from the proposed food use levels and intended uses.

From a critical evaluation of the available scientific data and information, it is concluded that the intended use of phytosterols/phytostanols derived from vegetable and tall oils, both free and esterified with common dietary fatty acids in traditional foodstuffs is safe. The data and information summarized in this dossier demonstrate that these ingredients, manufactured consistent with cGMP and meeting appropriate food-grade specifications, would be GRAS based on scientific procedures under the intended conditions of use, as described herein.

CONCLUSION

Following independent, critical evaluation of such data and information, the Panel unanimously concludes that phytosterols derived from vegetable and tall oils, both free and esterified with common dietary fatty acids, meeting appropriate food-grade specifications, and manufactured in accordance with current Good Manufacturing Practice (cGMP), are Generally Recognized As Safe (GRAS) at levels of 0.5 or 1.0 g/serving resulting in a total exposure of 11g/day.

We further conclude that the intended uses of phytosterols derived from vegetable and tall oils, both free and esterified with common dietary fatty acids, in traditional foodstuffs, manufactured consistent with cGMP and meeting appropriate food-grade specifications presented in the supporting dossier are GRAS based on scientific procedures. These data include the numerous published animal studies, clinical trials and the safe use of these materials and Cytellin™ in humans for several years.

It is our opinion that other qualified experts would concur with these conclusions.

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Appendix A

Product Specifications for Vegetable Oil and Tall Oil Derived Phytosterol and Phytosterol Ester Formulations (CoroWise™ Phytosterols)

Table 1 Vegetable Oil and Tall Oil Phytosterol Specifications			
Parameter	**Cargill Specification**		**Method of Analysis**
	Vegetable Oil Phytosterols	**Tall Oil Phytosterols***	
Total Des-MethylSterols (%) (based on 9-16 peaks)	≥ 92	> 99	Cargill Method QC_VE053
Moisture and Volatiles (%)	2.0 Max	3.0 Max	Cargill Method QC_VE072
Lead (ppm)	< 0.1 ppm	< 0.1 ppm	USP 28th ed, 2005, FCC 5th ed., 2003
Sulphated Ash (%)	0.1 Max	0.1 Max	FCC, 5th ed., 2003

Table 2 Vegetable Oil and Tall Oil Phytosterol Ester Specifications			
Parameter	**Cargill Specification**		**Method of Analysis**
	Vegetable Oil Phytosterol Esters (SE-C100)	**Tall Oil Phytosterol Esters (SE-C100E)**	
Total Sterols (%)	≥ 97	≥ 97	Cargill Method QC_VE053
Phytosterol Esters (%)	≥91	≥91	
Free Phytosterols (%)	≤6	≤6	
Des-Methyl Sterols (%)	≥59	≥59	
Acyl-glycerides (%)	≤5	≤5	
Acidity (mg/kg)	≤0.2	≤0.2	Cargill Method QC_VE072
Lead (ppm)	≤0.1	≤0.1	USP28, FCC 5th ed., 2003
Loss on drying (%)	≤0.1	≤0.1	FCC, 5th ed., 2003

Appendix B

Proposed Use Levels and Food Categories

Table 3 Summary of the Individual Proposed Food-Uses and Use-Levels for Phytosterols in the United States (2003-2004, 2005-2006 NHANES data)

Food Category	Proposed Food-Uses	Serving Size* (g or mL)	Phytosterols Level (g/serving)	Use-Level (%)
Alcoholic Beverages	Wine	240	0.5	0.21
Baked Goods and Baking Mixes	Bagels and English Muffins	55	0.5	0.91
	Biscuits	55	0.5	0.91
	Bread (whole grain and dietary fiber bread)[1]	50	0.5	1.00
	Breadcrumbs	30	0.5	1.67
	Cookies (low fat)	30 to 40	0.5	1.25 to 1.67
	Crackers	30	0.5	1.67
	French Toast, Pancakes, and Waffles	85 to 110	0.5	0.45 to 0.59
	Muffins	55	0.5	0.91
	Pizza Crusts	55	0.5	0.91
	Tortillas	55	0.5	0.91
Beverages and Beverage Bases	Cereal Beverages	240	1.0	0.42
	Non-Dairy Meal Replacement Beverages	240	1.0	0.42
Breakfast Cereals	Cooked Cereals	240	1.0	0.42
	RTE Breakfast Cereals (healthy adult cereals)	15 to 55	1.0	3.33 to 6.67
Cheeses	Cottage Cheese	110	1.0	0.91
	Cream Cheese and Cheese Spreads	30	0.5	1.67
	Natural Cheese	30	0.5	1.67
	Processed Cheese	30	0.5	1.67
Coffee and Tea	Coffee and Substitutes	240	0.5	0.21
	RTD Tea Beverages	240	1.0	0.42
Condiments and Relishes	Ketchup	15	0.5	3.33
Dairy Product Analogs	Cream Substitutes	15	1.0	6.67
	Imitation Milk (soy)	240	1.0	0.42
Egg Products	Egg Substitutes	50	1.0	2.00
Fats and Oils	Butter	15	1.0	6.67
	Margarine and Margarine-like Spreads	15	1.0	6.67
	Mayonnaise and Mayonnaise-Type Dressings	15	1.0	6.67
	Salad Dressings	30	1.0	3.33
	Vegetable Oils (including olive oil)	15	1.0	6.67
Fish Products	Frozen Fish Dinners	85	0.5	0.59
Frozen Dairy Desserts and Mixes	Frozen Yogurt	120	0.5	0.42
	Ice Cream	120 to 240	0.5	0.21 to 0.42
Grain Products and	Frozen Dinners	85	0.5	0.59

Table 3 Summary of the Individual Proposed Food-Uses and Use-Levels for Phytosterols in the United States (2003-2004, 2005-2006 NHANES data)

Food Category	Proposed Food-Uses	Serving Size* (g or mL)	Phytosterols Level (g/serving)	Use-Level (%)
Pastas	Grain-Based Dishes (rice, barley, lentils)	140 to 195	0.5	0.26 to 0.36
	Health Bars (breakfast, granola, protein)	40	1.0	2.50
	Pasta and Noodles	140	1.0	0.71
Gravies and Sauces	Sauces (including white, tomato, salsa, and vegetable-based sauces)	5 to 60	0.5	0.83 to 10.00
Hard Candy	Hard Candy and Mints	2	0.5	25.00
Herbs, Seeds, Spices, Seasonings, Blends, Extracts, and Flavorings	Spices	1.25	1.0	80.00
Jams and Jellies	Jams, Jellies, and Preserves	15	0.5	3.33
Milk, Whole, and Skim	Fluid Milk	240	1.0	0.42
Milk Products	Dairy-Based Creamers	15 to 30	1.0	3.33 to 6.67
	Flavored Milk Beverages	120 to 240	1.0	0.42 to 0.83
	Meal Replacement Beverages	240	1.0	0.42
	Sour Cream and Dips	30	1.0	3.33
	Yogurt	225	1.0	0.44
Nuts and Nut Products	Nut Butters	30	0.5	1.67
Processed Fruits and Fruit Juices	Dried Fruits	40	0.5	1.25
	Fruit Drinks and Ades	240	1.0	0.42
	Fruit Juices and Smoothies	240	1.0	0.42
	Fruit-Based Nectars	240	1.0	0.42
Processed Vegetables and Vegetable Juices	Vegetable Juices	240	1.0	0.42
Snack Foods	Savory Snacks (potato, popcorn, pretzel, corn, rice cakes)	30	1.0	3.33
Soft Candy	Chocolate Confectionary and Chewy Candies	40	0.5	1.25
Soups and Soup Mixes	Soups (vegetable and pasta-based)	245	0.5	0.20

SUBMISSION END