ORIGINAL SUBMISSION

NutraSource, Inc.
6309 Morning Dew Ct, Clarksville, MD 21029
(410)-531-3336 or (301) 875-6454

June 11, 2013

Dr. Antonia Mattia
Office of Food Additive Safety (HFS-255)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5 100 Paint Branch Parkway
College Park, MD 20740

RECEIVED
JUN 18 2013
OFFICE OF
FOOD ADDITIVE SAFETY

Subject: GRAS notice for Rice Fiber 310 (rice hull fiber)

Dear Dr. Antonia Mattia:

On behalf of SunOpta Ingredients, we are submitting for FDA review a GRAS notification for Rice Fiber 310, rice hull fiber. The attached documentation contains the specific information that addresses the safe human food uses for the subject notified substance. We believe that this determination and notification are in compliance with proposed Sec. 170.36 of Part 21 of the Code of Federal Regulations (21 CFR section170.36) as published in the Federal Register, Vol. 62, No. 74, FR 18937, April 17, 1997.

We enclose an original and two copies of this notification for your review. Please feel free to contact me if additional information or clarification is needed as you proceed with the review. We would appreciate your kind attention to this matter.

Sincerely,
(b) (6)

Susan Cho, Ph.D.
Susanscho1@yahoo.com
Agent for SunOpta Ingredients

enclosure

GRAS Notification for

SunOpta's

Rice Fiber 310

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

Prepared by: NutraSource, Inc.
6309 Morning Dew Court
Clarksville, MD 21029
Tel: 410-531-3336
Susanscho1@yahoo.com

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I. GRAS EXEMPTION CLAIM

I.A. Claim of exemption from the requirement for premarket approval requirements pursuant to Proposed 21 CFR 5 170.36(~)(1)

SunOpta Ingredients Group (the notifier) has determined that its Rice Fiber 310, rice hull fiber, is Generally Recognized As Safe (GRAS), 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, under the conditions of its intended use in food. Therefore, the use of rice hull fiber is exempt from the requirement of premarket approval.

Signed

Susan Cho Date:
Agent for
SunOpta Ingredients Group
1001 S. Cleveland Street, Cambridge, MN 55008

I.B. Notifier's Name and Address

SunOpta Ingredients Group
Attention: Jim Podolske
1001 S. Cleveland Street, Cambridge, MN 55008
Phone number: 781-276-5164
Fax number: 781-276-5101
E mail address: jim.podolske@sunopta.com

I.C. Name of GRAS substance

Rice Fiber 310 or rice hull fiber, manufactured by SunOpta Ingredients Group.

I.D. Product description

SunOpta's Rice Fiber 310 is processed from rice hull by a proprietary hydrothermal process. Rice Fiber 310 which consists of mostly insoluble dietary fiber can be added to food for several purposes. Examples include raising total fiber content, reducing caloric content, and controlling water activity of foods and beverages. Rice hull fiber has >91% total fiber, of which >97% is insoluble fiber. The rice hull fiber contains no sulfites, added flavors, components from an animal source, BHA, BHT, genetically altered plant material, or irradiated material.

I.E. Applicable conditions for use of the notified substance

Rice Fiber 310 is a natural source of rice fiber (mostly from rice hull and partly from rice bran). Rice Fiber 310 is proposed for general food use at concentrations consistent with current Good Manufacturing Process (cGMP). Rice Fiber 310 has many food applications, including, but not limited to, prepared foods, general foods (such as snack foods, bakery products, cereals, crackers, pasta products, dough conditioners, beverages, sports beverages), meal replacement, gluten-free foods, and medical foods. Medical foods are defined as food which is formulated to

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6/11/2013

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be consumed or administered enterally under the supervision of a physician, and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. Intended use excludes infant formulas and foods that fall under USDA jurisdiction, such as catfish, poultry, pork, beef, and egg products. Consumption of Rice Fiber 310 is not expected to exceed 25-28 g per day.

I.F. Basis for GRAS determination

In accordance with 21CFR 170.30, the intended use of Rice Fiber 310 has been determined to be GRAS based on scientific procedures. A comprehensive search of the scientific literature also was conducted for this review. There is sufficient qualitative and quantitative scientific evidence, including human and animal data, to determine safety-in-use for Rice Fiber 310. The safety determination of Rice Fiber 310 is based on the totality of available evidence on Rice Fiber 310 as well as evidence for components of Rice Fiber 310 such as cellulose and hemicelluloses. Studies of related fibers such as rice bran fiber and grain fibers further corroborate its safety.

Like other grain fibers, rice hull fibers are composed of mostly cellulose and arabinoxylans, hemicellulose , and lignin. In particular, Rice Fiber 310 and rice bran fiber share similar composition and physicochemical properties: Most of these fibers consist of cellulose, arabinoxylans, and lignins and are insoluble in water (>90% insoluble fibers). These insoluble fibers are expected to have similar metabolism in humans; insoluble fibers act as a bulking agent in the colon to relieve constipation and are fermented to short chain fatty acids (SCFA) and some gases although their degree of fermentation is less than that of soluble fibers. Thus, no systemic risks related to consumption of rice hull fiber are expected.

Toxicity studies of Rice Fiber 310 showed no safety concerns. Ames test with and without metabolic activation as well as *in vivo* bone marrow micronucleus test in Kunming mice showed that Rice Fiber 310 lacks mutagenicity and genotoxicity. A Subchronic toxicity study in rats showed that administration of Rice Fiber 310 at doses up to 5% in diet did not show any abnormalities. The authors concluded that the no-observed-adverse-effect-level (NOAEL) for Rice Fiber 310 was much higher than 5.0% in the diet for both genders (females, 3,800 mg/kg body weight [BW]/day; males, 4,110 mg/kg BW/day). Also, rice bran and rice bran fibers, whose fiber compositions are similar to that of rice hull fiber, have been GRAS ingredients.

In addition, evaluation of rice hull and components of Rice fiber 310 also did not raise safety concerns. Like other grain fibers, rice hull fiber consists of cellulose, hemicellulose (mostly arabinoxylans), and lignins. Cellulose has been recognized as GRAS since 1973; up to 60% in diet did not show adverse effects. Hemicellulose in grain fibers has been proven safe for a long time. Throughout the human history, humans have consumed grain fibers which consist of cellulose and hemicelluloses (non cellulosic polysaccharides mostly consists of arabinoxylans) and lignin. No adverse effects of grain fibers or their components were reported even in some countries where consumption levels of total fiber and grain fiber are much higher than those of Americans. For example, the Finnish population has much higher intake levels of total fiber and grain fiber than do Americans; their 87.5th and 99th percentile intakes of grain fibers are 29 and

51 g, respectively (Montonen et al., 2003). In this Finnish population, grain fiber intake was inversely associated with risk reduction of type 2 diabetes without having any adverse effects. In other studies with various populations including Americans, consumption of grain fiber have been associated with positive health benefits (risk reductions of cardiovascular disease, type 2 diabetes, and obesity) without having any adverse effects. Recently, the American Society of Nutrition has emphasized the importance of grain fibers in human health and documented that consumption of grain fibers was not associated with any adverse effects.

The Institute of Medicine (IOM) recommends increased intakes of total fiber: Recommended intakes of total fiber are 25 g per day for adult women and 38 g per day for adult men. Unfortunately, most Americans do not meet recommended intakes with an average of 19.2 and 14.4 g per day for adult men and women, respectively. The consumption of Rice Fiber 310 may be to help Americans improve their fiber intake.

The information/data provided by SunOpta Ingredients Group in this report and supplemented by the publicly available toxicity data on Rice Fiber 310, its components, and related fibers provide a sufficient basis for an assessment of the safety of Rice Fiber 310 in the proposed use as a food ingredient that is prepared according to appropriate specifications and used according to cGMP.

Therefore, the proposed use of Rice Fiber 310 is safe within the terms of the Federal Food, Drug, and Cosmetic Act (meeting the standard of reasonable certainty of no harm). It is also GRAS by consensus among experts. In addition, it 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.

I.G. Availability of information

The data and information that serve as the basis for this GRAS determination will be sent to the FDA upon request. They are also available for the FDA's review and copying at reasonable times at the office of SunOpta Ingredients Group or NutraSource, Inc.

II. DETAILED INFORMATION ABOUT THE IDENTITY OF THE NOTIFIED SUBSTANCE

II.A. Common or trade name: Rice Fiber 310 or rice hull fiber

II.B. Standards of identity: We note that an ingredient that is lawfully added to food products may be used in a standardized food only if it is permitted by the applicable standard of identity that is located in Title 21 of the Code of Federal Regulations.

II.C. Background

SunOpta's Rice Fiber 310 is processed from rice hull by a proprietary hydrothermal process. Rice Fiber 310 which consists of mostly insoluble dietary fiber can be added to food for several purposes. Examples include raising total fiber content, reducing caloric content, and controlling water activity of foods and beverages.

Grain fiber (or cereal fiber), such as rice hull fiber, rice bran, or oat hull fiber, have been used to produce various types of food products. Examples include: breakfast cereals, baked goods, rice cakes, tea, pasta, and noodles. Rice has been cultivated for two thousand years. Rice hull and rice bran fiber have been recognized as an excellent source of fiber.

Inadequate intake of dietary fiber increases risk of chronic diseases such as diverticular disease/constipation, heart disease, cancer, diabetes, metabolic syndrome, and overweight/obesity (IOM, 2002, 2006). Americans consume approximately one half of the recommended intake levels of total fiber (King et al., 2012; Thompson et al., 2005). Thus, the IOM (IOM, 2002, 2006) and Dietary Guidelines for Americans (USDA/US DHHS, 2005, 2010) recommend increased consumption of fiber-rich foods.

II.D. Physicochemistry and structure of Rice Fiber 310

Rice hull fiber has >91% total fiber, of which >97% is insoluble dietary fiber. The rice hull fiber contains no sulfites, added flavors, components from an animal source, BHA, BHT, genetically altered plant material, or irradiated material.

<u>General Physical Properties</u>

Color: Cream to beige
Flavor: Bland to slightly sweet, no off flavors
Physical form: Fine powder (particle size; > 40% retained on Mesh # 325, > 20% retained on Mesh # 200, and less than 10% retained on Mesh #100)
Water holding capacity: >300% of fiber weight

II.E. Manufacturing Process

Manufacturing process for SunOpta's Rice Fiber 310 is shown in Figure 1.

Briefly, the process involves the following procedure:

1) Slurry generation process
2) Alkaline silicone solubilization
3) Dewatering 1

4) Wet solids recovery 1
5) Re-slurry 1
6) Alkaline peroxide bleaching and delignification
7) Dewatering 2
8) Solids recovery 2
9) Re-slurry 2
10) Adjustment of pH with acid
11) Dewatering 3 and
12) Milling/drying.

Detailed procedure

1. Rice hulls are cleaned using mechanical detachers, gravity separators, sieves, and air classifiers to separate rice hull from any residual impurities.
2. Ground rice hull is suspended in clean water (10-20% solids concentration) to form a slurry in a reception tank at 38-60 ^{o}C.
3. Food grade sodium hydroxide is added to adjust the pH to 11.0 – 11.7. Temperature control is important to avoid a temperature increase above 61 ^{o}C.
4. The suspension is well blended in an alkaline environment at 38-60 ^{o}C for 5-10 h to extract ash, rice protein, and starch.
5. The rice hull fiber is separated from aqueous solution containing silicon dioxide (dissolved as sodium silicate) and some dissolved lignin by a decanter-type centrifugal separator, followed by washing with clean water. The liquid phase is pumped and sent to a sewer for waste treatment.
6. The wet, silicone-free solids from the decanter are re-suspended in water to form a slurry ("sluice water").
7. The resulting slurry is fed to a tank or series of tanks for alkaline peroxide bleaching/delignification with some addition of an alkaline solution to keep the pH between 9.5 – 9.7.
8. There is live steam injected into Tank T5 to increase the temperature to 82-85 ^{o}C. The silicon-free solids spend about 8 h of mean residence time as it goes through 2 stirred tanks (T5 and T6). The alkaline peroxide treatment is performed at a temperature at 80-88 °C. The silicon free solids require 4-8 hours of mean residence time to reach the desired product functionality.
9. The slurry coming out of the alkaline peroxide bleaching/delignification is fed to a continuous decanter where the liquid phase is separated from the wet solids. The liquid phase is again pumped for waste water treatment.
10. The wet solid is again re-suspended in water to form a slurry and is mixed with an acid (such as sulfuric acid) to reach a pH of 2.5 - 4.0. This step helps reduce yellowness in the final product.
11. The slurry out of the acidification step is dewatered and the wet solid is sent for milling using wet mills in series. These wet mills also dry the product at the same time as they reduce its particle size.
12. Rice fiber then is packaged and stored at room temperature. Rice fiber produced in this manner has silky mouth-feel and excellent water adsorption properties. Rice fiber is produced under the Good Manufacturing Process (GMP). In addition, additional quality

control (QC) programs (such as plant sanitation, pest control, chemical control, and preventative maintenance programs) are routinely performed at SunOpta's manufacturing facilities. Laboratory use meets OSHA regulations.

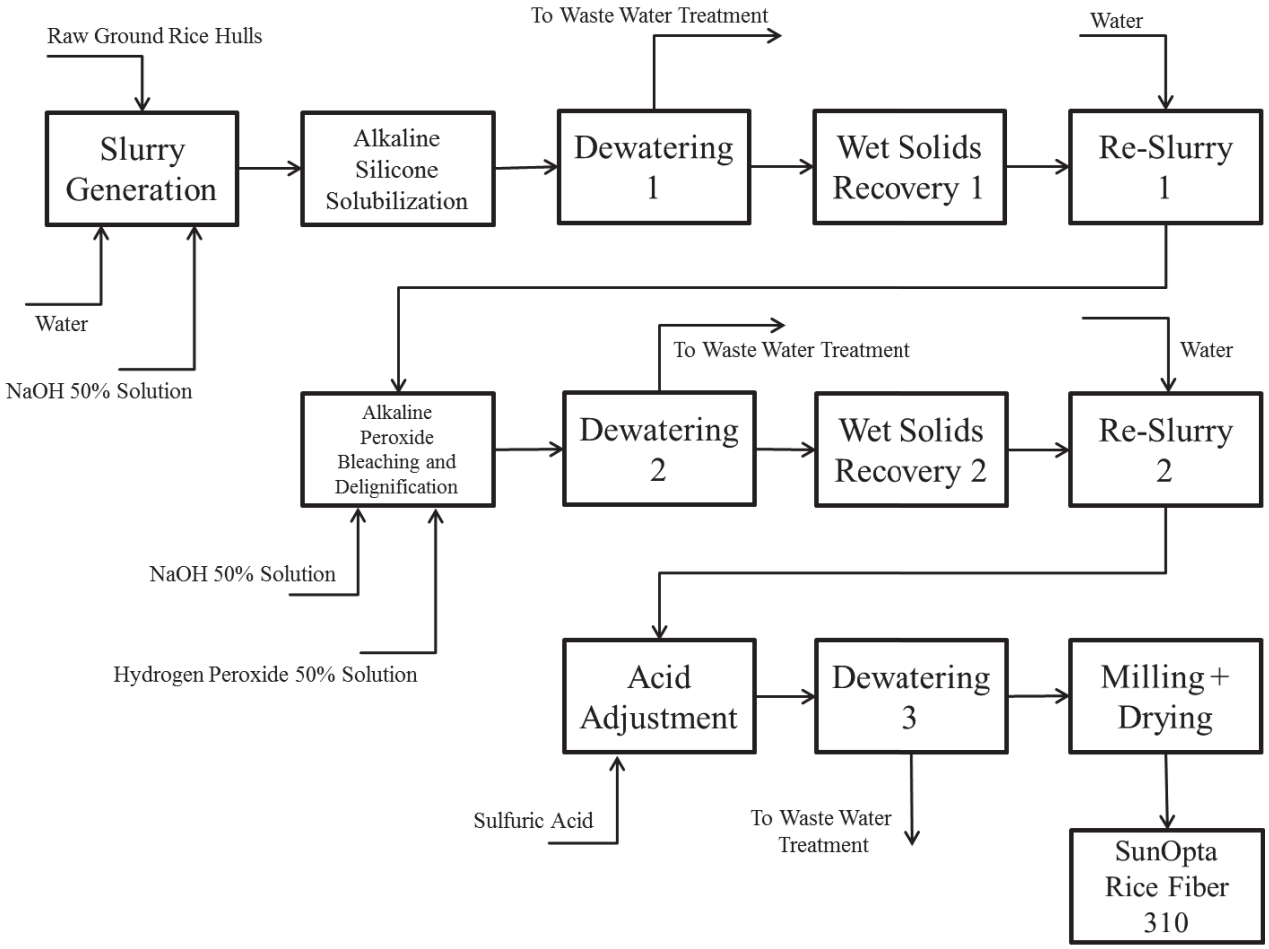


Figure 1. SunOpta Rice Fiber 310 manufacturing process flow diagram

Quality Control

A typical analysis of raw ground rice hulls shows the following results (as is basis).

Table1. Composition of incoming raw ground rice hulls before processing

Analyte	Range	Method
Ash	18% - 22%	AOAC 930.22
Starch	2% - 3%	ECL 123/72
Protein (Nx6.25)	2% - 3%	AOAC 991.20.I
Total Dietary Fiber	63% - 66%	AOAC 985.29

II.F. Specifications

Table 2 lists specifications of rice hull fiber.

Table 2. Specifications of rice hull fiber

Macronutrient	Value	Unit	Analytical method
Total fiber (dry wt. basis)	>91	%	AOAC 991.43
Protein	<1.5	%	AOAC 992.15
Starch or sugars	<0.1	%	By difference
Fat	<0.5	%	AOAC 996.06
Moisture	<4.0	%	AOAC 934.01
Silicon	<1.5	%	Perkin-Elmer AA method, 2001
Ash	<4.0	%	AOAC 923.03
Lead	<1	ppm	AOAC 990.08
Arsenic	<1	ppm	AOAC 990.08
pH, 5% slurry	6.5-7.4	pH	
Microbiological Specifications			
Total plate count	<1,000	cfu/g	FDA-BAM Chap. 3
Coliform	<3	cfu/g	FDA-BAM Chap. 4
Salmonella	Negative	cfu/g	FDA-BAM Chap. 5
Yeast and mold	<20	cfu/g	FDA-BAM Chap. 19

cfu = colony forming units; BAM = Bacteriological Analytical Manual, January, 2001.

III. INTENDED USES AND EXPOSURE ESTIMATES

III.A. Food sources of rice hull fiber

Rice Fiber 310 is a natural source of rice fiber (mostly from rice hull and partly from rice bran).

<u>Composition of dietary fiber of Rice-Fiber 310 and related fiber ingredients</u>

The composition analysis shows that Rice Fiber 310 consists of approximately 49% cellulose, 34% hemicelluloses (of which 70% are arabinoxylans), and 17% Klason lignin. As shown in Table 3, the composition of Rice Fiber 310 is comparable to those of other grain fibers such as rice bran, oat hull fibers, oat bran and wheat bran, which are already recognized as

GRAS ingredients. In particular, Rice Fiber 310 and rice bran fiber share similar composition and physicochemical properties: Most of these fibers consist of cellulose, arabinoxylans, and lignins and are insoluble in water (>90% insoluble fibers). These insoluble fibers are expected to have similar metabolism in humans; insoluble fibers act as a bulking agent in the colon to relieve constipation and are fermented to SCFA and some gases although their degree of fermentation is less than that of soluble fibers. Thus, our GRAS review has included toxicity data of rice bran and rice bran fibers to corroborate the safety of Rice Fiber 310, rice hull fiber.

Table 3. Total fiber composition of various grain components

	Rice Fiber 310[1]	Rice hull[2]	Rice bran[3]	Oat hull[2,4]	Oat bran[4,5]	Wheat bran[5,6]
Total fiber	94.0		20.9-27.0		18.4	30-84.3
Composition of total fiber, %						
Hemicellulose	33.6	33.7	44.7	48.3		Up to 70
Cellulose	49.2	47.5	31.5	38.8		Up to 29
Klason lignin	17.2	18.6	17.5	11.6	10.3	8.3-18.4
Distribution of soluble and insoluble fiber, %						
Soluble fiber	7	NA	<10	0.9	20.2	<10
Insoluble fiber	93	NA	>90	99.1	79.8	>90
Neutral sugar composition, % of total fiber						
Arabinose res.	2.7		20.2		9.5	17.5
Xylose res.	21.1		19.2		14.5	34.8
Mannose res.	0.5		NA		2.8	0.6
Galactose res.	1.0		2.8		2.3	1.5
Glucose res.	54.7		33.9		54.7	21.1
Uronic acid res.	1.9		6.3		5.6	5.2

*[1]Data from Dr. PerAman's lab, Swedish University of Agriculture, Uppsala, Sweden, using the AOAC method 994.13;[2]Data from Rasper, 1979. Rice hull composition data are for the insoluble fiber fraction; [3]Data from Hsu et al. (1996; cellulose/hemicelluloses/lignin composition) and Mod et al. (1978; neutral sugar composition of hemicellulose); [4]Soluble/insoluble fiber distribution data from Theander and Aman 1979; [5]Data from Theander et al., 1995 (AOAC 994.13; neutral sugar composition); [6]Ortiz and Lafond, 2012, (cellulose/hemicelluloses/lignin composition); Data from Neutral sugar residue values are reported as their polymeric form by multiplying 0.9 on the values of monomers as measured by GLC (AOAC 994.13). Estimation of cellulose content for Rice Fiber 310 and rice bran is based on the assumption that 90% of glucose residues in insoluble fibers are present in a cellulose form.

III.B. Intended use

Intended use of Rice Fiber 310 is similar to that of rice bran fiber which is described in GRN 373. Rice Fiber 310 is proposed for general food use at concentrations consistent with cGMP. Rice Fiber 310 has many food applications, including, but not limited to, prepared foods, general foods (such as snack foods, bakery products, cereals, crackers, pasta products, dough conditioners, beverages, sports beverages), meal replacement, gluten-free foods, and medical foods. Medical foods are defined as food which is formulated to be consumed or administered

enterally under the supervision of a physician, and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation. Intended use excludes infant formulas and foods that fall under USDA jurisdiction, such as catfish, poultry, pork, beef, and egg products. In most cases, concentration of rice hull fiber approaches technically feasible maximums (approximately 5-10% in beverages and some bakery products and 25% in ready-to-eat cereals) while being acceptable from a sensory perspective.

III. C. Probable consumption of rice hull fiber

Consumption of Rice Fiber 310 is not expected to exceed 25-28 g per day. The IOM, the National Academy of Sciences (NAS), has recommended a daily intake of 14 g fiber per 1,000 calories for Americans (IOM, 2002, 2006).

Despite the recommendations of the IOM, most Americans consume inadequate amounts of dietary fiber. The median intakes of fiber in the U.S. were estimated to be approximately one half of the recommended levels, the Daily Reference Intakes (DRI). Average daily fiber consumption was 15.6 g in 1999-2000 and 15.9 g in 2007-2008 (King et al., 2012). Thus, it is reasonable to conclude that fiber intake status did not change significantly over the past decade. It is expected that food manufacturers would replace current fiber ingredients with Rice Fiber 310 for new product development. Thus, it is not likely that the availability of a new rice hull fiber ingredient will significantly boost fiber intake levels in the American population.

IV. BASIS FOR GRAS DETERMINATION

IV.A. Current regulatory status

Cellulose, a major component of rice hull fiber, has been recognized as a GRAS substance since 1973 (LSRO, 1973). Also, xylose and arabinose, major components of rice hull fiber, also are considered as GRAS. In addition, FDA had no question on the safety of other fiber ingredients from grain sources (GRN 261 and 342, oat hull fibers; GRN 373, rice bran fiber) whose total fiber composition is similar to that of Rice Fiber 310. These fibers mostly consist of cellulose, hemicelluloses (arabinoxylans), and lignin. FDA allowed three health claims related to dietary fiber intake and reduced risk of heart disease and cancer: 1) the reduced risk of cancer claim for fiber containing grain products, fruits, and vegetables (21CFR 101.76; FDA 1993a), 2) the reduced risk of coronary heart disease (CHD) claim for fruits, vegetables, and grain products that contain fiber, in particular soluble fiber (21CFR 101.77; FDA, 1993b), and 3) soluble fiber from certain foods and risk of coronary heart disease (21CFR 101.81; FDA, 2008). To be eligible for using the health claim, a food product must contain at least 2.5 g of total fiber per reference amount customarily consumed (RACC) in food. Foods providing 2.5 g fiber/serving from rice hull fiber is qualified for at least one health claim (the reduced risk of cancer claim for fiber containing grain products, fruits, and vegetables), if they meet the jelly bean rules (i.e., as part of low sodium and low fat diets).

Silica, a very minor component of Rice Fiber 310 (less than 1.5%) is also recognized as a GRAS ingredient (GRN 321).

IV.B. Intended technical effects

Rice hull fiber can be used as an ingredient in foods and beverages at concentrations consistent with cGMP.

IV.C. Review of safety data

IV.C.1. Metabolic fate of rice hull fiber

Rice hull is composed of dietary fiber (>91%) and silicon (<1.5%).

Dietary fiber components

Rice hull fibers are composed of mostly cellulose, arabinoxylans (hemicellulose), and lignin (Kumagai et al., 2003; Watanabe, 1983). The cellulose fraction of rice hull fiber fully resembles that of other fiber sources. Majority of cellulose is recovered in the feces as it remains largely undigested in the upper gastrointestinal tract and is not highly fermented in the colon (Spiller et al., 1980; Stephen, 1989). Thus, consumption of large quantity of fiber with high percentage of cellulose does not result in gastrointestinal discomfort. Therefore, the metabolism of cellulose derived from rice hull fiber does not raise safety concerns and no systemic toxicity is expected following ingestion of rice hull fiber.

The metabolic fate of the hemicellulose moiety of rice hull fiber fully resembles that of other non-digestible, hemicelluloses from rice bran and wheat bran. These insoluble fibers remain largely undigested in the upper gastrointestinal tract and are fermented in the colon leading to production of gases and SCFA which lowers the pH of the colon (Tomlin and Read, 1988). A number of health effects have been reported for SCFA, including improvement in bowel function, calcium absorption, lipid metabolism, and reduction of the risk of colon cancer (Scheppach et al., 2001). Any plant-derived dietary fiber that comprises sources of fermentable fiber (arabinoxylans, hemicelluloses) leads to generation, absorption and excretion of the same metabolites (H_2, CO_2, SCFA) as those produced upon consumption of rice hull fiber. Therefore, the metabolism of hemicelluloses derived from rice hull fiber does not raise safety concerns and no systemic toxicity is expected following ingestion of rice hull fiber.

Silicon component

Typical rice hulls contains approximately 20% of silica. However, SunOpta's purified rice hull fiber contains less than 1.5% silica. When 6 mo old lambs were fed 200 g/day rice hulls (containing up to 31 g silica/day) for 15 days, approximately 90% and 4% of silica were recovered in feces and urine, respectively (Mahmoud et al., 1982). Since most of silica is excreted in feces and urine, no systemic toxicity is expected following ingestion of small amount of silica.

IV.C.3. Safety studies in animals

Major components in grain fibers are cellulose, arabinoxylans (major components of hemicelluloses), and lignin. In particular, Rice Fiber 310 and rice bran fiber share similar composition and physicochemical properties: Most of these fibers consist of cellulose, arabinoxylans, and lignins and are insoluble in water (>90% insoluble fibers). These insoluble fibers are expected to have similar metabolism in humans. Thus, in addition to the safety studies of Rice Fiber 310 and rice hull (raw material from which Rice Fiber 310 is extracted), our GRAS review has included safety studies of components of Rice Fiber 310, such as cellulose and hemicellulose, in particular arabinoxylan, as well as related fibers such as rice bran and rice bran fibers.

IV.C.3. 1. Safety studies of SunOpta's Rice Fiber 310

IV.C.3. 1.1. A mutagenicity study of Rice Fiber 310

Gao et al. (2013) evaluated the potential mutagenicity and genotoxicity of rice fiber using a bacterial reverse mutation assay. In a reverse mutation assay using five strains of *Salmonella typhimurium* (TA97, TA98, TA100, TA102 and TA1535), Rice Fiber 310 (5000, 2500, 1250, 625 and 312.5 μg/plate) did not increase the number of revertant colonies in any tester strain regardless of metabolic activation by S9 mix.

IV.C.3. 1.2. A genotoxicity study of Rice Fiber 310

An *in vivo* bone marrow micronucleus test in Kunming mice dosed by oral gavage at up to 2000 mg/kg BW/day showed no significant or dose-dependent increases in the frequency of micronucleated polychromatic erythrocytes (Gao et al., 2013). These data indicate a low risk of genotoxic activity in Rice Fiber 310.

IV.C.3. 1.3. Subchronic toxicity study of Rice fiber 310 in rats

This 90-day feeding study in Sprague-Dawley rats investigated the subchronic toxicity of Rice fiber 310. Animals were randomly divided into four groups that received diets containing 0%, 2.5%, 3.75%, or 5.0% (w/w) Rice Fiber 310 for 90 days. Daily clinical observations and weekly measurements of BW and food consumption were recorded. Ophthalmic examinations were performed at pre-test and termination. At the end of study, hematology, clinical biochemistry outcomes, and urine analysis were measured. In addition, histological examinations were performed on all tissues from animals in the control and high-dose groups. No treatment-related abnormalities were observed from ophthalmic, serum biochemistry, hematology, urinalysis, or histological examinations. The authors concluded that NOAEL for Rice Fiber 310 was 5.0% for both genders (females, 3,800 mg/kg BW/day; males, 4,110 mg/kg BW/day).

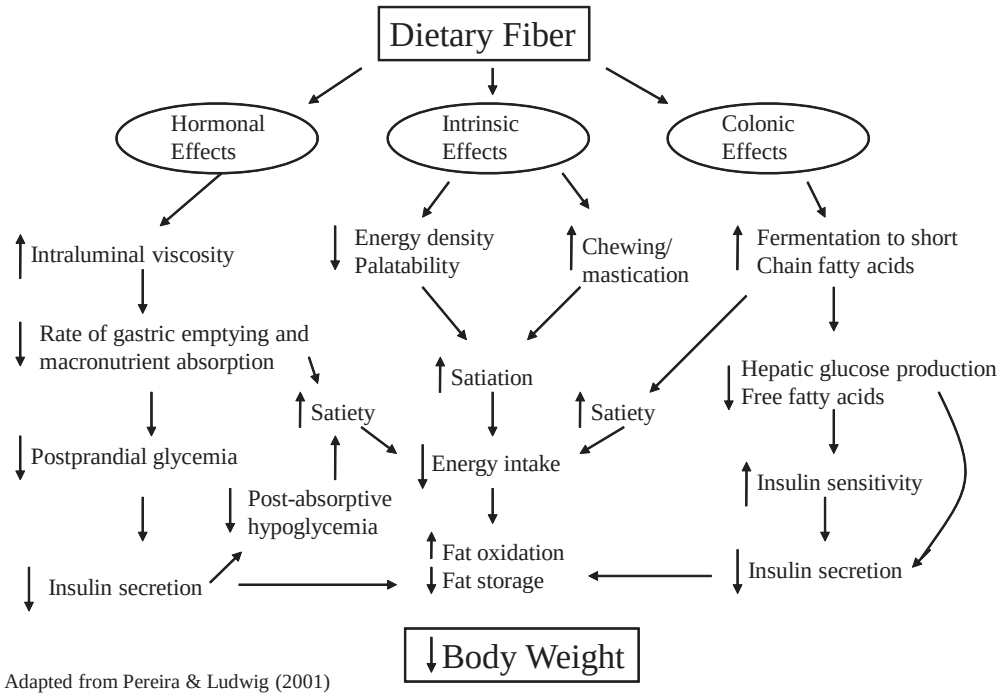
In this study, the only minor changes (not significant) observed were a tendency of decreased body weights (p=NS) and decreased serum concentrations of fasting blood glucose and total cholesterol in males rats ($P<0.05$) which are not considered to be toxicological concerns.

Instead, these changes are considered as positive health benefits. It is well known that consumption of fiber rich foods is associated with decreased food intakes and body weight loss. Howarth et al. (2001) summarized 10 human randomized clinical trials on the effects of dietary fiber on energy intake, and body weight. With ad libitum energy intake, the average effect of increasing dietary fiber across all the studies indicated that an additional 14 g of fiber per day resulted in a 10% decrease in energy intake and a weight loss of over 1.9 kg through about 3.8 months of intervention. Several mechanisms of action have been proposed for the action of dietary fiber/non-digestible carbohydrates in weight control (Pereira and Ludwig, 2001; Figure 2): 1) Fiber displaces available calories and nutrients from the diet; dietary fiber or non-digestible carbohydrates have lower calories (0-2 Kcal/g) than digestible carbohydrates (4 Kcal/g), 2) fiber increases chewing which limits intake by promoting the secretion of saliva and gastric juice, resulting in increased satiety; 3) fiber delays gastric emptying, 4) fiber improves insulin sensitivity which leads to weight control, and 5) fiber has hormonal effects that lead to increased satiety.

These characteristics of fiber have become the basis of a few authoritative statements on the beneficial effects of fiber on calorie intakes and body weight control. The term "authoritative statement" comes from the Food and Drug Administration Modernization Act (FDAMA) legislation that was enacted in November of 1997. FDAMA permits claims based on current, published authoritative statements from "a scientific body of the United States with official responsibility for public health protection or research directly related to human nutrition . . . or the National Academy of Sciences (NAS) or any of its subdivisions." FDA (1998) states that other federal agencies may also qualify as appropriate sources for such authoritative statements (FDA, 1998). Along with NAS (or any of its subdivisions), the agency currently considers that the following federal scientific bodies may be sources of authoritative statements: the Center for Disease Ccontrol, the National Institute of Health, and the Surgeon General within Department of Health and Human Services (DHHS); and the Food and Nutrition Service, the Food Safety and Inspection Service, and the Agricultural Research Service within the Department of Agriculture.

1) The NAS (2001) states the satiety benefits of dietary fiber as follows: "Diets high in fiber are associated with slower stomach emptying, which induces a short-term increase in satiety (Roberfroid, 1993). This may modulate caloric intake and the rate of nutrient absorption. In addition, the reduced caloric density of diets rich in fiber has been suggested to be an asset in weight maintenance."
2) "Foods low in fat and high in naturally occurring fiber appear to induce satiety in humans at lower levels of caloric intake than do high fat, low fiber foods." (Surgeon General's Report (US DHHS, 1988, p. 292).
3) "There are two kinds of fiber: insoluble fiber, which exerts its effects primarily in the digestive system, and soluble fiber, which has effects on substances in the blood stream. Diets high in both kinds of fiber tend to be bulky, and since fiber itself does not contribute calories, foods high in fiber tend to contain fewer calories in the same volume of food. These characteristics of high-fiber diets may help assuage hunger and thus contribute to weight loss." (NAS Eat for Life, 1992).
4) "The high fiber content of many whole grains may also help you to feel full with fewer calories." (USDA/US DHHS, 2010).

Figure 2. Effects of dietary fiber on body weight



Adapted from Pereira & Ludwig (2001)

IV.C.3. 2. Safety studies of rice hulls or rice husk

The terms, rice hull and rice husk, have been interchangeably used in the literature.

IV.C.3. 2.1. Studies reporting antioxidant and anti-mutagenic activities of rice hulls or rice husk

Rice husk represents approximately 20% of unmilled rice and is a byproduct of the rice milling industry. Rice husks offer the valuable nutritional advantage that they contain an antioxidant defense system to protect the rice seed from oxidative stress (Asamarai et al., 1996; Butsat and Siriamornpun, 2010a, 2010b; Bursat et al., 2009; Jeon et al., 2006; Lee et al., 2003; Osawa et al., 1985; Ramarathnam et al., 1988, 1989). Ferulic acid and p-coumaric acid are known to be major phenolics present in rice husks (Butsat and Siriamornpun, 2010a, 2010b; Butsat et al., 2009). Isovitexin present in rice hull is also known to be a potent antioxidant (Huang et al., 2005).

Okuno and Miyazawa (2007) reported that components of rice husk showed a suppressive effect on umu gene expression of the SOS response in *Salmonella typhimurium* TA1535/pSK1002 against the mutagen, Trp-P-1, which requires liver metabolizing enzyme. Gene expression was suppressed by 32.6% at less than 0.60 mM. Furthermore, rice husk extract had anti-mutagenic activities against other mutagens, such as 2-amino-3,4-dimethylimidazo[4,5-

f]quinoline (MeIQ), activated MeIQ, furylfuramide (AF-2), MNNG, and UV-irradiation. Thus, rice bran and husk can be considered as valuable sources of bioactive components with high antioxidant and anti-mutagenic properties.

IV.C.3. 2.2. Short term effects of rice hull on feed consumption, GI functions, and/or body weight gain

As summarized in Table 4, short term studies reported rice hulls at the dose of up to 10-60% in the diet did not show adverse effects in various animals (Fraga et al., 1991; Hodge et al., 1986; Khokhar , 1984; Kinser et al., 1988; Lu et al., 2011; Mahmoud et al., 1984; Singh and Gupta, 1984; Verstegen et al., 1990; Watson et al., 1986 Yu et al., 1998).

Table 4. Short term studies reporting no adverse effects of rice hulls in animals.

Animal	Dose, % in the feed	Duration	Primary endpoints	Reference
Subacute effects of rice hull				
Calves	33.8-58.5% replacement for wheat straw	7 d	Digestibility, consumption of dry matter	Singh and Gupta, 1984
Dairy cattle	50% rice husk	14 d	dry matter intake, nitrogen retention, nitrogen free extract digestibility	Khokhar, 1984
Rabbit	10% crude fiber from RH	15 d	mean GI retention time, cecal crude fiber and SCFA concentration	Fraga et al., 1991
Sheep	10-30%	15 d	live weight, feed intake, ruminal pH	Verstegen et al., 1990
Sheep	25%	18-21 d	nutrient digestion, flow of digesta	Kinser et al., 1988
Sheep	20-40%	21 d	live weight, feed intake, apparent digestibility	Hodge et al., 1986
Sheep	20-40%	30 d	ruminal fermentation, ruminal pH	Watson et al., 1986
Lambs	200 g/day rice hull containing up to 31 g silica/day	15 d	dry matter digestibility	Mahmoud et al., 1984
Ganders	20, 40, and 60%	21 d	feed intake, daily weight gain, organ wt, thickness of the gastric walls, gizzard length, all gut components lengths	Lu et al., 2011
Geese	13.2%	4 wk	food intake, daily weight gain, the relative weight, length and histopathology of the small intestine	Yu et al., 1998

d=day; wk=week

<u>Calves and dairy cattle</u>

When wheat straw was replaced with alkali-treated rice husk (replacement level: 33.8-58.5%) for 7 days, the dry matter digestibility and consumption of dry matter and roughage were

not changed in calves (Singh and Gupta, 1984). Also, a diet containing 50% rice husk did not adversely impact daily dry matter intake, nitrogen retention, or nitrogen free extract digestibility when adult dairy cattle were maintained on rice husk and wheat straw based feeds for 19 days (Khokhar, 1984).

Rabbit

Fraga et al. (1991) investigated the effect of type of fiber on rate of passage and on production of soft feces by finishing rabbits. Five diets, formulated to provide 10% crude fiber (CF) expressed on a dry matter (DM) basis, were tested for 15 days in 130 rabbits. Sixty percent of this dietary fiber was supplied by alfalfa hay, citrus pulp, beet pulp, grape marc, or rice hulls in the diets. Cecal CF level and molar proportion of acetic acid were significantly higher and molar proportion of butyric acid were lower in rice hull compared with alfalfa diets. Diet had no influence on daily soft feces excretion (10 g DM/day). Mean gastrointestinal retention time was found to be higher (21.3 h) in the rice hull-based diet. No adverse effects of rice hulls were reported.

Sheep

Kinser et al. (1988) determined effects of feeding corncobs, rice hulls, or a combination of both on nutrient digestion and flow of digesta through the gastrointestinal tract of multiple-cannulated sheep, as well as ruminal, digestive, and metabolic characteristics of early-weaned lambs fed pelleted 75% concentrate-25% roughage diets for 18-21 days. In trial 1, apparent total DM, organic matter, and neutral detergent fiber (NDF) digestibilities decreased and nitrogen digestibility increased as the percentage of dietary corncobs decreased and percentage of rice hulls increased. Site of NDF digestion appeared to shift from the upper to the lower digestive tract as percentage of corncobs decreased and percentage of rice hulls increased. In trial 2, apparent DM digestibility decreased as corncobs were replaced with rice hulls in the diet. Neutral detergent fiber digestibility was not affected by diet except in larger lambs at higher intakes, with NDF digestibility generally decreasing as percentage of dietary rice hulls increased. Nitrogen digestibility was not affected by replacing corncobs with rice hulls in the diet. Ruminal pH decreased as rice hulls replaced corncobs in the diet. The authors concluded that rice hulls can be effectively substituted for corncobs in sheep diets when added at levels up to 25% of the total diet. No adverse effects of rice hulls were reported.

Watson et al. (1986) reported that high wheat (74%) diets lowered the ruminal pH and that addition of rice hulls (20-40%) to wheat-based diet for 30 days helped stabilize ruminal fermentation and increase ruminal pH in sheep. However, Verstegen et al. (1990) found that addition of rice hulls (10-30%) to a grain based diet for 15 days did not change live weights, feed intakes, or ruminal pH. No adverse effects of rice hulls were reported from either study. From a 21 day feeding study, Hodge et al. (1986) reported that rice hulls (20-40%) can be safely added to wheat-based diet without impacting organic matter intake, apparent digestibility, or live weights of sheep.

Ganders

Lu et al. (2011) investigated the directionality, scaling and reversibility of phenotypic responses of the gastrointestinal tract of adult ganders to rice husk diluted dietary switching. A total of 96 140-day-old ganders were acclimatized to a basal diet for 2 weeks. The birds were randomly assigned to 4 treatments (0, 20, 40, or 60% rice husk by weight) for 21 days. Increasing rice husk content significantly increased feed intake. The weights of geese fed on the 600 g/kg rice husk diet for 21 days were reduced (60% vs. control: 3.10 vs. 3.36 kg) although the body weights were not significantly different among the groups at day 42. At day 21, thickness of the two gastric walls, gizzard length (60% vs. control: 3.04 vs. 2.51 cm/kg, $p<0.05$), and all gut components lengths (60% vs. control: 2.89 vs. 2.42 cm/kg, $p<0.05$) increased significantly in birds fed the 600 g/kg rice husk diet compared with the other three groups. No significant differences were noted in the relative weights or lengths of the gastrointestinal tract, except for the ceca (60% vs. control: 1.65 vs. 1.31 cm/kg, $p<0.05$), which were significantly heavier in birds fed on 60% rice husk diet. It should be noted that the trophic effect of fermentable fiber on colonic epithelial cell proliferation has been attributed to SCFA production resulting from the anaerobic fermentation of structural oligo- and polysaccharides by bacteria (Sakata, 1987; Sakata and von Englehardt, 1983). Increased cecum weights following consumption of other indigestible carbohydrates in rodents is a well established phenomenon and is not considered to have toxicological relevance to humans (WHO, 1987). No adverse effects of rice hulls were reported.

Geese

Yu et al. (1998) examined the effects of dietary fiber sources on growth and on the development of the gastrointestinal tract of growing geese. Six-week-old female White Roman geese were randomly divided into 6 groups with 6 dietary treatments for 4 weeks. Diets were isoenergetic and isonitrogenous and contained alfalfa meal (27.7%), barley bran (23.9%), rice hulls (13.2%), cellulose (6.3%), pectin (6.2%), or lignin (6.2%) as the major dietary sources of fiber. Rice hull fiber did not adversely impact food intake, daily weight gain, food conversion, or the relative weight and length of the small intestine. No histopathological damage of the villi was observed in the different intestinal segments of the geese on any of the treatments.

Lambs

Mahmoud et al. (1984) found no adverse effects from lambs consuming 200 g/day rice hull containing up to 31 g silica/day for 15 days.

IV.C.3. 2.3. Subchronic effects of rice hull on feed consumption, body weight, GI functions, and metabolism

Subchronic studies in various animals reported no adverse effects of rice hull at the dose of up to 60% in the diet (Table 5; Gierus et al. 1993; Santos et al., 1979;Vijayagopalan and Kurup, 1972).

Table 5. Subchronic studies reporting no adverse effects of rice hull in animals.

Animal	Dose, % in the feed	Duration	Primary endpoints	Reference
Subchronic effects of rice hull				
Rabbit	11-29%	72 d	feed intake body weight gain	Gierus et al. 1993
Rat	a polysaccharide fraction isolated from the defatted bran and husk of paddy rice	4 mo	Blood lipids, hepatic NAD-NADP conc., myocardial lipoprotein lipase activity	Vijayagopalan and Kurup, 1972
Calves	25-60%	24 wk	milk fat production, body weight, feed consumption	Santos et al., 1979

Rabbit

Gierus et al. (1993) investigated effects of rice hulls on growth performance of 30 day-old weaned rabbits. Rabbits were fed one of 5 diets containing rice hulls (RH) and/or Bermuda grass (BG) as fiber sources in the following proportions (BG/RH) 0/17.5, 15/11, 0/29, 14.7/19.1, or 48.5/0 for diets A, B, C, D, and E, respectively, for 72 days. The time necessary to attain 2 kg of live body weight was not affected by the diets. However, diets C and D resulted in a lower body weight gain (g, control, 1010; C, 813; D, 719 g; $p<0.05$) probably because of the high concentration of acid detergent fiber (ADF) in the diet (23-24%). No adverse effects of rice hulls were reported.

Rats

Vijayagopalan and Kurup (1972) reported hypolipidemic activity of a polysaccharide fraction isolated from the defatted bran and husk of paddy rice in rats fed a high fat-cholesterol diet for 4 mo. Rats receiving this substance had the lowest concentration of hepatic NAD-NADP, the highest level of myocardial lipoprotein lipase, and a normal blood glucose concentration after an oral glucose load. No adverse effects of a polysaccharide fraction isolated from the defatted bran and husk of paddy rice were reported.

Calves

Santos et al. (1979) evaluated fine milled rice hull as a potential livestock feed in 12 Murrah buffalo calves. Calves received fine rice bran concentrate feed (control; 50% in the feed) or rice hull feed (50, 100, or 120% of replacement of rice bran with fine milled rice hull) for 24 wk. All 4 types of feed produced comparable milk fat production, body weights, and feed consumption. Thus, authors concluded that fine milled rice hull can be used satisfactorily as a complete substitute to the fine rice bran. No adverse effects of rice husk were reported in any of the studies.

IV.C.3.3. Safety studies on components of rice hull fiber

Toxicity studies of purified cellulose (a major fiber component in rice bran) and other cereal brans showed no adverse effects (Anderson et al., 1992).

IV.C.3.3.1. Safety studies of cellulose, a major component of rice hull fiber

Summary: In 1973, cellulose was recognized as a GRAS substance (Anderson et al., 1992; LSRO, 1973). Anderson et al. (1992) also reviewed the safety of cellulose. The comprehensive review of Anderson et al. (1992) concluded that human exposure to cellulose would not result in any adverse health effects. Details of review are described below and in Table 6. Overall, most of cellulose is recovered in the feces as it remains largely undigested in the upper gastrointestinal tract and is not fermented in the colon to gases and SCFA. Thus, gastrointestinal discomfort is not expected with consumption of cellulose. Consumption of large quantity of cellulose also did not affect gastrointestinal morphology. The only possible effect might be on body weight mostly due to its caloric dilution effect. Therefore, the metabolism of cellulose does not raise safety concerns and no systemic toxicity is expected following ingestion of cellulose.

Effects of cellulose on tumor

The review of Anderson et al. (1992) found that chronic ingestion of purified cellulose over the lifespan of rats and mice did not increase spontaneous disease or neoplasia (in the mammary glands, colon, or bladder of rats), nor did it significantly alter the absorption or metabolism of dietary components. Several studies evaluated the role of exogenous cellulose on tumor incidence based on the assumption that diets containing exogenous cellulose should lead to an increased cancer rate when administered subsequent to a dose of a site specific carcinogen. In various models, cellulose did not display tumor promoting activity at large doses. In rats, 10-30% cellulose in the diet was administered for 24 weeks after exposure to azoxymethane (AOM) to induce large bowel tumors (Nigro et al., 1979). Tumor rates in animals ingesting cellulose were lower compared to fiber free diets. Diets containing up to 46% cellulose were protective against mammary tumor promotion for 120 or 134 days after exposure to 7,12-dimethylbenz[α]anthracene (DMBA; Kritchevsky et al., 1984).

Effects of cellulose on reproductive performance and growth

No adverse effects were noted on reproduction or neonate development in rats using 30% cellulose in the diet (Anderson et al., 1992; LSRO, 1973).Also, 5% cellulose diet did not cause any abnormal reproductive performance such as pups per litter, pup survival, and pup growth in mice and rats (Anderson et al., 1992; Bieri et al., 1977). Teratogenic effects were not observed.

Evaluation of effects of cellulose on growth revealed that cellulose had no adverse effects in rats and mice. Growth rates for up to 18 weeks after weaning were not affected in both rats and mice when 5% cellulose diet was administered (Anderson et al., 1992; Bieri et al., 1977; Hove and King, 1979). Dietary concentrations of 20% cellulose for 4 weeks did not retard growth of rats (Hove and King, 1979). Rat pups consuming diet containing 28.6% cellulose had decreased carcass fat due to lower calorie intake related to caloric dilution effects of cellulose (Wojcik and Delorme, 1983). Also, rat pups consuming 10% and 20% cellulose diets gained less body weight due to caloric dilution of diet and no increased food consumption to compensate caloric dilution (Sundaravalli et al., 1971). However, feeding 40% levels of cellulose in isocaloric, isonitrogenous diets did not affect growth when compared to a diet with 5% cellulose (Anderson et al., 1987). As discussed in the section of Subchronic toxicity study of Rice Fiber

310 in rats, effects of total fiber and cellulose on body weight are mostly due to caloric dilution and are considered as positive attributes.

Effects of cellulose on the gastrointestinal tract

As the gastrointestinal tract directly exposed to ingested cellulose, which remains intact in the large intestine, the effect on intestinal structure and physiology are important endpoints for the safety evaluation of cellulose. Several studies showed that large doses of cellulose did not adversely alter cell morphology or cell dynamics in the gastrointestinal tract in mice and rats (Vahouny et al., 1981; Goodlard and Wright, 1983; Lupton et al., 1988).

Efficacy studies

Several efficacy studies testing the effect of cellulose on glycemic responses and digestibility reported no adverse effects of cellulose in cats, dogs, mice, and rats (Table 6; Delorme et al., 1981; Hasegawa et al., 1990; Nelson et al., 1991, 1998, 2000; Schwartz et al., 1980; Vahouny et al., 1987, 1988). Doses up to 20% cellulose in diet were tested and the duration of the studies were up to 8 months.

Table 6. Studies showing no adverse effects of cellulose in animals

Animal	% cellulose in diet	Duration	Primary measurement endpoints	Reference
Carcinogenesis				
Rat treated with AOM	10, 20, or 30%	24 wk	Large bowel cancer incidence	Nigro et al., 1979
Rat treated with DMBA	8-46%	120 or 134 d	Mammary tumor promotion	Kritchevsky et al., 1984
Reproductive performance and growth				
Rat	30%	3 generations	Reproductive performance	LSRO, 1973
Rat and mice	5%	Up to 18 wk after weaning	Teratogenic effects and growth rates	Bieri et al., 1977
Rat, weaning males	20%	4 wk	Wt gain, food consumption, cecal wt, cecal SCFA	Hove and King, 1979
Rat pups	4.8, 9.1, 16.7, or 28.6%	4 wk	Wt gain, food consumption, carcass fat	Wojcik and Delorme, 1983
Rat pups	Up to 40%	4 wk	Wt gain, food consumption	Anderson et al., 1987
Rat pups	5, 10, or 20%	4 wk	Weight gain, food consumption	Sundaravalli et al., 1971
Gastrointestinal effects				
Mice	30%	1 wk	Body wt, histology of the intestine	Goodlard and Wright, 1983
Rat	15%	6 wk	Body wt, histology of the intestine	Vahouny et al., 1981
Rat	10%	35 wk	Body wt, histology of the intestine	Lupton et al., 1988
Efficacy studies showing no adverse effects of cellulose				
Cats with naturally acquired diabetes mellitus	12%	24 wk	caloric intake, body weight, or postprandial serum glucose concentration	Nelson et al., 2000
Dogs with naturally acquired diabetes mellitus	12%	8 mo	Pre- and postprandial serum glucose concentration; urinary excretion of glucose	Nelson et al., 1998
Dogs with alloxan-induced diabetes mellitus	15%	8 wk	postprandial serum glucose concentration;	Nelson et al., 1991
Rat	10%	5 wk	intestinal glucose absorption	Schwartz et al., 1980
Rat, weaning	5, 10, 20, or 40%	4 wk	Growth and digestibility	Delorme et al., 1981
Streptozocin induced diabetes mice	20%	8 wk	Growth rate, insulin secretion	Hasegawa et al., 1990
Rat	10%	4 wk	Fecal mass	Vahouny et al., 1987, 1988

IV.C.3.3.2. Safety of hemicellulose (mostly arabinoxylans), a second major component of rice hull fiber

Other fiber ingredients based on an arabinoxylose backbone, such as wheat bran (52-64% arabinoxylan; up to 70% hemicelluloses) and psyllium (85% arabinoxylan), are known for their fecal bulking effects and gastrointestinal regularity improvement without having negative effects on mineral bioavailability (Cho et al., 2001; Marteau et al., 1994; Slavin, 2008). These hemicellulose-rich fibers are fermented by intestinal microflora to produce SCFA that support colonic health. However, fermentation in the large intestine can result in the formation of gases (including hydrogen, carbon dioxide, and methane), which is often associated with flatulence and intestinal discomfort. Intestinal discomfort can be a transient symptom since the human body is able to adapt to higher intakes of dietary fiber over time. Overall, metabolites of hemicelluloses such as SCFA, CO_2, and H_2, do not raise safety concerns and no systemic risks are expected from the metabolism of hemicellulose fraction of Rice Fiber 310.

IV.C.3.4. Safety of rice bran fiber

Summary: Acute toxicity and mutagenicity tests of brown rice or rice bran fiber showed no adverse effects (Zhai et al., 1992). Consumption of defatted, heat-stabilized, or raw rice bran showed no adverse effects on animal health or feed nutritional quality when fed as 60% of the diet of chicks (Mujahid et al., 2004; Sayre et al., 1987), 30% of the diet of lambs (Tabeidian and Sadeghi, 2009), or up to 40% of the diet of pigs (Calvert et al., 1985).

IV.C.3.4. 1. Antimutagenic, antigenotoxic, and anticarcinogenic activities of rice bran fiber or rice bran

There is no evidence that rice bran or rice bran fiber is carcinogenic or mutagenic. Instead, rice bran and its fiber components showed anticarcinogenic, antimutagenic, and antitumor activities *in vitro* and in vivo studies (Aoe et al., 1993; CIREP, 2006; Higashi-Okai et al., 2004; Sera et al., 2005; Takenaka and Itoyama, 1993; Takeshita et al., 1992; Verschoyle et al., 2007; Zha et al., 2009). Inositols and inositol derivatives (Ogawa, 1999), γ-oryzanol (CIREP, 2006), phytic acid (Norazalina et al., 2010), tocols (Sun et al., 2009), phenols (Rao et al., 2010), and other flavones (Renuka Devi and Arumughan, 2007) are known as active components of rice bran.

IV.C.3.4.2. Safety of rice bran fiber observed from efficacy studies in animals

Several animal (hamster, rat, or chick) studies investigated cholesterol lowering actions of rice bran or rice bran fiber (Tables 7 and 8; Adrizal and Ohtani, 2002; Anderson et al., 1994; Ayano et al. 1980; Hundemer et al., 1991; Johnson et al., 1989; Kahlon 1989, 1990, 1992a, 1992b, 1993, 1996, 1998, 1999, 2000; Newman et al.,1992; Rouanet et al.,1993; Takenaka and Itoyama, 1993; Topping et al., 1990). In these studies, the concentration of up to 60% rice bran or 5% rice bran fiber in the diet and the length of studies were up to 3 weeks. No studies reported adverse effects of rice bran or rice bran fiber.

Table 7. Animal studies reporting no adverse effects of rice bran fiber

Animal	Dose, g/day	Duration	Endpoint	Reference
Rat	Rice bran hemicellulose	2 wk	Peripheral blood leukocytes, lymphocytes	Takenaka and Itoyama, 1993
Broiler chicks	Rice bran fiber as non-starch polysaccharides, 15% in diet	7 d	Nutrient digestibility	Adrizal and Ohtani, 2002

Table 8. Animal studies reporting no adverse effects of rice bran

Animal	Dose, g/day	Duration	Primary endpoints	Reference
Hamster	Full-fat RB containing 10% TDF	3 wk	Plasma and liver cholesterol	Kahlon et al., 1989
Hamster	Defatted RB, defatted parboiled RB, full-fat RB, parboiled RB, OB, or wheat bran vs. cellulose; all diets contained 0.5% cholesterol and 10% TDF	3 wk	Weight gain, feed intake, plasma and liver lipid profiles	Kahlon et al., 1990
Hamster	11, 22, 33, or 44% full-fat RB, 35% defatted RB vs. cellulose control containing 10% TDF and 0.3% cholesterol; 2 additional controls (44% full-fat RB and 10% cellulose) without 0.3% cholesterol	3 wk	Plasma and liver cholesterol	Kahlon et al., 1992a
Hamster, male	Defatted RB, full-fat RB, or defatted RB+ RB oil vs. 10% cellulose; all diets contained 0.3% cholesterol and 10% TDF	3 wk	Plasma and liver cholesterol	Kahlon et al., 1992b
Hamster	Stabilized RB, OB, or RB+OB vs. cellulose; all diets contained 0.25% cholesterol and 10% TDF	3 wk	Plasma cholesterol	Kahlon et al., 1993
Hamster	Raw or stabilized RB vs. cellulose, containing 10% TDF and 0.3% cholesterol	3 wk	Plasma and liver cholesterol	Kahlon et al., 1996
Hamster	RB or wheat bran containing 10% TDF and 0.3% cholesterol	3 wk	Plasma and liver cholesterol	Kahlon et al., 1998
Hamster	RB or OB vs. cellulose control containing 10% TDF and 0.5% cholesterol. Some diets had an additional 0.1% vitamin E.	6 wk	Plasma and liver cholesterol	Kahlon et al., 1999
Hamster	RB diet vs. white or brown rice control containing 10% TDF and 0.5% cholesterol	3 wk	Plasma and liver cholesterol	Kahlon et al., 2000
Rat	10% stabilized rice bran vs. 10% cellulose or fiber-free control diet	4 wk	Plasma and liver cholesterol	Johnson et al., 1989
Rat	Raw or parboiled RB vs. wheat bran control; all diets had 10% TDF, 1% cholesterol, and 0.2% cholic acid	3 wk	Plasma and liver cholesterol	Rouanet et al.,1993
Mice	Five sources of dietary fiber from full-fat RB, soy fiber, OB, barley bran, or mixed bran containing 7% TDF vs. fiber-free diet control; all diets contained 0.06% cholesterol	3 wk	Plasma and liver cholesterol	Hundemer et al., 1991
Chick	60% defatted (24% TDF) or full-fat RB (20-21% TDF) vs. corn/soy control (10.5-18.7% TDF) with 0.5% cholesterol	10 d	Plasma lipid profile	Newman et al., 1992
Rat	Heat-stabilized RB vs. unprocessed wheat bran containing 7% TDF and no cholesterol; with or without fish oil	10 d	Plasma and hepatic lipid profiles, cecal VFAs	Topping et al., 1990
Rat	6% TDF from RB or cellulose diet containing 1% cholesterol and 0.2% cholic acid	3 wk	Plasma and hepatic lipid profiles, body	Anderson et al., 1994

			weight gain	

OB=oat bran; RB=rice bran; TDF=total dietary fiber; VFAs= volatile fatty acids

IV.C.3.5. Studies involving silica

Silica present in different range grasses is known as a cause for siliceous urinary calculi (Blackman and Bailey, 1971). However, Varia reported that rice hulls (200 g/day for 110 d) containing up to 31 g silica/day did not result in any calculi in the urinary tract of 6 mo old lambs (Mahmoud et al., 1982). The FDA had no question on the GRAS notice of synthetic silica (GRN 321; FDA, 2010) as a food ingredient.

IV.C.4. Human Clinical Studies of rice hull fiber

No randomized clinical trials (RCTs) have been reported on rice hull fiber. However, the history of rice hull fiber consumption suggests that rice hull fiber is safe for human consumption. Rice hull fiber has been marketed for 2 years in USA and no adverse effects have been reported for foods formulated with rice hull fiber.

IV.C.4.1. Human clinical studies showing no adverse effects of cellulose, a major component of rice hull fiber

Stephen's (1989) review of human studies (10-24 g cellulose) reported that cellulose significantly increased stool weights (Eastwood et al, 1973; Flemings et al, 1983; Kies et al, 1984; Slavin et al, 1985), reduced mean transit time (Slavin et al, 1985; Wrick et al, 1983; Hillman et al, 1983), and increased stool frequency (Eastwood et al, 1973; Flemings et al, 1983; Slavin et al, 1985). No adverse effects of cellulose were reported.

Table 9 shows additional human clinical studies showing no adverse effects of cellulose (Hillman et al., 1985; Mickelsen et al., 1979; Niemi et al., 1988; Park and Jhon, 2009; Spiller et al., 1980). Tested doses were up to 25 g per day and for up to 8 weeks. In general, cellulose intake decreased intestinal transit time and increased fecal weight (relieving constipation) without having adverse effects. In observational studies with 203 consecutive appendectomized children with histologically proved appendicitis and 1922 controls, cellulose intake was correlated to lower incidence of appendicitis (Adamidis et al., 2000). In another observational study with 291 children with constipation and 1602 controls, only cellulose and pentose intakes were independently inversely correlated with chronic constipation (Roma et al., 1999). No studies reported adverse effects of cellulose.

Table 9. Human clinical studies showing no adverse effects of cellulose

Subject	Dosage of cellulose	Duration	Results/Primary measurement endpoints	Ref.
10 Healthy Volunteers	15g MCC/d	8 Weeks	No effect on total cholesterol	Hillman et al., 1985
10 Healthy Volunteers	14g Powdered Cellulose /d	3 weeks	Decrease transit time, Increase fecal bulk	Spiller et al., 1980
6 College Males	23g Powdered Cellulose /d	8 Weeks	More weight loss and more satiety	Mickelsen et al., 1979
8 Constipated Volunteers	25g Powdered Cellulose	6 Days	Lower blood triglyceride, Increase in HDL, no change in serum glucose, improved bowel movement comfort, increase stool volume and quality	Park and Jhon, 2009
18 subjects with T2D		12 wk	No effect on fasting serum glucose and lipid profiles	Niemi et al., 1988

D=day

IV.C.4.2. Human clinical studies showing no adverse effects of hemicellulose, a second major component of rice hull fiber

Hemicellulose (mostly arabinoxylan)-rich fiber such as psyllium (85% arabinoxylan) has been proven safe for human consumption. Based on numerous human RCTs, FDA has approved health claims for psyllium and oat bran and risk reduction of heart disease (FDA, 2008). No safety concerns have been reported for arabinoxylan rich fibers.

IV.C.4.3. Human clinical studies showing no adverse effects of grain fibers whose fiber composition are similar to rice hull fiber

Rice hull fiber is categorized into grain fiber. Like other grain fibers, rice hull fiber consists of cellulose, hemicellulose (mostly arabinoxylans), and lignins. Based on the extensive literature review, the IOM (2002, 2006) and Technical Committee report for Dietary Guidelines for Americans (USDA and US DHHS, 2010) have emphasized the importance of increased intake of total fiber, in particular grain fibers. Recently, from a systematic review, the American Society of Nutrition has summarized that consumption of grain fibers was associated with the risk reductions of type 2 diabetes, obesity, and CVD without having any adverse effects (Cho et al., 2013).

Throughout the human history, humans have consumed grain fibers which consist of cellulose and hemicelluloses (non cellulosic polysaccharides mostly consists of arabinoxylans) and lignin (Rasper, 1979). No adverse effects of grain fibers or their components were reported even in some countries where consumption levels of total fiber and grain fiber are much higher than those of Americans. For example, the Finnish population has almost 2 times higher fiber intake levels than Americans; their mean daily intake levels of total fiber and grain fibers are estimated to be 26 g and 18 g, respectively (Montonen et al., 2003). The 87.5th and 99th

percentile intakes of grain fibers are 29 and 51 g, respectively. In this Finnish population, grain fiber intake was inversely associated with risk reduction of type 2 diabetes without having any adverse effects. The data indicates that high intakes of grain fiber (as high as 51 g per day) and their components, hemicelluloses, cellulose, and lignin not only are safe, but also offers health benefits. In other studies with various populations including Americans, consumption of grain fiber have been associated with positive health benefits (risk reductions of cardiovascular disease, type 2 diabetes, and obesity) without having any adverse effects (Cho et al., 2013; Flight and Clifton, 2006; Koh-Banerjee et al., 2004; Schulze et al., 2007). These grain fibers are subjected to colonic fermentation to produce SCFA, CO_2 and H_2, the same compounds produced from the metabolism of rice hull fiber. Thus, no systemic risks related to consumption of rice hull fiber are expected.

IV.C.4.4. Human clinical studies showing no adverse effects of rice bran fiber or rice bran

Numerous RCTs have been done on rice bran fiber and rice bran whose fiber compositions are similar to that of rice hull fiber (Table 10; Cara et al., 1992; Cheng et al., 2010; Gerhardt and Gallo, 1998; Hegsted et al., 1993; Kestin et al., 1990; Maeda et al., 2004; Miyoshi et al., 1986; Ranhotra et al., 1989; Rodrigues Silva et al., 2005; Sanders and Reddy, 1992; Tomlin and Read, 1988). The maximum dosage of rice bran fiber (or total fiber from rice bran) tested was up to 28 g/day and the duration of the study was up to 6 wk (Maeda et al., 2004). Rice bran fiber also has fecal bulking effects to promote intestinal regularity (Miyoshi et al., 1986; Tomlin and Read, 1988). No adverse effects of rice bran fiber were reported from any of these studies.

Rice bran has been tested for its hypocholesterolemic and hypoglycemic effects in normal, hypercholesterolemic, or diabetic human subjects (Table 10; Cara et al., 1992; Cheng et al., 2010; Gerhardt and Gallo, 1998; Hegsted et al., 1993; Ranhotra et al., 1989; Rodrigues Silva et al., 2005; Sanders and Reddy, 1992). The maximum dosage of rice bran and rice bran fiber (or total fiber from rice bran) tested was 100 g/day (Hegsted et al., 1993) and the length of the study was up to 12 weeks (Cheng et al., 2010). Rice bran is known to enhance viscosity of the gastrointestinal contents (Dikeman et al., 2006), which attenuates blood glucose and lipid responses. No adverse effects of rice bran were reported from any of these studies.

IV.C.5. Allergenicity

Unlike wheat and wheat products (containing gliadin), rice bran and rice bran fiber were found to be anti-allergenic (Choi et al., 2007). However, two cases have been reported: 1) a 17-year-old female who threw raw rice at a wedding developed acute erythema of the hands, edema of the eyelids, dyspnea, and cough—prick tests, open scratch, and handling tests, and radioallergosorbent (RAST) tests were positive for rice; 2) an atopic female developed similar symptoms after handling rice at a wedding as well as during handling of raw rice for cooking (CIREP, 2006). It is noteworthy that positive responses to other cereal grains also were observed in these rice-positive women (CIREP, 2006). It may be possible that raw rice used at the weddings may have contained some other impurities. So far, no case of allergenicity has been reported for rice hull fiber.

Table 10. Human studies reporting no adverse effects of rice bran or rice bran fiber

Subjects	Daily dose, g/day	Dura-tion	Measurement endpoints	Reference
50 elderly, age 70-95 yr	0.5 g/day arabinoxylan, rice bran fiber, from rice bran hydrolysate	6 wk	Common cold symptoms	Maeda et al., 2004
5 healthy young men	27.9 vs. 13.7 g/day of rice bran fiber (neutral detergent fiber) from brown rice	2 wk	Fecal weight, water and fat excretion; fasting blood lipid profile	Miyoshi et al., 1986
8 normal healthy males	17.1 g rice bran fiber (as indigestible residue) from rice	10 d	Fecal volume and frequency	Tomlin and Read, 1988
11 subjects with moderately elevated blood cholesterol	100 g rice bran or oat bran vs. wheat flour	3 wk	Fasting blood lipid profiles	Hegsted et al., 1993
44 moderately hypercholesterolemic adults	84 g heat-stabilized, full-fat rice bran or oat bran vs. rice starch	6 wk	Fasting blood lipid profiles	Gerhardt and Gallo, 1998
24 mildly hypercholesterolemic men	60 g/day rice bran containing 11.8 g TDF vs. baseline	4 wk	Fasting blood lipid profiles	Kestin et al., 1990
17 moderately hypercholesterolemic and hyper-triglyceridemic individuals	30 g rice bran, 30 g oat bran, or usual diet	6 wk	Fasting blood lipid profiles	Ranhotra et al., 1989
18 normo-cholesterolemic subjects	15 or 30 g rice bran vs. 15 g wheat bran	3 wk	Fasting blood lipid profiles	Sanders and Reddy, 1992
6 normolipidemic males	Rice bran diet containing 2.8 g TDF	Single dose	Postprandial lipidemia	Cara et al., 1992
28 subjects with NIDDM	20 g stabilized rice bran	12 wk	Fasting blood glucose, insulin and lipid profiles, insulin sensitivity	Cheng et al., 2010
11 subjects with NIDDM	Rice bran diet containing 40 g TDF	1 wk	Fasting blood glucose	Rodrigues Silva et al., 2005

IV.C.6. Potential adverse effects

The IOM (2002, 2006) has not established Tolerable Upper Intake Levels (UL) for fiber in Americans. The UL is defined as a safe upper level for consumption over a lifetime or the highest level of a daily nutrient intake that will most likely present no risk of adverse health effects in almost all individuals in the general population. It is not expected that consumption of rice hull fiber, insoluble fiber, is associated with gastric discomfort which is normally observed for soluble fibers, rapidly fermentable fibers. Also consumption of rice hull

fiber, when eaten in accordance with the IOM recommendations, is not expected to disturb mineral balance.

Consistent with the IOM, the FDA has not established the maximum daily dosage levels of dietary fiber when it issued the final rule of health claims related to fiber containing grain products (FDA, 1993a, 1993b). Also, the American Dietetic Association's position paper addressed no serious health hazards related to fiber intakes in the American population (Slavin, 2008).

V. SUMMARY OF THE BASIS FOR THE NOTIFIER'S DETERMINATION THAT RICE FIBER 310 IS GRAS

The objective of this Generally Recognized as Safe (GRAS) determination is to summarize the available safety information on Rice Fiber 310, rice hull fiber, used as an ingredient in foods and beverages as a source of dietary fiber.

Documentation qualifying a substance as GRAS has been compiled. Such documentation includes technical evidence and common knowledge of safety as recognized by qualified experts (the Expert Panel). Technical evidence of safety includes the chemical identity of the substance, the method of manufacture, analytical data on composition and specifications, safety data from animal and human clinical studies, current fiber intake status and fiber intake recommendations set by various government agencies (such as the IOM and the USDA), and nutritional benefits as identified by animal and human clinical studies. Therefore, the proposed use of rice hull fiber is not only safe within the terms of the Federal Food, Drug, and Cosmetic Act (meeting the standard of reasonable certainty of no harm), but it is also GRAS according to Title 21 Code of Federal Regulations (21 CFR) because of this consensus among experts. We conclude that Rice Fiber 310 is safe and GRAS for its intended use in food.

Rice Fiber 310 is proposed for general food use at concentrations consistent with cGMP. Rice Fiber 310 has many food applications, including, but not limited to, prepared foods, general foods (such as snack foods, bakery products, cereals, crackers, pasta products, dough conditioners, beverages, sports beverages), meal replacement, gluten-free foods, and medical foods. Consumption of Rice Fiber 310 is not expected to exceed 25-28 g per day.

Over 90% of the U.S. population does not meet the recommended intakes of total fiber. The Technical committee of the Dietary Guidelines for Americans (DGA) has classified dietary fiber as a shortfall nutrient that is low in the American diet. Symptoms caused by fiber deficiency (such as constipation) can be alleviated by rice hull fiber. There is broad-based and widely disseminated knowledge concerning the chemistry and health benefits of rice hull fiber and its components in both humans and animals.

Toxicity studies of Rice Fiber 310 showed no safety concerns. Ames test with and without metabolic activation as well as *in vivo* bone marrow micronucleus test in Kunming mice showed that Rice Fiber 310 lacks mutagenicity and genotoxicity. A Subchronic toxicity study in rats showed that administration of Rice Fiber 310 at doses up to 5% in diet did not show any abnormalities. The authors concluded that the NOAEL for Rice Fiber 310 was much higher than 5.0% (the highest level tested) in the diet for both genders (females, 3,800 mg/kg BW/day; males, 4,110 mg/kg BW/day). Also, short term studies (7-30 days) of rice hull in various animals showed that consumption of rice hull fiber at 10-60% of the diet did not cause any adverse effects. Subchronic studies (12-24 wk) also reported no adverse effects of rice hull at the dose of up to 60% in the diet of animals. In addition, rice bran and rice bran fibers, whose fiber composition is similar to that of rice hull fiber, have been GRAS ingredients.

Further evaluation of safety of components of Rice fiber 310 also did not raise safety concerns. Rice hull fiber is categorized into grain fiber or cereal fiber. Like other grain fibers, rice hull fiber consists of cellulose, hemicellulose (mostly arabinoxylans), and lignins. Cellulose has been recognized as GRAS since 1973; up to 60% in diet did not show adverse effects. Hemicellulose in grain fibers has been proven safe for a long time. Throughout history, humans have consumed grain fibers which consist of cellulose and hemicelluloses (non cellulosic polysaccharides mostly consists of arabinoxylans) and lignin. No adverse effects of grain fibers or their components were reported even in some countries where consumption levels of total fiber and grain fiber are much higher than those of Americans. For example, the Finnish population has much higher intake levels of total fiber and grain fiber than do Americans; their mean daily intake levels of total fiber and grain fibers are estimated to be 26 g and 18 g, respectively. The 87.5th and 99th percentile intakes of grain fibers are 29 and 51 g, respectively. In this Finnish population, grain fiber intake was inversely associated with risk reduction of type 2 diabetes without having any adverse effects. The data indicates that high intakes of grain fiber (as high as 51 g per day) and their components, hemicelluloses, cellulose, and lignin not only are safe, but also offers health benefits. In other studies with various populations including Americans, consumption of grain fiber have been associated with positive health benefits (risk reductions of cardiovascular disease, type 2 diabetes, and obesity) without having any adverse effects.

This GRAS determination for Rice Fiber 310 is based on scientific procedures in accordance with section 201(s) (21 U.S.C. §321(s)) of the Federal Food, Drug, and Cosmetic Act (21U.S.C.§301 et. seq.) set forth at 21 CFR 170.30. In general, materials of natural biological origin that have no significant detrimental effect and no known health hazard are eligible for GRAS status.

VI. DISCUSSION OF INFORMATION INCONSISTENT WITH GRAS DETERMINATION

We are not aware of information that would be inconsistent with a finding that the proposed use of rice hull fiber preparations in foods and beverages, meeting appropriate specifications and used according to GMP, is GRAS.

VII. CONCLUSIONS

We, the undersigned expert panel members, Susan Cho, Ph.D., Joanne Slavin, Ph.D., Kelly Swanson, Ph.D., and George C. Fahey, Jr., Ph.D., have individually and collectively critically evaluated the materials summarized in the rice hull fiber GRAS report. This GRAS determination for Rice Fiber 310 is based on scientific procedures. Numerous human and animal studies examined the health benefits of rice hull fiber, rice bran, rice bran fiber, and cereal fibers. There are no reports of safety concerns in any of the studies. SUNOPTA utilizes a HACCP-controlled manufacturing process and rigorously tests its final production batches to verify adherence to quality control specifications. The literature indicates that grain fiber including rice hull fiber offers consumers a safe fiber source.

The information/data provided by SUNOPTA in this report and supplemented by the publicly available literature/toxicity data on Rice Fiber 310, rice hull, and related fibers (rice bran and rice bran fiber) as well as components of Rice Fiber 310 (cellulose and hemicelluloses) provide a sufficient basis for an assessment of the safety of Rice Fiber 310 for the proposed use as an ingredient in food when prepared according to appropriate specifications and used according to cGMP.

Therefore, not only is the proposed use of Rice Fiber 310 safe within the terms of the Federal Food, Drug, and Cosmetic Act (meeting the standard of reasonable certainty of no harm), but because of this consensus among experts, it is also GRAS.

Susan Cho, Ph.D.
President, NutraSource, Inc., Clarksville, MD 21029

Signature: _____ Date: _____

Joanne Slavin, Ph.D.
Professor, University of Minnesota, St. Paul, MN

Signature: _____ Date: _____

George C. Fahey, Jr., Ph.D.
Professor Emeritus, University of Illinois, Urbana, IL 61801

Signature: _____ Date: _____

Kelly Swanson, Ph.D.
Associate professor, University of Illinois, Urbana, IL 61801

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Susan Cho, Ph.D.
President, NutraSource, Inc., Clarksville, MD 21029

Signature: (b) (6) [redacted] Date: 6/1/2013

Joanne Slavin, Ph.D.
Professor, University of Minnesota, St. Paul, MN

Signat (b) (6) [redacted] Date: 5-31-13

George C. Fahey, Jr., Ph.D.
Professor Emeritus, University of Illinois, Urbana, IL 61801

Signature (b) (6) [redacted] Date: 5/28/13

Kelly Swanson, Ph.D.
Associate professor, University of Illinois, Urbana, IL 61801

Signatu (b) (6) [redacted] Date: 5/28/13

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APPENDIX A. INDIVIDUAL EXPERTS' OPINION ON THE SAFETY OF RICE HULL FIBER

Joanne Slavin, Ph.D., R.D.

Rice hull fiber is safe for human consumption. Human studies support that both cellulose and hemicellulose, the fiber components in highest concentration in rice hull fiber, are well tolerated in human subjects and improve gut health, as measured by increased stool weight and speeded gastrointestinal transit. Grain fibers, including rice, have also been extensively studied and found to have beneficial effects in human subjects. Grain consumption is well tolerated at much higher levels than the proposed intakes of rice hull fiber and found to be safe and effective in human subjects.

Numerous RCTs are published on rice bran fiber and rice bran whose fiber compositions are similar to that of rice hull fiber. No adverse effects of rice bran fiber were reported from any of these studies. The IOM has not established Tolerable Upper Intake Levels (UL) for fiber in Americans. Consumption of rice hull fiber, which is most insoluble fiber, should be well tolerated in human subjects and not be associated with gastrointestinal tolerance issues or impaired mineral balance.

Over 90% of the U.S. population does not meet the DRI for total fiber. The 2010 Dietary Guidelines for Americans (DGA) classified dietary fiber as a shortfall nutrient that is low in the American diet. Symptoms caused by fiber deficiency (such as constipation) can be alleviated by rice hull fiber. There is broad-based and widely disseminated knowledge about the chemistry and health benefits of rice hull fiber in both humans and animals.

It is my professional opinion that rice hull fiber is safe and effective for human consumption and can provide the additional fiber needed in the American diet.

George Fahey, Jr., Ph.D.

My professional opinion is that Rice Fiber 310 manufactured by SunOpta Ingredients Group, Chelmsford, MA, is GRAS. I hold this opinion for the following reasons:

1. Rice Fiber 310 is processed from rice hulls using a proprietary hydrothermal process. It is a natural source of rice fiber, mostly from hull but partly from bran. It contains 91% total dietary fiber, 97% of which is insoluble dietary fiber (i.e., cellulose, arabinoxylans, hemicelluloses, and lignin). It contains no sulfites, added flavors, components from animal sources, synthetic antioxidants, genetically altered plant material, or irradiated material. This particular product contains only 1.5% silica unlike typical rice hulls that may contain as much as 20% silica.

2. The manufacturing process for preparation of Rice Fiber 310 is well-defined, and the chemical, microbiological, and sensory properties of the final product make it suitable as a value-added food ingredient.

3. Toxicity studies (i.e., Ames test with and without metabolic activation; in vivo bone marrow micronucleus test in Kunming mice) show that Rice Fiber 310 lacks mutagenicity and genotoxicity properties.

4. Very similar products (i.e., rice bran and rice bran fiber) whose fiber composition is very similar to that of Rice Fiber 310 have been GRAS ingredients for years.

5. The no-observed-adverse-effect-level (NOAEL) for Rice Fiber 310 was much higher than the 5% concentration tested in the diets of male and female rats.

6. Large numbers of animal safety studies indicated no adverse effects with Rice Fiber 310.

7. Human clinical studies of the components of Rice Fiber 310, and of rice bran fiber and rice bran, showed no adverse effects, the implication being that Rice Fiber 310, while not studied directly, should respond in like fashion.

8. Given that Rice Fiber 310 is a high fiber product, overconsumption is highly unlikely and, if it occurred, would manifest itself in the form of gastrointestinal upset and excess gas production, neither of which are serious symptoms.

Kelly Swanson, Ph.D.

This opinion statement is in support of the GRAS notification for the Rice Fiber 310 product produced by SunOpta Ingredient Group. Based on the published literature, I believe that Rice Fiber 310 is safe for consumption and its intended use in foods. A brief justification for this is provided below.

Americans consume approximately half of the recommended level of dietary fiber. Products such as Rice Fiber 310 may not only be GRAS, but may be used to boost daily fiber intake and provide health benefits. There are several health claims pertaining to fiber consumption. Not only do fibers contribute to gastrointestinal health by promoting laxation, beneficially manipulating the microbiome, and increasing short-chain fatty acid production, but they aid in weight management by reducing caloric content and promoting satiety.

Rice hull fiber has similar composition and physicochemical properties as other grain-based fibers. Rice hulls are >90% fiber, primarily composed of cellulose, hemicelluloses, and lignin. Cellulose has had GRAS status since 1973. Arabinose and xylose, which make up the arabinoxylan chains composing much of the hemicellulose in rice fiber, also have GRAS status. Safety studies (mutagenicity; genotoxicity; chronic toxicity) in animal models have not demonstrated any adverse events from rice fiber consumption, even at doses (10-40% of diet) that were much higher than would be consumed by humans.

Consumption of rice hull fiber is not expected to exceed 25 to 28 g/d in the human population. Human studies have demonstrated that cellulose and hemicellulose consumption at those concentrations are not only safe, but may provide some of the health benefits listed above. Safety of other grain-based fibers has also been demonstrated in humans. Because rice hull fiber has a similar composition and is only moderately fermented in the gut, intestinal gas production and gastrointestinal discomfort are minimal so risks of consuming these fibers are minor at the intended doses.

To conclude, given the published research on the topic, I believe that the Rice Fiber 310 product produced by SunOpta Ingredient Group should be considered GRAS.

Sincerely,

(b) (6)

Kelly Swanson
Associate Professor
Department of Animal Sciences
University of Illinois, Urbana, IL 61801

Susan S. Cho, Ph.D.

Toxicity studies of Rice Fiber 310 showed no safety concerns. Ames test with and without metabolic activation as well as *in vivo* bone marrow micronucleus test in Kunming mice showed that Rice Fiber 310 lacks mutagenicity and genotoxicity. A Subchronic toxicity study in rats showed that administration of Rice Fiber 310 at doses up to 5% in diet (females, 3,800 mg/kg BW/day; males, 4,110 mg/kg BW/day) did not show any abnormalities. Also, short term studies (7-30 days) and subchronic studies of rice hull in various animals reported no adverse effects at the dose of up to 60% rice hull in the diet of animals. In addition, rice bran and rice bran fibers, whose fiber composition is similar to that of rice hull fiber, have been GRAS ingredients.

Like other grain fibers, rice hull fiber consists of cellulose, hemicellulose (mostly arabinoxylans), and lignins. Cellulose has been recognized as GRAS since 1973; up to 60% in diet did not show adverse effects. Hemicellulose in grain fibers has been proven safe for a long time. Rice hull fiber is categorized into grain fiber. Throughout history, humans have consumed grain fibers which consist of cellulose and hemicelluloses (non cellulosic polysaccharides mostly consists of arabinoxylans) and lignin. No adverse effects of grain fibers or their components were reported even in some countries where consumption levels of total fiber and grain fiber are much higher than those of Americans.

Over 90% of the U.S. population does not meet the DRI of total fiber. The USDA Dietary Guidelines (DG) Committee has classified dietary fiber as a shortfall nutrient that is low in the American diet. Symptoms caused by fiber deficiency (such as constipation) can be alleviated by rice hull fiber. There is broad-based and widely disseminated knowledge concerning the chemistry and health benefits of rice hull fiber and its components in both humans and animals.

Pages 000056-000067 of Curriculum Vitae removed in accordance with the Privacy Act of 1974.

Pages 000068-000138 have been removed in accordance with copyright laws. References are as follows:

Anderson RL, Owens JW, Timms CW. The toxicity of purified cellulose in studies with laboratory animals. Cancer Lett. 1992;63:83-92.

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Okuno Y, Miyazawa M. Suppressive components in rice husk against mutagens-induced SOS response using *Salmonella typhimurium* TA1535/pSK1002 umu test. Nat Prod Res. 2007;21:805-809.

Yu B. Effect of different sources of dietary fibre on growth performance, intestinal morphology and caecal carbohydrases of domestic geese. Br Poult Sci. 1998; 39:560-567.

Institutitionen för livsmedelsvetenskap
Department of Food Science

Analysis of dietary fiber content and dietary fiber composition of Rice-Fiber 310 (SunOp USA). The Uppsala method (AOAC 994.13) has been used and results are given as percent of dry matter (average of duplicate analysis).

Ara res.	2.59
Xyl res.	20.03
Man res.	0.49
Gal res.	0.89
Glu res.	51.96
UA res.	1.76
Klason lignin	16.25
Sum	93.97

Uppsala 2012-02-29

Per Åman
Professor

Postadress / *Postal address*: P.O. Box 7051, S-750 07 UPPSALA, SWEDEN
Besöksadress / *Visiting address*: Undervisningsplan 6c, ULTUNA
Tel.: +46 (0)18-67 20 45
Fax: +46 (0)18-67 29 95
E-mail: Per.Aman@lmv.slu.se

COVANCE

Report Number:	498121-0
Report Date:	09-Jan-2012
Report Status:	Final

Certificate of Analysis

SunOpta Ingredients
1001 Cleveland St. South
Cambridge Minnesota 55008 United States

Sample Name:	Skid 7	Covance Sample:	1139499
Project ID	SUNOPTA-20120104-0001	Receipt Date	04-Jan-2012
PO Number	3134264	Receipt Condition	Ambient temperature
Lot Number	26211334	Login Date	04-Jan-2012
Sample Serving Size		Storage Condition	-20 (+/- 10) Degrees Celsius
Description	Rice Hull Fiber	Online Order	13190

Analysis	Result
Silicon	
Silicon	1.37 %

Method References	Testing Location
Silicon (SICO_S:5)	**Covance Laboratories Inc.**
Perkin-Elmer, Analytical Methods for Atomic Absorption Spectrophotometry, Norwalk, CT (2000).	

Testing Location(s)	Released on Behalf of Covance by
Covance Laboratories Inc.	**Lori Ross - Associate Director**

3301 Kinsman Blvd
Madison WI 53704
608-242-2712 x4170

These results apply only to the items tested. This certificate of analysis shall not be reproduced, except in its entirety, without the written approval of Covance.

COVANCE
THE DEVELOPMENT SERVICES COMPANY

Phone: 608-241-4471
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Analyte: Silicon

Mnemonic: SICO

Scope: This method is applicable to most matrices including feeds, food products, minerals, animal tissues, plants, and water samples.

Principle: Most samples are dried, precharred, ashed overnight at 500 C ±50 , then fused with a mixture of sodium borate and sodum carbonate. Finally, the sample is dissolved in dilute hydrochloric acid. The amount of silicon is determined by comparing the absorbance of the unknown sample, measured by the atomic absorption spectrophotometer, to the absorbance of the standard solutions.

Limit of Quantitation: Most matrices - 300 ppm

Precision: Has not been determined

Sample Required: 10 grams

Method Reference: Perkin-Elmer, Analytical Methods for Atomic Absorption Spectrophotometry, Norwalk, CT, January 1982.

Date: 02/18/02

Final Report

MEDALLION LABS
9000 Plymouth Avenue North, Minneapolis MN 55427
1-800-245-5615 (763) 764-4453 Fax: (763) 764-4010

Completion Date: January 05, 2012
Date Submitted: December 16, 2011
Medallion Company ID: SUNOPTA01
Company Code: 12848

Mehwish Kanwar
SunOpta Ingredients
1001 S. Cleveland St.
Cambridge, MN 55008
Email: mehwish.kanwar@sunopta.com

Library Number: 2011-MED-13645
PO Number: 3133550

Fax: 763-689-4820

Medallion Labs Sample ID: 2011-MED-13645-01 Rice
Customer Sample ID: Lot 26211334 #7

Assay Group	Test	Results
[2]Calories	Calories	376 Calories/100 g
	Calories from Fat	1 Calories/100 g
	Calories from Saturated Fat	0 Calories/100 g
	Calories (Insoluble Fiber Subtracted)	7 Calories/100 g
[2]Carbohydrates	Carbohydrates	92.6 %
	Carbohydrates, Available	0.5 %
Metals Screen 2	Metals Screen	Discount
Moisture	Moisture	2.542 %
Ash, Overnight	Ash	3.651 %
Protein, by Dumas	Protein (6.25)	1.13 %
Fats, by Gas Chromatography	Total Fat	0.10 %
	Saturated Fat	0.05 %
	Monounsaturated Fat	0.03 %
	cis-cis Polyunsaturated Fat	0.01 %
	trans Fat	0.00 %
Dietary Fiber	Insoluble Fiber	92.1 %
	Soluble Fiber	1.0 %
	Total Fiber	93.1 %
Cholesterol	Total Cholesterol	Less than 1.0 mg/100g
Sugars	Fructose	Less than 0.1 %
	Glucose	Less than 0.1 %
	Sucrose	Less than 0.1 %
	Maltose	Less than 0.1 %
	Lactose	Less than 0.1 %
	Total Sugars	0.00 %
Calcium	Calcium	63.4 mg/100g
Iron	Iron	6.53 mg/100g
Sodium	Sodium	404 mg/100g
Copper	Copper	0.118 mg/100g
Potassium	Potassium	4.22 mg/100g
Magnesium	Magnesium	39.9 mg/100g
Manganese	Manganese	10.2 mg/100g

Medallion Labs maintains A2LA accreditation to ISO/IEC 17025 for the specific tests listed in A2LA Certificate # 2769.01.

Medallion's services, including this report, are provided subject to all provisions of Medallion's Standard Terms and Conditions, a copy of which appears at www.medlabs.com.

Limits of Detection and Measurement Variability are available upon request.

[2] This test is not considered in-scope of our current A2LA accreditation. For a listing of in-scope tests, please visit www.medlabs.com.

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Final Report

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Results Approved By: Pragati Shinde (Authorized Reviewer)

Method References:

Assay Group	Method Reference
Arsenic	AOAC: 985.01, 990.08, 975.03
Ash, Overnight	AOAC: 923.03
Calcium	AOAC: 975.03, 985.01, 990.08
Calories	Determined through calculation
Carbohydrates	Determined through calculation
Carotenoids	AOAC: 2005.07*
Cholesterol	AOAC: 976.26*
Copper	AOAC: 975.03, 985.01, 990.08
Dietary Fiber	AOAC: 991.43*
Fats, by Gas Chromatography	AOAC: 996.06*
Iron	AOAC: 975.03, 985.01, 990.08
Lead	AOAC: 985.01, 990.08, 975.03
Magnesium	AOAC: 975.03, 985.01, 990.08
Manganese	AOAC: 975.03, 985.01, 990.08
Mercury	EPA 7473
Moisture	AOAC: 925.10; AACC: 44-15A, 44-31*
Phosphorus	AOAC: 975.03, 985.01, 990.08
Potassium	AOAC: 975.03, 985.01, 990.08
Protein, by Dumas	AOAC: 992.15; AACC: 46-30
Sodium	AOAC: 975.03, 985.01, 990.08
Sugars	AOAC: 977.20*
Vitamin A Retinol	AOAC: 2001.13; AACC: 86-06
Vitamin C	AOAC: 967.22, 984.26*
Zinc	AOAC: 975.03, 985.01, 990.08

* This method has been modified.

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SUBMISSION END