ORIGINAL SUBMISSION

February 23, 2011

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Division of Biotechnology and GRAS Notice Review

Dr. Robert Martin
Division of Biotechnology and GRAS Notice Review
Office of Food Additive Safety-CFSAN
U.S. Food and Drug Administration
5100 Paint Branch Parkway (HFS-255)
College Park, MD 20740-3835

Re: GRAS exemption claim for rice bran fiber as an ingredient in foods

Dear Dr. Martin,

This is to notify you that CJ America claims that the use of the substance described below (rice bran fiber) is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because CJ America has determined such use to be Generally Recognized As Safe (GRAS).

On behalf of CJ America, NutraSource (an independent consulting firm) assembled a panel of experts highly qualified by scientific training and experience to evaluate the safety of the intended uses of rice bran fiber. The panel included Dr. Susan Cho (NutraSource, Clarksville, MD), Dr. Joanne Slavin (University of Minnesota, St. Paul, MN), and Dr. George C. Fahey, Jr. (University of Illinois, Emeritus, Urbana, IL). Following independent critical evaluation of the available data and information, the panel has determined that the use of rice bran fiber (that is manufactured by CJ America) described in the enclosed notification is GRAS based on scientific procedures.

After reviewing the available data, the Expert Panel also concluded in its February 2011 statement that CJ America's rice bran fiber can be safely used as a food ingredient. 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.

Notifier's name and Address: CJ America, Inc.
Attention: Jennifer Jang (e mail address: jenniferjang@cj.net)
Address: 3500 Lacey Rd. Suite 230, Downers Grove, IL 60515
Phone number: 630-241-0112; Fax number: 630-241-2502

Name of GRAS substance: Rice bran fiber (Common or trade name: Riber® 50)

Product description: CJ's rice bran fiber is processed from defatted rice bran by a proprietary hydrothermal process. Rice bran fiber consists of mostly insoluble dietary fiber added to food for several purposes. Examples include raising total dietary fiber

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(TDF) content, reducing caloric content, controlling water activity, and modifying the rheological properties of foods and beverages. Rice bran fiber has □40□ TDF (of which □90□ is insoluble dietary fiber) and a particle size of □100 microns (Table 1). The rice fiber contains no sulfites, added flavors, components from an animal source, BHA, BHT, genetically altered plant material, or irradiated material.

Specifications:

Table 1. Specifications of rice fiber

Macronutrient	□	Unit	Analytical method
TDF (dry wt. basis)[a]	□40	□	AOAC 991.43
Protein	□15	□	AOAC 984.13
Starch	□25	□	AOAC 996.11
Fat	□1.5	□	AOAC 954.02
Moisture	□8.0	□	AOAC 934.01
Ash	□16	□	AOAC 900.02
pH, 5□ slurry	7.3□0.5	pH	
Microbiological Specifications			
Total plate count	□10,000	cfu/g	FDA-BAM2[b] Chap. 3
S. aureus	Negative	cfu/g	FDA-BAM2 Chap. 4
E. coli	Negative	cfu/g	FDA-BAM2 Chap. 4
Salmonella	Negative	cfu/g	FDA-BAM2 Chap. 5
Yeast and mold	□200	cfu/g	FDA-BAM2 Chap. 19

[a]TDF□total dietary fiber; cfu □colony forming units.
[b]BAM □Bacteriological Analytical Manual, January, 2001.

Applicable conditions of use of the notified substance

Rice bran is proposed for general food use at concentrations consistent with cGMP. Examples of food applications include, but are not limited to, prepared foods, nutraceuticals, functional 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. There will be a self-limiting effect of the use of rice bran fiber in food for organoleptic limitations and technological reasons. In most cases, concentration of rice bran 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.

Probable consumption of rice bran fiber

The Institute of Medicine (IOM), the National Academy of Sciences (NAS), has recommended a daily intake of 14 g fiber per 1,000 calories for Americans. 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 (42 to 62) of the recommended levels, the Daily Reference Intakes (DRI). Over 90 of the U.S. population did not meet the daily recommended intake of fiber. Thus, both IOM and the USDA (Dietary Guidelines for Americans) recommend increased consumption of dietary fiber for Americans.

Currently, more than 30 types of fiber ingredients are available for food formulations. Despite the availability of various fiber ingredients, fiber intake by Americans has been steadily low over the past several years. Average (aged 6 mo to 74 yr) daily fiber consumption was 13.3 g in 1976-1980 (NHANES II) and 14.8 g in 2003-2006 (2003-2006 NHANES). Considering the differences in both dietary survey methodology and fiber analytical methods between the 1970s and 2000s, it is reasonable to conclude that fiber intake status did not change significantly over the past two or three decades.

Application of conventional fiber ingredients (e.g., wheat bran, rice bran, and corn bran) to food and beverage formulations has been limited due to their gritty mouth feel and insoluble nature. Compared to conventional rice bran, rice bran fiber has improved mouth feel and functionality such as water holding capacity. Rice bran fiber is expected to be used as a replacement for conventional fiber ingredients. Thus, it is not likely that the availability of a new rice bran fiber ingredient will significantly boost fiber intake levels in the American population.

Basis of GRAS determination

Through scientific procedures.

Review and copying statement

The data and information that serve as the basis for this GRAS determination will be sent to the FDA upon request, or are available for the FDAs review and copying at reasonable times at the office of CJ America, Inc. or Nutrasource, Inc.
We enclose an original and two copies as well as a word file of this notification for your review. If you have any questions, please contact me.

Sincerely,

Susan Cho, Ph.D.
Chief Science Officer
NutraSource, Inc.
6309 Morning Dew Ct.
Clarksville, MD 21029
Phone: 301-875-6454
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We enclose an original and two copies as well as a word file of this notification for your review. If you have any questions, please contact me.

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(b) (6)

Susan Cho, Ph.D.
Chief Science Officer
NutraSource, Inc.
6309 Morning Dew Ct.
Clarksville, MD 21029
Phone: 301-875-6454
E mail: susanscho1@yahoo.com

Executive Summary

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

We, the undersigned expert panel members, Susan Cho, Ph.D., Joanne Slavin, Ph.D., and George C. Fahey, Jr., Ph.D., have individually and collectively critically evaluated the materials summarized in the rice bran fiber GRAS report. We conclude that rice bran fiber is safe and GRAS for its intended use in food.

Over 90% of the U.S. population does not meet the daily recommended intake (DRI) of fiber. The USDA Dietary Guidelines (DG) Committee has classified dietary fiber as a shortfall nutrient that is low in the American diet (USDA 2004, 2005, 2010). Symptoms caused by fiber deficiency (such as constipation) can be alleviated by rice bran fiber. There is broad-based and widely disseminated knowledge concerning the chemistry and health benefits of rice bran fiber in both humans and animals.

Rice bran fiber is naturally present in the diet. It has a long history of safe use as a dietary fiber ingredient. Rice bran fiber, like most beta-linked fibers, is not digested by human pancreatic or brush border enzymes and the compounds are not expected to be absorbed intact. Rice bran fiber reaches the large intestine where it is fermented by the colonic microflora to short-chain fatty acids (SCFA; e.g. acetate, propionate, and butyrate) that promote colon health. Both full-fat and defatted rice bran have shown no adverse effects on animal health or feed nutritional quality when fed at up to 60% in chick diets or up to 40% in pig diets. There are no indications of significant adverse effects related to rice bran fiber in the publicly available literature.

This GRAS determination for rice bran fiber is based on scientific procedures and through experience based on common use in foods 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. Rice bran fiber is of biological origin and is a concentrated fiber mechanically isolated from defatted rice bran. Rice bran has been safely consumed in the U.S. for over 100 years without known detrimental effects. Rice bran fiber does not represent a known health hazard.

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 Institute of Medicine [IOM] and the US. Department

of Agriculture [USDA]), and nutritional benefits as identified by animal and human clinical studies.

Therefore, the proposed use of rice bran 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.

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: _____

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

Signature: (b) (6) Date: 2/20/2011

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

Sig (b) (6) Date: 2-16-11

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

Signature: (b) (6) Date: 2/17/11

I. Identity of Substance

A. Common or trade name: Riber® 50 or rice bran fiber

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.

C. Background

CJ's rice bran fiber is processed from defatted rice bran by a proprietary hydrothermal process. Rice bran fiber consists of mostly insoluble dietary fiber added to food for several purposes. Examples include raising total dietary fiber (TDF) content, reducing caloric content, controlling water activity, and modifying the rheological properties of foods and beverages.

Rice bran and brown rice (containing rice bran) 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. Historically, rice has constituted an important commercial crop since it was a dietary staple for people in regions around the world. Leading rice-producing countries include the United States, China, and other Asian countries. Although rice bran is used mostly as animal feed, some is processed for human consumption.

Consumption of rice in developing countries is around 68.5 kg/person/yr and 12.8 kg/person/yr in developed countries (Kahlon, 2009). Rice is harvested from fields called paddies. In the rice milling process, the hull is first removed to produce brown rice. Brown rice consists of the bran layer, germ, and endosperm (starch). Bran and germ are concentrated sources of vitamins, minerals, flavones, and other phytonutrients present in brown rice. One hundred kilograms of paddy rice on milling yields 10-12 kg rice bran. Rice bran contains the enzyme, lipase, which rapidly degrades the oil and makes the bran rancid and inedible (Kahlon, 2009). To extend shelf life, rice bran is either defatted with hexane or heat-stabilized to deactivate lipase activities (Randall et al., 1985).

Each year, between 63 and 76 million tons of rice bran (rice milling byproduct) is produced in the world and more than 90% of rice bran is sold as animal feed. The remainder is either defatted or stabilized to be used as value-added ingredients. In the U.S., rice oil is extracted from 15-20% of the rice bran (Kahlon, 2009). Rice bran has been recognized as an excellent source of fiber. The total dietary fiber (TDF) content of full-fat rice bran ranges from 20-27% with less than 2% as soluble dietary fiber.

Inadequate intake of dietary fiber increases risk of chronic diseases. Examples include diverticular diseases/constipation, heart disease, cancer, diabetes, metabolic syndrome, and overweight/obesity (IOM, 2002, 2006). Americans consume approximately one half of the recommended intake levels, the Daily Reference Intakes (DRI). Thus, the IOM

(IOM, 2002, 2006) and USDA Dietary Guidelines for Americans (2004, 2005, 2010) recommend increased consumption of fiber-rich foods.

The USDA, in partnership with a non-profit organization, provides a nutritious rice bran drink to preschool children in Latin American countries. Healthy meal replacement drinks made from stabilized rice bran have been introduced in the market.

D. Physicochemistry and structure of rice bran fiber

Rice bran fiber has >40% TDF (of which >90% is insoluble dietary fiber) and a particle size of <100 microns (Table 1). The rice fiber contains no sulfites, added flavors, components from an animal source, BHA, BHT, genetically altered plant material, or irradiated material.

General Physical Properties

Color: Cream to beige
Flavor: Bland to slightly sweet, no off flavors
Physical form: Fine powder
Odor: Natural clean cereal, no off odors
Particle size distribution: <100 microns

Defatted rice bran fiber and sugar beet fiber are known to have comparable water holding capacities (rice bran fiber, 4.89 ml/g vs. sugar beet fiber, 4.56 ml/g; Abdul-Hamid and Luan, 2000).

E. Manufacturing Process

1. Defatted rice bran is cleaned using mechanical detachers, gravity separators, sieves, and air classifiers to separate rice bran from rice fragments and any residual impurities.
2. The defatted rice bran is suspended in clean water (15% solids concentration) in a reception tank at 25 - 30°C.
3. Food grade sodium hydroxide is added to adjust the pH to 9.0 - 9.5.
4. The suspension is well blended in an alkaline environment at 35 - 40°C for 2 h to extract rice protein and starch.
5. The rice bran fiber is separated from aqueous solution containing protein and starch by a decanter-type centrifugal separator, followed by washing with clean water until the pH reaches 6.7-7.0.
6. The separated rice bran fiber with approximately 65% moisture is dried until the moisture reaches 8%.
7. To control microbial activities and to develop a deep and roasted aroma, rice bran fiber is roasted at 95 - 98°C for 5 - 10 minutes in a roasting chamber.
8. Rice bran fiber, after cooling, is subjected to a pulverization to particle sizes of <100 um (using Jet Sieve analyses).
9. Rice bran fiber then is packaged in paper bags coated with polyethylene and stored at room temperature.
10. Rice bran fiber produced in this manner has silky mouth-feel and excellent water adsorption properties. Rice bran 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 CJ's manufacturing facilities. Laboratory use meets OSHA regulations.

F. Specifications

Table 1 lists specifications of rice bran fiber.

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Macronutrient	%	Unit	Analytical method
TDF (dry wt. basis)[a]	>40	%	AOAC 991.43
Protein	<15	%	AOAC 984.13
Starch	<25	%	AOAC 996.11
Fat	<1.5	%	AOAC 954.02
Moisture	<8.0	%	AOAC 934.01
Ash	<16	%	AOAC 900.02
pH, 5% slurry	7.3±0.5	pH	
Microbiological Specifications			
Total plate count	<10,000	cfu/g	FDA-BAM2[b] Chap. 3
S. aureus	Negative	cfu/g	FDA-BAM2 Chap. 4
E. coli	Negative	cfu/g	FDA-BAM2 Chap. 4
Salmonella	Negative	cfu/g	FDA-BAM2 Chap. 5
Yeast and mold	<200	cfu/g	FDA-BAM2 Chap. 19

[a]TDF=total dietary fiber; cfu = colony forming units.
[b]BAM = Bacteriological Analytical Manual, January, 2001.

II. Natural occurrence and exposure to rice bran fiber

A. Food sources of rice bran fiber

Rice bran and brown rice are natural sources of rice bran fiber.

B. Intended use

Rice bran is proposed for general food use at concentrations consistent with cGMP. Examples of food applications include, but are not limited to, prepared foods, nutraceuticals, functional 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. There will be a self-limiting effect of the use of rice bran fiber in food for organoleptic limitations and technological reasons. In most cases, concentration of rice bran 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.

C. Probable consumption of rice bran fiber

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). Table 2 summarizes recommended intake levels of fiber in different age and gender groups.

Table 2. Dietary reference intakes of TDF, g/d

Age, year	Male	Female
1-3	19	19
4-8	25	25
9-13	31	26
14-18	38	26
19-50	38	25
51+	30	21

Despite the recommendations of the IOM, most Americans consume inadequate amounts of dietary fiber. Fiber intake for the U.S. population ages 2 years and older was calculated based on food consumption data reported in the most recent National Health and Nutrition Examination Survey (NHANES 2003-2006). The NHANES was compiled by the U.S. Department of Health and Human Services, National Center for Health Statistics and the Nutrition Coordinating Center. NHANES was conducted between 2003-2006 with non-institutionalized individuals in the U.S. to collect data from a nationally representative sample of individuals of all ages. All estimates were generated with USDA sampling weights to adjust for differences in representation of subpopulations. As shown in Table 3, the median intakes of fiber in the U.S. were estimated to be approximately one half (42 to 62%) of the recommended levels, the Daily Reference Intakes (DRI). Over 90% of the U.S. population did not meet the daily recommended intake of fiber (data not shown). Thus, the USDA Dietary Guidelines (DG) Committee classified dietary fiber as a shortfall nutrient that is low in the American diet (USDA, 2004). Both IOM and the USDA recommend increased consumption of dietary fiber for Americans.

Table 3. The fiber intake status of Americans (NHANES, 2003-2006)

Age, year	Mean daily intake, g fiber/d		% of DRI	
	Male	Female	Male	Female
2-5	11.2	11.2	48.2	48.2
6-12	13.3	13.3	43.6	43.6
13-18	16.1	12.3	42.8	45.2
19-54	16.3	13.8	48.1	62.3
55+	16.6	13.7	59.3	47.3

Currently, more than 30 types of fiber ingredients are available for food formulations. These ingredients include wheat bran, corn bran, rice bran, oat bran, oat hull fiber, oat beta-glucan, barley beta-glucan, psyllium, wheat fiber, and guar gum. Despite the availability of various fiber ingredients and various agencies' recommendations for increased consumption of dietary fiber, fiber intake by Americans has been steadily low over the past several years. Average (aged 6 mo to 74 yr) daily fiber consumption was 13.3 g in 1976-1980 (NHANES II; Lanza et al., 1987) and 14.8 g in 2003-2006. Fiber analysis and intake estimates for the 1970's were based on Southgate's unavailable carbohydrates method (1979) that generally reported approximately 5-6% lower values than the current TDF analytical methods (AOAC Methods 991.43 and 985.29; Cho et al., 1997). Thus, TDF intake in the 1970's was estimated to be approximately 14.1 g.

Considering the differences in both dietary survey methodology and fiber analytical methods between the 1970's and 2000's, it is reasonable to conclude that fiber intake status did not change significantly over the past two or three decades.

Fiber availability data support scientific data on fiber intake trends in Americans. The availability of dietary fiber from grain products and fruit has remained steady since 1995, while dietary fiber availability from vegetables, legumes, nuts, and soy declined in 2005 (USDA, 2007). Per capita dietary fiber in the food supply data show that available fiber may not meet the DRIs for Americans (USDA, 2007); the weighted per capita requirement for fiber ranged from 28-30 g, while available fiber in the food supply was 24-25 g per capita. On average, the difference between per capita fiber in the food supply and the per capita fiber required to meet the estimated average requirement was 12.6% over the last 10 yr (USDA, 2007). Due to waste during food processing and storage of ingredients and finished foods, the actual difference would be much larger than the theoretical value of 12.6%. The data suggest that more fiber ingredients should be available to help Americans meet recommended intakes.

Application of conventional fiber ingredients (e.g., wheat bran, rice bran, and corn bran) to food and beverage formulations has been limited due to their gritty mouth feel and insoluble nature. In the past two decades, numerous new fiber ingredients have been developed to improve mouth feel and functionality in foods. Compared to conventional rice bran, rice bran fiber has improved mouth feel and functionality such as water holding capacity. Rice bran fiber is expected to be used as a replacement for conventional fiber ingredients. Thus, it is not likely that the availability of a new rice bran fiber ingredient will significantly boost fiber intake levels in the American population.

III. Basis for GRAS determination

A. Current regulatory status.

Rice bran is a GRAS ingredient because it is a substance of natural biological origin that has been widely consumed for its nutrient properties prior to January 1, 1958, without known detrimental effects and for which no health hazard is known.

Basis of GRAS determination: In section 201(s) (21 U.S.C. §321(s)) of the Federal Food, Drug, and Cosmetic Act (21U.S.C.§301 et. seq.) ("the Act"), is set forth at 21 CFR 170.30, the following is provided to briefly set the stage regarding the GRAS process (FDA, 2008):
1) Any substance of natural biological origin that has been widely consumed for its nutrient properties prior to January 1, 1958, without known detrimental effect, for which no health hazard is known, and which has been modified by processes first introduced into commercial use after January 1, 1958, which may reasonably be expected significantly to alter the composition of the substance.
2) Distillates, isolates, extracts, and concentration of extracts of GRAS substances. In general, materials of natural biological origin that have no significant detrimental effect and no known health hazard are eligible for GRAS status. Rice bran fiber is of biological origin, and is a concentrated fiber mechanically isolated from defatted rice bran which has been safely consumed in the U.S. for over 100 years, without known detrimental effects.

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 TDF per reference amount customarily consumed (RACC) in food. In addition, the FDA has approved the following 2 health claim notifications related to diets rich in whole grain foods under the 1997 FDA Modernization Act (FDAMA): 1) Diets rich in whole grain foods and other plant foods and low in total fat, saturated fat, and cholesterol, may help reduce the risk of heart disease and certain cancers (filed by General Mills, 1999; FDA, 1999), and 2) Whole grain foods with moderate fat content may help reduce the risk of heart disease (filed by Kraft, 2003; FDA, 2003).

The USDA, through its Dietary Guidelines (DG) for Americans, recommends that Americans increase consumption of whole grain foods in which fiber and bran are known to be active components (USDA, 2005, 2010). Whole grains consist of 3 main components: endosperm (mostly starch), germ, and bran. The bran components are known to exert important physiological benefits due to their high content of fiber and phytochemicals, including phytic acid (Cho, 2006).

A. **Intended technical effects**

Rice bran fiber can be used as an ingredient in foods and beverages as a food ingredient.

B. **Review of safety data**

1. Metabolic fate of rice bran fiber

Rice bran fiber, like most beta-linked fibers, is not digested by human pancreatic or brush border enzymes and the compounds are not expected to be absorbed intact. Rice bran enhances the viscosity of the gastrointestinal contents (Dikeman et al., 2006), which attenuates blood glucose and lipid concentrations. Once rice bran fiber reaches the large intestine, it is fermented by the colonic microflora to SCFAs (e.g., acetate, propionate, and butyrate) that promote colon health. Rice bran and its fiber also have fecal bulking effects to promote intestinal regularity (Miyoshi et al., 1986; Tomlin and Read,1988). Symptoms caused by fiber deficiency (such as constipation) can be alleviated by rice bran fiber.

2. Safety studies

2.1. Preclinical studies of rice bran fiber

Consumption of defatted, heat-stabilized, or raw rice bran has shown no adverse effects on animal health or feed nutritional quality when fed as 60% of the diet of chicks (Mujajhid et al., 2004; Sayer et al., 1987, 1988), 30% in lambs (Tabeidian and Sadeghi, 2009), or up to 40% of the diet of pigs (Calvert et al., 1985).

2.1.1. Effects of rice bran on growth

<u>Effects of processing of rice bran on growth and organ weights</u>

Sayre et al. (1987) observed that chickens fed a 60% heat-treated rice bran diet produced weight gains similar to those of chicks fed a 60% corn diet and that the heat-treated rice bran diet produced significantly greater weight gains than the 60% raw rice bran diet (raw RB, 441 g/3 wk vs. heat-treated RB, 568 g/3 wk, $P<0.05$). The quantity of feed required per unit weight gain was significantly ($P<0.05$) less for chickens given heat-treated rice bran (1.59) as compared to raw bran (1.86).

Sayre et al. (1988) and Mujajhid et al. (2004) also observed that processing rice bran by extrusion cooking or roasting improved performance of chicks. Extrusion cooking resulted in the best performance, followed by roasting, while non-significant differences were observed between raw and pelleted bran (weight gain, g/6 wk: extrusion $1991^{a}\pm249$, roasting $1881^{b}\pm310$, pelleting $1787^{c}\pm339$, raw rice bran $1788^{c}\pm347$; lack of a common superscript letter indicates a significant difference, $P<0.05$; Mujajhid et al., 2004). In this study, raw, extruded, roasted, and pelleted rice brans with three inclusions of antioxidants (0, 125, and 250 ppm) were used at 0, 10, 20, 30, 40, and 50% in the diets of broiler chicks. Increasing the amount of rice bran in broiler diets resulted in significantly negative effects on growth performance when rice bran was fed at up to 50% of the diet for 6 wk (0%: $2296^{a}\pm24$, 10%: $2172^{b}\pm61$, 20%: $1949^{c}\pm103$, 30%: $1738^{d}\pm122$, 40%:$1575^{e}\pm121$, 50%:$1442^{f}\pm119$). No significant differences were observed

in mortality or dressing percentage due to different processes or concentrations of rice bran in the diet. Organ weights were significantly higher on raw and pelleted rice bran as compared to extruded and roasted bran (liver, g; extrusion, 2.11^{a}±0.08; roasting, 2.12^{a}±0.07; raw, 2.20^{b}±0.16; pelleted, 2.22^{b}±0.16). However, these values were within the normal range. Treating rice bran with antioxidants had no significant effect on broiler performance.

The presence of these heat labile anti-nutritional factors (such as trypsin inhibitors, pepsin inhibitors, and an anti-thiamine factor) is a reason for poor performance of chicks when the content of raw or pelleted rice bran is increased (Kumar and Chaudhuri, 1976; Lu et al., 1991; Tashiro and Ikegami, 1996; Tashiro and Maki, 1986).

Comparison of full-fat and defatted rice bran with wheat and corn

Kahlon et al. (1990) studied the influence of stabilized or parboiled rice brans (full-fat or defatted), oat bran, or a cellulose control on weight gain in 4-wk old hamsters. All diets contained 10% cellulose and 0.5% cholesterol. Weight gain after 3 wk was similar in all groups except the parboiled rice bran group that had less ($P<0.05$) than all other groups (weight gain; control, 2.9; stabilized RB, 2.8; defatted rice bran, 2.8; parboiled rice bran, 2.3; defatted parboiled RB, 2.7; oat bran, 3.1 g/d). No adverse effects of stabilized full-fat or defatted rice bran were observed.

Other studies also reported that rice bran, corn, and other types of brans (oat or wheat bran) and rice bran fiber had comparable weight gains in rats (Ayano et al., 1980; Johnson et al., 1989), mice (Hundemer et al., 1991), geese (Hsu et al., 1996), and chicks (Sayer et al., 1987). Administration of hemicellulose extracted from rice bran fiber (10% in diet) had no effect on the body weight and relative tissue weight in rats (Takenaka and Itoyama, 1993).

Hematology

Hemicellulose extracted from rice bran fiber increased peripheral blood leukocytes in rats (Takenaka and Itoyama,1993). Wistar male rats were fed 10% RBF or various proportions of a hemicelluloses-containing diet for 2 wk. The number of peripheral blood leukocytes and lymphocytes was increased by 10% in rats fed a 10% hemicellulose diet compared with a control diet ($p < 0.01$). The proportion of each lymphocyte subset was not significantly changed.

2.1.2. Safety of rice bran fiber observed from metabolism studies in animals (hamster, rat, chick)

Several animal studies (hamster, rat, chick) studies investigated cholesterol lowering actions of rice bran or rice bran fiber (Tables 4 and 5; Anderson et al., 1994; Aoe et al., 1989a; 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; Suzuki and Aoyama, 1992; Takenaka and Itoyama, 1993; Topping et al., 1990). In these studies, the concentration of up to 60% rice bran or 5% rice bran fiber of the diet and the length of studies was up to 18 mo. No studies reported adverse effects

of rice bran or rice bran fiber. A study investigating the effects of defatted rice bran fiber (non-starch polysaccharides extracted from defatted rice bran, 15% in diet for 7 d) on the nutrient digestibility also reported no adverse effects of rice bran fiber (Adrizal and Ohtani, 2002). Aoe et al. (1989b) reported that rice bran hemicelluloses, high methoxylated pectin, and cellulose (2% in diet for 17 d) had comparable effects on body weight gain, feed efficiencies, and histological changes.

Table 4. Animal studies reporting no adverse effects of rice bran

Animal	Dose, g/d	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-fatRB, 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 and cecal VFAs	Topping et al., 1990
SD rat	6% TDF from RB or cellulose diet containing 1% cholesterol and 0.2% cholic acid	3 wk	Plasma and hepatic lipid profiles and body weight gain	Anderson et al., 1994

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

Table 5. Animal studies reporting no adverse effects of rice bran fiber

Animal	Dose, g/d	Duration	Endpoint	Reference
Rat	Neutral detergent fiber or acid detergent fiber isolated from defatted rice bran vs. cellulose control, 5% in diet, with 1% cholesterol and 0.25% cholic acid	3 wk	Serum and liver cholesterol and weight gain	Ayano et al. 1980
Rat	Hemicellulose fraction from defatted RB vs. high methoxylated pectin, 2% in diet	9 d	Weight gain, feed efficiency, serum cholesterol, and histological changes	Aoe et al., 1989a
Rat	Hemicellulose fraction from defatted RB vs. high methoxylated pectin vs.cellulose, 2% in diet	17 d	Weight gain, feed efficiency, and histological changes	Aoe et al., 1989b
Rat	Rice bran hemicellulose	2 wk	Peripheral blood leukocytes and lymphocytes	Takenaka and Itoyama, 1993
Rat	Rice bran fiber, 5% in diet	18 mo	Ability to reduce toxicity against 5% dye in a diet	Suzuki and Aoyama, 1992
Broiler chicks	Rice bran fiber as non-starch polysaccharides, 15% in diet	7 d	Nutrient digestibility	Adrizal and Ohtani, 2002

2.1.3. Antimutagenic, antigenotoxic, and anticarcinogenic activities of 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 and antimutagenic activities in in vitro and in vivo studies (Table 6; Aoe et al., 1993; CIREP, 2006; Hidashi-Okai et al., 2004; Sera et al., 2005; Takenaka et al., 1991; Takenaka, 1992; Takeshita et al., 1992; Verschoyle et al., 2007). Inositols and inositol derivatives (Ogawa, 1999), γ-oryzanol (CIREP, 2006), phytic acid (Norazalina et al., 2010), tocols (Sun et al., 2009), phytic acid (Norazalina et al., 2010), phenols (Rao et al., 2010), and other flavones (Renuka Devi and Arumughan, 2007) are known as active components of rice bran.

Table 6. Studies showing antimutagenic and/or anticarcinogenic activities of rice bran or rice bran fiber

Type of rice bran	Test measure	Tested mutagens or carcinogenesis model	Reference
Rice bran hemicelluloses	Chemically induced large bowel tumors in male rats	1,2-dimethylhydrazine (DMH)	Aoe et al., 1993
Rice bran fiber	Binding capacity, *in vitro*	Various mutagens and carcinogens such as heterocyclic amines*, six nitroarenes, 4-nitroquinoline-N-oxide, benzo[a]pyrene, furylfuramide, formaldehyde, and fecal mutagens (glucuronides and sulfates)	Sera et al., 2005
Rice bran fiber	Binding capacity, *in vitro*	Polycyclic biphenyl (PCB)	Takenaka et al., 1991
Rice bran fiber	Thymus atrophy in rats as an index of toxicity.	Bis(tri-n-butyltin)oxide	Takenaka, 1992
Rice bran saccharide	Chemically induced cancer in Wistar rats	N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG)	Takeshita et al., 1992
α-Glucan isolated from rice bran saccharide	Inhibition of Meth-A fibrosarcoma tumor in BALB/C mice	Subcutaneous inoculations of Meth-A fibrosarcoma cells (6 × 104 cells/mouse)	Takeo et al., 1988
Rice bran saccharide	Inhibition of fibrosarcoma tumor in BDF1 mice	Subcutaneous inoculations of Meth-A fibrosarcoma cells (6 × 104 cells/mouse)	Takeo et al., 1988
α-Glucan isolated from rice bran saccharide	Inhibition of lung carcinogenesis in BALB/C mice	Subcutaneous inoculations of Lewis lung carcinoma cells (105 cells/mouse)	Takeo et al., 1988
Rice bran saccharide	Inhibition of lung carcinogenesis in BDF1 mice	subcutaneous inoculations of Lewis lung carcinoma cells (105 cells/mouse)	Takeo et al., 1988
Rice bran ethanolic extract	umu C gene expression in SOS response associated with DNA damage in *S. typhimurium* (TA 1535/pSK 1002)	3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1)	Hidashi-Okai et al., 2004
Rice bran	Cancer inhibition effects in TAg, TRAMP, or Apc(Min) mice	Genetic mouse models of breast, prostate, and intestinal carcinogenesis	Verschoyle et al., 2007

*Heterocyclic amines include PCB, polychlorinated dibenzofurans (PCDF), and polychlorinated-p-dioxines (PCDD).

Antimutagenic activities of rice bran fiber

Rice bran fiber is known to have binding capacity to various mutagens and carcinogens (e.g., heterocyclic amines, six nitroarenes, 4-nitroquinoline-N-oxide, benzo[a]pyrene, furylfuramide, and formaldehyde) and mutagens (e.g., glucuronides and sulfates), as well as metabolites in urine (Sera et al., 2005; Takenaka, 1992). The binding effects were related to lignin content.

Hidashi-Okai et al. (2004) reported antimutagenicity of rice bran extract. When the effect of rice bran extract on umu C gene expression in SOS response associated with DNA damage in *Salmonella typhimurium* (TA 1535/pSK 1002) induced by Trp-P-1 was analyzed, a dose-dependent suppressive activity against Trp-P-1-induced umu C gene expression was observed.

Takenaka et al. (1991) reported that rice bran fiber stimulated rat fecal excretion of PCB in rats fed diets containing rice bran fiber, lignin, and cholestyramine. Takenaka (1992) reported that bis(tri-n-butyltin)oxide (TBTO; a biocide, 25 ppm) toxicity (measured as thymus atrophy) in rats was reduced by the administration of 10% rice bran fiber diet for 2 wk (relative thymus weight; TBTO control, 0.08 vs. rice bran fiber +TBTO, 0.2 g/kg BW, $p<0.05$).

Anticarcinogenic activities of rice bran fiber

Aoe et al. (1993) reported that water-soluble rice bran hemicellulose (RBH) played a preventive role in 1,2-dimethylhydrazine (DMH)-induced large bowel carcinogenesis in Fischer 344 rats. Rats were fed a basal control diet or a diet containing 2% or 4% RBH at 5 wk of age. At 6 wk of age, all animals were given an intraperitoneal injection of DMH (20 mg/kg BW) at weekly intervals for 20 wk and autopsied 7 wk after the last injection. The incidence of DMH-induced colon tumors was significantly lower in rats fed the 4% RBH diet than in rats fed the basal control diet (adenoma, 7 vs. 3; adenocarcinoma, 32 vs. 19; $p < 0.05$). The number of colon tumors per rat was also significantly lower in rats fed the 4% RBH diet than in rats fed the basal control diet (0.9 vs. 1.6; $p < 0.05$).

Verschoyle et al. (2007) reported cancer inhibition effects of rice bran in genetic mouse models of breast, prostate, and intestinal carcinogenesis. This study tested the hypothesis that rice bran interferes with development of tumors in tumor-associated glycoprotein (Tag), TRansgenic adenocarcinoma of the mouse prostate (TRAMP), or Apc(Min) mice, genetic models of mammary, prostate, and intestinal carcinogenesis, respectively. Mice received rice bran (30%) in an AIN-93G diet throughout their post-weaning lifespan. In TAg and TRAMP mice, rice bran did not affect carcinoma development. In TRAMP or wild-type C57Bl6/J mice, dietary rice bran increased kidney weight by 18 and 20%, respectively. Consumption of rice bran reduced numbers of intestinal adenomas in Apc(Min) mice by 51% ($P<0.01$) compared to mice on the control diet. In parallel, dietary rice bran decreased intestinal hemorrhages in these mice, as reflected by increased hematocrit. At 10% of the diet, rice bran did not significantly retard Apc(Min) adenoma development.

Likewise, low-fiber rice bran (30% of the diet) did not affect intestinal carcinogenesis, suggesting that the fibrous constituents of the bran inhibit carcinogenesis.
Other studies also reported anticarcinogenic properties of rice bran (Cai et al., 2004; Fan et al., 2006; Ghoneum and Gollapudi, 2005; Katayama et al., 2003; Kong et al., 2009; Luo et al., 2005; Miyoshi et al., 2001; Nam et al., 2005a, 2005b; Norazalina et al., 2010; Rao et al., 2010).

2.1.4. Antioxidant properties of rice bran

Rice bran polysaccharides exhibited good potential for reducing power, chelating ferrous ions, and scavenging effects of 2,2-azino-bis(3-ethylbenzthiazoline-6-sulphonate), 1,1-diphenyl-2-picrylhydrazyl (DPPH), and hydrogen peroxide (Zha et al., 2009). Defatted rice bran extracts and their phytochemical constituents, when assayed by cytochrome c and NBT methods, also showed scavenging effects of superoxide radical and DPPH, largely attributed to flavones, including tricin, phenolics, ferulic acid, and phytic acid (Cai et al., 2004; Renuka Devi and Arumughan, 2007).

2.2. Human Clinical Studies

Because the basic safety of rice bran fiber from rice bran is not in question, there are none of the conventional toxicity studies (such as acute, subacute, subchronic, or chronic toxicity studies) on rats or other species that one would expect to exist in the scientific literature. Instead, numerous human and animal studies examined the health benefits of rice bran (Aoe et al. 1993; Cheng et al. 2009), rice bran fiber (Maeda et al., 2004; Miyoshi et al., 1986; Tomlin and Read, 1988), and cereal fiber (Mozaffarian et al. 2003). Cereal fiber intake has been associated with risk reduction of diabetes (Schulze et al., 2007), heart diseases (Pereira et al., 2004), and obesity (Koh-Banerjee et al., 2004). In Western populations, there are no reports of safety concerns related to inherent cereal fibers including rice bran fiber.

Rice bran and rice bran fiber have been tested for their hypocholesterolemic, hypoglycemic, gastrointestinal, and immunomodulatory effects in normal, hypercholesterolemic, or diabetic human subjects (Cara et al., 1992; Cheng et al., 2010; Gerhardt and Gallo, 1998; Hegsted et al., 1993; 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 dosages of rice bran and rice bran fiber (or total fiber from rice bran) tested were 100 g/d (Hegsted et al., 1993) and 40 g/d (Rodrigues Silva et al., 2005), respectively (Tables 7 and 8). The length of the study was up to 12 wk for rice bran (Cheng et al., 2010) and 6 wk for rice bran fiber (Maeda et al., 2004. Rice bran is known to enhance viscosity of the gastrointestinal contents (Dikeman et al., 2006), which attenuates blood glucose and lipid responses. Rice bran and its fiber also have fecal bulking effects to promote intestinal regularity (Miyoshi et al., 1986; Tomlin and Read,1988).

Table 7. Human studies reporting no adverse effects of rice bran

Subjects	Dose, g/d	Duration	Measurement endpoints	Reference
11 subjects with moderately elevated blood cholesterol	100 g RB 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 RB or oat bran vs. rice starch	6 wk	Fasting blood lipid profiles	Gerhardt and Gallo, 1998
24 mildly hypercholesterolemic men	60 g/d RB containing 11.8 g TDF vs. baseline	4 wk	Fasting blood lipid profiles	Kestin et al., 1990
17 moderately hypercholesterolemic and hypertriglyceridemic individuals	Supplementation of 30 g RB and 30 g oat bran vs. usual diet	6 wk	Fasting blood lipid profiles	Ranhotra et al., 1989
20 healthy young men and women	Supplementation of 30 g defatted RB or 33.3 g full-fat RB vs. low fiber period	18 d	Fasting blood lipid profiles	Tsai and Ting, 1992
18 normo-cholesterolemic subjects	15 or 30 g RB vs. 15 g WB	3 wk	Fasting blood lipid profiles	Sanders and Reddy, 1992
6 normolipidemic males	RB diet containing 2.8 g TDF	Single dose	Postprandial lipidemia	Cara et al., 1992
28 subjects with NIDDM	20 g stabilized RB	12 wk	Fasting blood glucose, insulin and lipid profiles, insulin sensitivity	Cheng et al., 2010
11 subjects with NIDDM	RB diet containing 40 g TDF	1 wk	Fasting blood glucose	Rodrigues Silva et al., 2005

Rice bran contains many antioxidants such as phenolic acids (e.g., ferulic acid), vitamin E (alpha-tocopherol, alpha-tocotrienol, gamma-tocopherol, and gamma-tocotrienol) and gamma-oryzanol components (Xu et al., 2001). In addition to fiber, these antioxidants also may contribute to hypoglycemic and hypocholesterolemic effects of rice bran (Jung et al., 2007; Queresi et al., 2002; Xu et al., 2001). No human clinical studies reported adverse effects of rice bran or its fiber fraction.

Table 8. Human studies reporting no adverse effects of rice bran fiber

Subjects	Dose, g/d	Duration	Measurement endpoints	Reference
50 elderly, age 70-95 yr	Arabinoxylan from RB hydrolysate	6 wk	Common cold symptoms	Maeda et al., 2004
5 healthy young men	27.9 vs. 13.7 g of neutral detergent fiber/d 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 indigestible residue from rice	10 d	Fecal volume and frequency	Tomlin and Read, 1988

2.3. 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 (1992) 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 (1994) developed similar symptoms after handling rice at a wedding as well as during handling of raw rice for cooking. It is noteworthy that positive responses to other cereal grains also were observed in these rice-positive women (CIREP, 2006).

C. Safety (Tolerable Upper Intake Levels) of dietary fiber addressed by the Institute of Medicine, the National Academy of Sciences

The IOM (2002) 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. The IOM states that "Although occasional adverse gastrointestinal symptoms were observed with the consumption of dietary and functional fibers, serious chronic adverse effects have not been observed".

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 (Marlett et al., 2002).

IV. Conclusions

This GRAS determination for rice bran fiber is based on scientific procedures and through experience based on common use in foods. Rice bran and brown rice have a long history of use in foods in the United States. Rice bran fiber is of natural biological origin and is an isolate of rice bran, a GRAS ingredient, that has been widely consumed for its nutrient properties prior to 1958, without known detrimental effects, and for which no health hazard is known. Rice grain's safety is well-established based on its historic use as a food. There are abundant literature references describing the composition of the rice kernel and its parts, including the bran layer.

Also, numerous human and animal studies examined the health benefits of rice bran, rice bran fiber, and cereal fibers. There are no reports of safety concerns in any of the studies. CJ utilizes a HACCP-controlled manufacturing process and rigorously tests its final production batches to verify adherence to quality control specifications. The literature indicates that rice bran and rice bran fiber offers consumers a safe fiber source.

The information/data provided by CJ Jeiljedang in this report and supplemented by the publicly available literature/toxicity data on rice bran fiber provide a sufficient basis for an assessment of the safety of rice bran fiber for the proposed use as an ingredient in food when prepared according to appropriate specifications and used according to GMP. Key findings are summarized here:

1. Rice bran fiber is well characterized and of consistent quality across lots and free from chemical and microbial contamination.
2. Rice bran fiber has a long history of use in foods and beverages in the U.S.
3. Manufacturing processes for obtaining rice bran fiber have been safely used for many years in the food industry.
4. The safety and nutritional benefits of rice bran fiber are well established by human clinical trials and animal studies of rice bran. There are no indications of significant adverse effects related to rice bran and rice bran fiber consumption in the publicly available literature.
5. Increased consumption of dietary fiber has been recommended by the USDA Dietary Guidelines Committee and the IOM. Rice bran fiber is an excellent source of dietary fiber.

Therefore, not only is the proposed use of rice bran fiber 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.

V. 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 bran fiber preparations in foods and beverages, meeting appropriate specifications and used according to GMP, is GRAS.

VI. 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:

CJ America
3500 Lacey Rd, Suite 230
Downers Grove, IL 60515
TEL: 630-241-0112

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Pages 000037-000356 have been removed in accordance with copyright laws. Please see appended bibliography list of the references that have been removed from this request

SUBMISSION END

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NA- Not applicable

AM

Mosley, Sylvester

From: Susan S Cho [susanscho1@yahoo.com]
Sent: Thursday, April 21, 2011 4:00 PM
To: Carlson, Susan; Mosley, Sylvester
Subject: Rice bran fiber GRN 373
Attachments: GRAS Exemption Claim for rice bran fiber 4-20-11 supplement.docx; Riber GRAS 4-19-2011 amendment.doc; Riber GRAS 4-19-2011 amendment - showing changes.doc

Dear Drs. Carlson and Mosley,

We have added some pivotal toxicological data of related compounds (such as wild brown rice and cellulose, a fiber component in rice bran fiber, as well as mutagenicity studies on wheat bran, which has similar composition) to the GRAS self affirmation document. Panelists re-sign the GRAS self affirmation document.

Today, I sent you signed documents of GRN 373 Amendment/supplement by overnight mail.
Meanwhile, please take a look at e files.

In the 'Riber GRAS 4-19-2011 amendment-showing changes' doc, blue font indicates changes or new additions.
The portions which were deleted (for example, examples of food application and statement about historic use in the conclusion section) are not shown.

Please let me know if you have further questions or concerns.

Happy Easter!
Sincerely,

Susan
Susan Cho, Ph.D.
NutraSource
6309 Morning Dew Ct
Clarksville, MD 21029
410-531-3336(O)
301-875-6454 (C)

April 20, 2011

Dr. Robert Martin
Division of Biotechnology and GRAS Notice Review
Office of Food Additive Safety-CFSAN
U.S. Food and Drug Administration
5100 Paint Branch Parkway (HFS-255)
College Park, MD 20740-3835

RECEIVED
APR 26 2011
BY: (b) (6)

Re: Supplement to GRAS exemption claim for rice bran fiber as an ingredient in foods and beverages (GRN 373)

Dear Dr. Martin,

This is to notify you that CJ America claims that the use of the substance described below (rice bran fiber) is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because CJ America has determined such use to be Generally Recognized As Safe (GRAS).

On behalf of CJ America, NutraSource (an independent consulting firm) assembled a panel of experts highly qualified by scientific training and experience to evaluate the safety of the intended uses of rice bran fiber. The panel included Dr. Susan Cho (NutraSource, Clarksville, MD), Dr. Joanne Slavin (University of Minnesota, St. Paul, MN), and Dr. George C. Fahey, Jr. (University of Illinois, Emeritus, Urbana, IL). Following independent critical evaluation of the available data and information, the panel has determined that the use of rice bran fiber (that is manufactured by CJ America) described in the enclosed notification is GRAS based on scientific procedures.

After reviewing the available data, the Expert Panel also concluded in its February 2011 statement that CJ America's rice bran fiber can be safely used as a food ingredient. 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.

Notifier's name and Address: CJ America, Inc.
Attention: Jennifer Jang (e mail address: jenniferjang@cj.net)
Address: 3500 Lacey Rd. Suite 230, Downers Grove, IL 60515
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Name of GRAS substance: Rice bran fiber (Common or trade name: Riber® 50)

Product description: CJ's rice bran fiber is processed from defatted rice bran by a proprietary hydrothermal process. Rice bran fiber consists of mostly insoluble dietary

fiber added to food for several purposes. Examples include raising total dietary fiber (TDF) content, reducing caloric content, controlling water activity, and modifying the rheological properties of foods and beverages. Rice bran fiber has >40% TDF (of which >90% is insoluble dietary fiber) and a particle size of <100 microns (Table 1). The rice fiber contains no sulfites, added flavors, components from an animal source, BHA, BHT, genetically altered plant material, or irradiated material.

Specifications:

Table 1. Specifications of rice fiber

Macronutrient		Unit	Analytical method
TDF (dry wt. basis)[a]	>40	%	AOAC 991.43
Protein	<15	%	AOAC 984.13
Starch	<25	%	AOAC 996.11
Fat	<1.5	%	AOAC 954.02
Moisture	<8.0	%	AOAC 934.01
Ash	<16	%	AOAC 900.02
pH, 5% slurry	7.3±0.5	pH	
Arsenic	<1	ppm	
Lead	<1	ppm	
Microbiological Specifications			
Total plate count	<10,000	cfu/g	FDA-BAM2[b] Chap. 3
S. aureus	Negative	cfu/g	FDA-BAM2 Chap. 4
E. coli	Negative	cfu/g	FDA-BAM2 Chap. 4
Salmonella	Negative	cfu/g	FDA-BAM2 Chap. 5
Yeast and mold	<200	cfu/g	FDA-BAM2 Chap. 19

[a]TDF=total dietary fiber; cfu = colony forming units.
[b]BAM = Bacteriological Analytical Manual, January, 2001.

Applicable conditions of use of the notified substance

Rice bran fiber is proposed for general food use at concentrations consistent with cGMP.

Probable consumption of rice bran fiber

Rice bran fiber consumption is not expected to exceed 25-28 grams per day. Application of conventional fiber ingredients (e.g., wheat bran, rice bran, and corn bran) to food and beverage formulations has been limited due to their gritty mouth feel and insoluble nature. Compared to conventional rice bran, rice bran fiber has improved mouth feel and functionality such as water holding capacity. Rice bran fiber is expected to be used as a replacement for conventional fiber ingredients. Thus, it is not likely that the availability of a new rice bran fiber ingredient will significantly boost fiber intake levels in the American population.

The Institute of Medicine (IOM), the National Academy of Sciences (NAS), has recommended a daily intake of 14 g fiber per 1,000 calories for Americans. 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 (42 to 62%) of the recommended levels, the Daily Reference Intakes (DRI).

Currently, more than 30 types of fiber ingredients are available for food formulations. Despite the availability of various fiber ingredients, fiber intake by Americans has been steadily low over the past several years. Average (aged 6 mo to 74 yr) daily fiber consumption was 13.3 g in 1976-1980 (NHANES II) and 14.8 g in 2003-2006 (2003-2006 NHANES). Considering the differences in both dietary survey methodology and fiber analytical methods between the 1970's and 2000's, it is reasonable to conclude that fiber intake status did not change significantly over the past two or three decades.

Basis of GRAS determination

Through scientific procedures.

Review and copying statement

The data and information that serve as the basis for this GRAS determination will be sent to the FDA upon request, or are available for the FDA's review and copying at reasonable times at the office of CJ America, Inc. or Nutrasource, Inc.
We enclose an original and two copies as well as a word file of this notification for your review. If you have any questions, please contact me.

Sincerely,

(b) (6)

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EXECUTIVE SUMMARY

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

We, the undersigned expert panel members, Susan Cho, Ph.D., Joanne Slavin, Ph.D., and George C. Fahey, Jr., Ph.D., have individually and collectively critically evaluated the materials summarized in the rice bran fiber GRAS report. We conclude that rice bran fiber is safe and GRAS for its intended use in food.

Over 90% of the U.S. population does not meet the daily recommended intake (DRI) of fiber. The USDA Dietary Guidelines (DG) Committee has classified dietary fiber as a shortfall nutrient that is low in the American diet (USDA 2004, 2005, 2010). Symptoms caused by fiber deficiency (such as constipation) can be alleviated by rice bran fiber. There is broad-based and widely disseminated knowledge concerning the chemistry and health benefits of rice bran fiber in both humans and animals.

Rice bran fiber consists of cellulose and hemicelluloses and is mostly insoluble in water. It is naturally present in the diet and has a long history of safe use as a dietary fiber ingredient. Rice bran fiber, like most beta-linked fibers, is not digested by human pancreatic or brush border enzymes and the compounds are not expected to be absorbed intact. Rice bran fiber reaches the large intestine where it is fermented by the colonic microflora to short-chain fatty acids (SCFA; e.g. acetate, propionate, and butyrate) that promote colon health. A 14-day acute toxicity study of wild brown rice in mice showed that consumption of rice bran fiber at 21,500 mg/kg BW/day (d) did not cause any adverse effects. In addition, no adverse effects were noted in toxicity or mutagenicity studies of purified cellulose and other insoluble cereal brans, such as wheat bran. Both full-fat and defatted rice bran have shown no adverse effects on animal health or feed nutritional quality when fed at up to 60% in chick diets or up to 40% in pig diets. There are no indications of significant adverse effects related to rice bran fiber in the publicly available literature.

Rice bran fiber is proposed for general food use at concentrations consistent with cGMP. Consumption of rice bran fiber is not expected to exceed 25-28 grams per day.

This GRAS determination for rice bran fiber 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. Rice bran fiber is of biological origin and is a concentrated fiber mechanically isolated from defatted rice bran. Rice bran has been

safely consumed in the U.S. for over 100 years without known detrimental effects. Rice bran fiber does not represent a known health hazard.

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 Institute of Medicine [IOM] and the US. Department of Agriculture [USDA]), and nutritional benefits as identified by animal and human clinical studies.

Therefore, the proposed use of rice bran 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.

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

Signature: (b) (6) Date: 4/21/2011

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

(b) (6)

Signature: Date: 4-19-11

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

(b) (6)

Signature: Date: 4/20/11

I. IDENTITY OF SUBSTANCE

A. Common or trade name: Riber® 50 or rice bran fiber

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.

C. Background

CJ's rice bran fiber is processed from defatted rice bran by a proprietary hydrothermal process. Rice bran fiber consists of mostly insoluble dietary fiber added to food for several purposes. Examples include raising total dietary fiber (TDF) content, reducing caloric content, controlling water activity, and modifying the rheological properties of foods and beverages.

Rice bran and brown rice (containing rice bran) 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. Historically, rice has constituted an important commercial crop since it was a dietary staple for people in regions around the world. Leading rice-producing countries include the United States, China, and other Asian countries. Although rice bran is used mostly as animal feed, some is processed for human consumption.

Consumption of rice in developing countries is around 68.5 kg/person/yr and 12.8 kg/person/yr in developed countries (Kahlon, 2009). Rice is harvested from fields called paddies. In the rice milling process, the hull is first removed to produce brown rice. Brown rice consists of the bran layer, germ, and endosperm (starch). Bran and germ are concentrated sources of vitamins, minerals, flavones, and other phytonutrients present in brown rice. One hundred kilograms of paddy rice on milling yields 10-12 kg rice bran. Rice bran contains the enzyme, lipase, which rapidly degrades the oil and makes the bran rancid and inedible (Kahlon, 2009). To extend shelf life, rice bran is either defatted with hexane or heat-stabilized to deactivate lipase activities (Randall et al., 1985).

Each year, between 63 and 76 million tons of rice bran (rice milling byproduct) is produced in the world and more than 90% of rice bran is sold as animal feed. The remainder is either defatted or stabilized to be used as value-added ingredients. In the U.S., rice oil is extracted from 15-20% of the rice bran (Kahlon, 2009). Rice bran has been recognized as an excellent source of fiber. The total dietary fiber (TDF) content of full-fat rice bran ranges from 20-27% with less than 2% as soluble dietary fiber.

Inadequate intake of dietary fiber increases risk of chronic diseases. Examples include diverticular diseases/constipation, heart disease, cancer, diabetes, metabolic syndrome, and overweight/obesity (IOM, 2002, 2006). Americans consume approximately one half of the recommended intake levels, the Daily Reference Intakes (DRI). Thus, the IOM

(IOM, 2002, 2006) and USDA Dietary Guidelines for Americans (2004, 2005, 2010) recommend increased consumption of fiber-rich foods.

The USDA, in partnership with a non-profit organization, provides a nutritious rice bran drink to preschool children in Latin American countries. Healthy meal replacement drinks made from stabilized rice bran have been introduced in the market.

D. Physicochemistry and structure of rice bran fiber

Rice bran fiber has >40% TDF (of which >90% is insoluble dietary fiber) and a particle size of <100 microns (Table 1). The rice fiber contains no sulfites, added flavors, components from an animal source, BHA, BHT, genetically altered plant material, or irradiated material.

General Physical Properties

Color: Cream to beige
Flavor: Bland to slightly sweet, no off flavors
Physical form: Fine powder
Odor: Natural clean cereal, no off odors
Particle size distribution: <100 microns

Defatted rice bran fiber and sugar beet fiber are known to have comparable water holding capacities (rice bran fiber, 4.89 ml/g vs. sugar beet fiber, 4.56 ml/g; Abdul-Hamid and Luan, 2000).

E. Manufacturing Process

1. Defatted rice bran is cleaned using mechanical detachers, gravity separators, sieves, and air classifiers to separate rice bran from rice fragments and any residual impurities.
2. The defatted rice bran is suspended in clean water (15% solids concentration) in a reception tank at 25 - 30°C.
3. Food grade sodium hydroxide is added to adjust the pH to 9.0 - 9.5.
4. The suspension is well blended in an alkaline environment at 35 - 40°C for 2 h to extract rice protein and starch.
5. The rice bran fiber is separated from aqueous solution containing protein and starch by a decanter-type centrifugal separator, followed by washing with clean water until the pH reaches 6.7-7.0.
6. The separated rice bran fiber with approximately 65% moisture is dried until the moisture reaches 8%.
7. To control microbial activities and to develop a deep and roasted aroma, rice bran fiber is roasted at 95 - 98°C for 5 - 10 minutes in a roasting chamber.
8. Rice bran fiber, after cooling, is subjected to a pulverization to particle sizes of <100 um (using Jet Sieve analyses).
9. Rice bran fiber then is packaged in paper bags coated with polyethylene and stored at room temperature.
10. Rice bran fiber produced in this manner has silky mouth-feel and excellent water adsorption properties. Rice bran 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 CJ's manufacturing facilities. Laboratory use meets OSHA regulations.

F. Specifications

Table 1 lists specifications of rice bran fiber.

Table 1. Specifications of rice bran fiber

Macronutrient	%	Unit	Analytical method
TDF (dry wt. basis)[a]	>40	%	AOAC 991.43
Protein	<15	%	AOAC 984.13
Starch	<25	%	AOAC 996.11
Fat	<1.5	%	AOAC 954.02
Moisture	<8.0	%	AOAC 934.01
Ash	<16	%	AOAC 900.02
Lead	<1	ppm	
Arsenic	<1	ppm	
pH, 5% slurry	7.3±0.5	pH	
Microbiological Specifications			
Total plate count	<10,000	cfu/g	FDA-BAM2[b] Chap. 3
S. aureus	Negative	cfu/g	FDA-BAM2 Chap. 4
E. coli	Negative	cfu/g	FDA-BAM2 Chap. 4
Salmonella	Negative	cfu/g	FDA-BAM2 Chap. 5
Yeast and mold	<200	cfu/g	FDA-BAM2 Chap. 19

[a]TDF=total dietary fiber; cfu = colony forming units.
[b]BAM = Bacteriological Analytical Manual, January, 2001.

II. NATURAL OCCURRENCE AND EXPOSURE TO RICE BRAN FIBER

A. Food sources of rice bran fiber

Rice bran and brown rice are natural sources of rice bran fiber.

B. Intended use

Rice bran fiber is proposed for general food use at concentrations consistent with cGMP.

C. Probable consumption of rice bran fiber

Consumption of rice bran fiber is not expected to exceed 25-28 grams 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). Table 2 summarizes recommended intake levels of fiber in different age and gender groups.

Table 2. Dietary reference intakes of TDF, g/d

Age, year	Male	Female
1-3	19	19
4-8	25	25
9-13	31	26
14-18	38	26
19-50	38	25
51+	30	21

Despite the recommendations of the IOM, most Americans consume inadequate amounts of dietary fiber. Fiber intake for the U.S. population ages 2 years and older was calculated based on food consumption data reported in the most recent National Health and Nutrition Examination Survey (NHANES 2003-2006). The NHANES was compiled by the U.S. Department of Health and Human Services, National Center for Health Statistics and the Nutrition Coordinating Center. NHANES was conducted between 2003-2006 with non-institutionalized individuals in the U.S. to collect data from a nationally representative sample of individuals of all ages. All estimates were generated with USDA sampling weights to adjust for differences in representation of subpopulations. As shown in Table 3, the median intakes of fiber in the U.S. were estimated to be approximately one half (42 to 62%) of the recommended levels, the Daily Reference Intakes (DRI). Over 90% of the U.S. population did not meet the daily recommended intake of fiber (data not shown). Thus, the USDA Dietary Guidelines (DG) Committee classified dietary fiber as a shortfall nutrient that is low in the American diet (USDA, 2004). Both IOM and the USDA recommend increased consumption of dietary fiber for Americans.

Table 3. The fiber intake status of Americans (NHANES, 2003-2006)

Age, year	Mean daily intake, g fiber/d		% of DRI	
	Male	Female	Male	Female
2-5	11.2	11.2	48.2	48.2
6-12	13.3	13.3	43.6	43.6
13-18	16.1	12.3	42.8	45.2
19-54	16.3	13.8	48.1	62.3
55+	16.6	13.7	59.3	47.3

Currently, more than 30 types of fiber ingredients are available for food formulations. These ingredients include wheat bran, corn bran, rice bran, oat bran, oat hull fiber, oat beta-glucan, barley beta-glucan, psyllium, wheat fiber, and guar gum. Despite the availability of various fiber ingredients and various agencies' recommendations for increased consumption of dietary fiber, fiber intake by Americans has been steadily low over the past several years. Average (aged 6 mo to 74 yr) daily fiber consumption was 13.3 g in 1976-1980 (NHANES II; Lanza et al., 1987) and 14.8 g in 2003-2006. Fiber analysis and intake estimates for the 1970's were based on Southgate's unavailable carbohydrates method (1979) that generally reported approximately 5-6% lower values than the current TDF analytical methods (AOAC Methods 991.43 and 985.29; Cho et al., 1997). Thus, TDF intake in the 1970's was estimated to be approximately 14.1 g.

Considering the differences in both dietary survey methodology and fiber analytical methods between the 1970's and 2000's, it is reasonable to conclude that fiber intake status did not change significantly over the past two or three decades.

Fiber availability data support scientific data on fiber intake trends in Americans. The availability of dietary fiber from grain products and fruit has remained steady since 1995, while dietary fiber availability from vegetables, legumes, nuts, and soy declined in 2005 (USDA, 2007). Per capita dietary fiber in the food supply data show that available fiber may not meet the DRIs for Americans (USDA, 2007); the weighted per capita requirement for fiber ranged from 28-30 g, while available fiber in the food supply was 24-25 g per capita. On average, the difference between per capita fiber in the food supply and the per capita fiber required to meet the estimated average requirement was 12.6% over the last 10 yr (USDA, 2007). Due to waste during food processing and storage of ingredients and finished foods, the actual difference would be much larger than the theoretical value of 12.6%. The data suggest that more fiber ingredients should be available to help Americans meet recommended intakes.

Application of conventional fiber ingredients (e.g., wheat bran, rice bran, and corn bran) to food and beverage formulations has been limited due to their gritty mouth feel and insoluble nature. In the past two decades, numerous new fiber ingredients have been

developed to improve mouth feel and functionality in foods. Compared to conventional rice bran, rice bran fiber has improved mouth feel and functionality such as water holding capacity. Rice bran fiber is expected to be used as a replacement for conventional fiber ingredients. Thus, it is not likely that the availability of a new rice bran fiber ingredient will significantly boost fiber intake levels in the American population.

III. BASIS FOR GRAS DETERMINATION

A. Current regulatory status.

Cellulose, a major component of rice bran fiber, has been recognized as a GRAS substance since 1972 (Anonymous, 1972). In addition, FDA had no question on the safety of other fiber ingredients from natural sources (GRN 116, carrot fiber; GRN 207, barley fiber; GRNs 261 and 342, oat hull fibers; GRN 262, sweet lupin fiber; and GRN 310, potato fiber).

Rice bran is a GRAS ingredient because it is a substance of natural biological origin that has been widely consumed for its nutrient properties prior to January 1, 1958, without known detrimental effects and for which no health hazard is known.

Basis of GRAS determination: In section 201(s) (21 U.S.C. §321(s)) of the Federal Food, Drug, and Cosmetic Act (21U.S.C.§301 et. seq.) ("the Act"), is set forth at 21 CFR 170.30, the following is provided to briefly set the stage regarding the GRAS process (FDA, 2008):
1) Any substance of natural biological origin that has been widely consumed for its nutrient properties prior to January 1, 1958, without known detrimental effect, for which no health hazard is known, and which has been modified by processes first introduced into commercial use after January 1, 1958, which may reasonably be expected significantly to alter the composition of the substance.
2) Distillates, isolates, extracts, and concentration of extracts of GRAS substances. In general, materials of natural biological origin that have no significant detrimental effect and no known health hazard are eligible for GRAS status. Rice bran fiber is of biological origin, and is a concentrated fiber mechanically isolated from defatted rice bran which has been safely consumed in the U.S. for over 100 years, without known detrimental effects.

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

TDF per reference amount customarily consumed (RACC) in food. In addition, the FDA has approved the following 2 health claim notifications related to diets rich in whole grain foods under the 1997 FDA Modernization Act (FDAMA): 1) Diets rich in whole grain foods and other plant foods and low in total fat, saturated fat, and cholesterol, may help reduce the risk of heart disease and certain cancers (filed by General Mills, 1999; FDA, 1999), and 2) Whole grain foods with moderate fat content may help reduce the risk of heart disease (filed by Kraft, 2003; FDA, 2003).

The USDA, through its Dietary Guidelines (DG) for Americans, recommends that Americans increase consumption of whole grain foods in which fiber and bran are known to be active components (USDA, 2005, 2010). Whole grains consist of 3 main components: endosperm (mostly starch), germ, and bran. The bran components are known to exert important physiological benefits due to their high content of fiber and phytochemicals, including phytic acid (Cho, 2006).

Foods providing 2.5 g fiber/serving from rice bran fiber may be qualified for two health claims (the reduced risk of cancer claim for fiber containing grain products, fruits, and vegetables and the reduced risk of CHD claim for fruits, vegetables, and grain products that contain fiber, in particular soluble fiber), if they meet the jelly bean rules (i.e., as part of low sodium and low fat diets).

A. Intended technical effects

Rice bran fiber can be used as an ingredient in foods and beverages as a food ingredient.

B. Review of safety data

1. Metabolic fate of rice bran fiber

Rice bran fiber, like most beta-linked fibers, is not digested by human pancreatic or brush border enzymes and the compounds are not expected to be absorbed intact. Like other dietary fibers, rice bran fiber reaches the large intestine without being hydrolyzed by human alimentary enzymes, and is fermented by the colonic microflora to SCFAs (e.g., acetate, propionate, and butyrate) that can be utilized as a caloric source by intestinal microflora. Rice bran fiber also has fecal bulking effects to promote intestinal regularity (Miyoshi et al., 1986; Tomlin and Read,1988). Symptoms caused by fiber deficiency (such as constipation) can be alleviated by rice bran fiber.

Rice bran enhances the viscosity of the gastrointestinal contents (Dikeman et al., 2006), which attenuates blood glucose and lipid concentrations.

2. Safety studies

2.1. Preclinical studies

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

Consumption of defatted, heat-stabilized, or raw rice bran has shown no adverse effects on animal health or feed nutritional quality when fed as 60% of the diet of chicks (Mujajhid et al., 2004; Sayer et al., 1987, 1988), 30% in lambs (Tabeidian and Sadeghi, 2009), or up to 40% of the diet of pigs (Calvert et al., 1985).

2.1.1. Acute toxicity study of wild brown rice

The chemical composition of wild brown rice is similar to that of other kinds of brown rice (approximately 1.9 g crude fiber). A 14-day acute toxicity study in mice showed no abnormal reaction to a diet containing 21,500 mg/kg BW of Chinese wild brown rice. None of the mice died (Zhai et al., 1996). The data indicate that brown rice is classified as a non-toxic substance.

2.1.2. Mutagenicity studies of wild brown rice

The bone marrow micronucleus and sperm abnormality tests conducted on Chinese wild brown rice with mice (10,000 mg/kg BW) were negative, as was the Salmonella mutagenicity test with S. typhimurium with or without S-9 mix (Zhai et al., 1996).

2.1.3. Toxicity studies of cellulose, a major component of rice bran fiber

From a review of animal studies, Anderson et al. (1992) found that chronic ingestion of purified cellulose over the lifespans 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. No adverse effects were seen on reproduction or neonate development in rats and mice using 5-30% exogenous cellulose in the diet. Also, dietary concentrations of exogenous cellulose up to 20% by weight did not retard growth in rats. The authors concluded that human exposure to cellulose would not cause any adverse health effects.

2.1.4. Mutagenicity studies of wheat bran, which has similar physicochemical properties as rice bran

Extracts from buckwheat and wheat bran showed no mutagenic activity with Salmonella typhimurium TA102 (Brindzová et al., 2009). As with rice bran fibers, those in buckwheat and wheat bran consist mostly of insoluble fibers and mixtures of cellulose and hemicelluloses. In the salmonella mutagenicity assay, wheat bran extract showed antimutagenic activities (Yu et al., 2001).

2.1.5. 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 and antimutagenic activities in in vitro and in vivo studies (Table 4a and 4b; Aoe et al., 1993; CIREP, 2006; Hidashi-Okai et al., 2004; Sera et al., 2005; Takenaka et al., 1991; Takenaka, 1992; Takeshita et al., 1992; Verschoyle et al., 2007). Inositols and inositol derivatives (Ogawa, 1999), γ-oryzanol (CIREP, 2006), phytic acid (Norazalina et al., 2010), tocols (Sun et al., 2009), phytic acid (Norazalina et al., 2010), phenols (Rao et al., 2010), and

other flavones (Renuka Devi and Arumughan, 2007) are known as active components of rice bran.

Table 4a. Studies showing antimutagenic and/or anticarcinogenic activities of rice bran fiber

Type of rice bran	Test measure	Tested mutagens or carcinogenesis model	Reference
Rice bran hemicelluloses	Chemically induced large bowel tumors in male rats	1,2-dimethylhydrazine (DMH)	Aoe et al., 1993
Rice bran fiber	Binding capacity, *in vitro*	Various mutagens and carcinogens such as heterocyclic amines*, six nitroarenes, 4-nitroquinoline-N-oxide, benzo[a]pyrene, furylfuramide, formaldehyde, and fecal mutagens (glucuronides and sulfates)	Sera et al., 2005
Rice bran fiber	Binding capacity, *in vitro*	Polycyclic biphenyl (PCB)	Takenaka et al., 1991
Rice bran fiber	Thymus atrophy in rats as an index of toxicity.	Bis(tri-n-butyltin)oxide	Takenaka, 1992

*Heterocyclic amines include PCB, polychlorinated dibenzofurans (PCDF), and polychlorinated-p-dioxines (PCDD).

Antimutagenic activities of rice bran fiber

Rice bran fiber is known to have binding capacity to various mutagens and carcinogens (e.g., heterocyclic amines, six nitroarenes, 4-nitroquinoline-N-oxide, benzo[a]pyrene, furylfuramide, and formaldehyde) and mutagens (e.g., glucuronides and sulfates), as well as metabolites in urine. The binding effects were related to lignin content.

Takenaka et al. (1991) reported that rice bran fiber stimulated rat fecal excretion of PCB in rats fed diets containing rice bran fiber, lignin, and cholestyramine. Takenaka (1992) reported that bis(tri-n-butyltin)oxide (TBTO; a biocide, 25 ppm) toxicity (measured as thymus atrophy) in rats was reduced by the administration of 10% rice bran fiber diet for 2 wk (relative thymus weight; TBTO control, 0.08 vs. rice bran fiber +TBTO, 0.2 g/kg BW, $p<0.05$).

Anticarcinogenic activities of rice bran fiber

Aoe et al. (1993) reported that water-soluble rice bran hemicellulose (RBH) played a preventive role in 1,2-dimethylhydrazine (DMH)-induced large bowel carcinogenesis in Fischer 344 rats. Rats were fed a basal control diet or a diet containing 2% or 4% RBH at 5 wk of age. At 6 wk of age, all animals were given an intraperitoneal injection of DMH (20 mg/kg BW) at weekly intervals for 20 wk and autopsied 7 wk after the last injection. The incidence of DMH-induced colon tumors was significantly lower in rats fed

the 4% RBH diet than in rats fed the basal control diet (adenoma, 7 vs. 3; adenocarcinoma, 32 vs. 19; $p < 0.05$). The number of colon tumors per rat was also significantly lower in rats fed the 4% RBH diet than in rats fed the basal control diet (0.9 vs. 1.6; $p < 0.05$).

Table 4b. Studies showing antimutagenic and/or anticarcinogenic activities of rice bran

Type of rice bran	Test measure	Tested mutagens or carcinogenesis model	Reference
Rice bran saccharide	Chemically induced cancer in Wistar rats	N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG)	Takeshita et al., 1992
α-Glucan isolated from rice bran saccharide	Inhibition of Meth-A fibrosarcoma tumor in BALB/C mice	Subcutaneous inoculations of Meth-A fibrosarcoma cells (6 × 104 cells/mouse)	Takeo et al., 1988
Rice bran saccharide	Inhibition of fibrosarcoma tumor in BDF1 mice	Subcutaneous inoculations of Meth-A fibrosarcoma cells (6 × 104 cells/mouse)	Takeo et al., 1988
α-Glucan isolated from rice bran saccharide	Inhibition of lung carcinogenesis in BALB/C mice	Subcutaneous inoculations of Lewis lung carcinoma cells (105 cells/mouse)	Takeo et al., 1988
Rice bran saccharide	Inhibition of lung carcinogenesis in BDF1 mice	subcutaneous inoculations of Lewis lung carcinoma cells (105 cells/mouse)	Takeo et al., 1988
Rice bran ethanolic extract	umu C gene expression in SOS response associated with DNA damage in *S. typhimurium* (TA 1535/pSK 1002)	3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1)	Hidashi-Okai et al., 2004
Rice bran	Cancer inhibition effects in TAg, TRAMP, or Apc(Min) mice	Genetic mouse models of breast, prostate, and intestinal carcinogenesis	Verschoyle et al., 2007

*Heterocyclic amines include PCB, polychlorinated dibenzofurans (PCDF), and polychlorinated-p-dioxines (PCDD).

Antimutagenic activities of rice bran

Hidashi-Okai et al. (2004) reported antimutagenicity of rice bran extract. When the effect of rice bran extract on umu C gene expression in SOS response associated with DNA damage in *Salmonella typhimurium* (TA 1535/pSK 1002) induced by Trp-P-1 was

analyzed, a dose-dependent suppressive activity against Trp-P-1-induced umu C gene expression was observed.

Anticarcinogenic activities of rice bran

Verschoyle et al. (2007) reported cancer inhibition effects of rice bran in genetic mouse models of breast, prostate, and intestinal carcinogenesis. This study tested the hypothesis that rice bran interferes with development of tumors in tumor-associated glycoprotein (Tag), TRansgenic adenocarcinoma of the mouse prostate (TRAMP), or Apc(Min) mice, genetic models of mammary, prostate, and intestinal carcinogenesis, respectively. Mice received rice bran (30%) in an AIN-93G diet throughout their post-weaning lifespan. In TAg and TRAMP mice, rice bran did not affect carcinoma development. In TRAMP or wild-type C57Bl6/J mice, dietary rice bran increased kidney weight by 18 and 20%, respectively. Consumption of rice bran reduced numbers of intestinal adenomas in Apc(Min) mice by 51% ($P<0.01$) compared to mice on the control diet. In parallel, dietary rice bran decreased intestinal hemorrhages in these mice, as reflected by increased hematocrit. At 10% of the diet, rice bran did not significantly retard Apc(Min) adenoma development.

Likewise, low-fiber rice bran (30% of the diet) did not affect intestinal carcinogenesis, suggesting that the fibrous constituents of the bran inhibit carcinogenesis.
Other studies also reported anticarcinogenic properties of rice bran (Cai et al., 2004; Fan et al., 2006; Ghoneum and Gollapudi, 2005; Katayama et al., 2003; Kong et al., 2009; Luo et al., 2005; Miyoshi et al., 2001; Nam et al., 2005a, 2005b; Norazalina et al., 2010; Rao et al., 2010).

2.1.6. Antioxidant properties of rice bran fiber

Rice bran fiber (polysaccharides) exhibited good potential for reducing power, chelating ferrous ions, and scavenging effects of 2,2-azino-bis(3-ethylbenzthiazoline-6-sulphonate), 1,1-diphenyl-2-picrylhydrazyl (DPPH), and hydrogen peroxide (Zha et al., 2009). Defatted rice bran extracts and their phytochemical constituents, when assayed by cytochrome c and NBT methods, also showed scavenging effects of superoxide radical and DPPH, largely attributed to flavones, including tricin, phenolics, ferulic acid, and phytic acid (Cai et al., 2004; Renuka Devi and Arumughan, 2007).

2.1.7. Safety of rice bran fiber observed from metabolism studies in animals (hamster, rat, chick)

Several animal studies (hamster, rat, chick) studies investigated cholesterol lowering actions of rice bran or rice bran fiber (Tables 5 and 6; Anderson et al., 1994; Aoe et al., 1989a; 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; Suzuki and Aoyama, 1992; Takenaka and Itoyama, 1993; Topping et al., 1990). In these studies, the concentration of up to 60% rice bran or 5% rice bran fiber of the diet and the length of studies was up to 18 mo. No studies reported adverse effects of rice bran or rice bran fiber. A study investigating the effects of defatted rice bran fiber

(non-starch polysaccharides extracted from defatted rice bran, 15% in diet for 7 d) on the nutrient digestibility also reported no adverse effects of rice bran fiber (Adrizal and Ohtani, 2002). Aoe et al. (1989b) reported that rice bran hemicelluloses, high methoxylated pectin, and cellulose (2% in diet for 17 d) had comparable effects on body weight gain, feed efficiencies, and histological changes.

Table 5. Animal studies reporting no adverse effects of rice bran fiber

Animal	Dose, g/d	Duration	Endpoint	Reference
Rat	Neutral detergent fiber or acid detergent fiber isolated from defatted rice bran vs. cellulose control, 5% in diet, with 1% cholesterol and 0.25% cholic acid	3 wk	Serum and liver cholesterol and weight gain	Ayano et al. 1980
Rat	Hemicellulose fraction from defatted RB vs. high methoxylated pectin, 2% in diet	9 d	Weight gain, feed efficiency, serum cholesterol, and histological changes	Aoe et al., 1989a
Rat	Hemicellulose fraction from defatted RB vs. high methoxylated pectin vs.cellulose, 2% in diet	17 d	Weight gain, feed efficiency, and histological changes	Aoe et al., 1989b
Rat	Rice bran hemicellulose	2 wk	Peripheral blood leukocytes and lymphocytes	Takenaka and Itoyama, 1993
Rat	Rice bran fiber, 5% in diet	18 mo	Ability to reduce toxicity against 5% dye in a diet	Suzuki and Aoyama, 1992
Broiler chicks	Rice bran fiber as non-starch polysaccharides, 15% in diet	7 d	Nutrient digestibility	Adrizal and Ohtani, 2002

Table 6. Animal studies reporting no adverse effects of rice bran

Animal	Dose, g/d	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-fatRB, 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 and cecal VFAs	Topping et al., 1990
SD rat	6% TDF from RB or cellulose diet containing 1% cholesterol and 0.2% cholic acid	3 wk	Plasma and hepatic lipid profiles and body weight gain	Anderson et al., 1994

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

2.1.8. Effects of rice bran on growth and hematology

Effects of processing of rice bran on growth and organ weights

Sayre et al. (1987) observed that chickens fed a 60% heat-treated rice bran diet produced weight gains similar to those of chicks fed a 60% corn diet and that the heat-treated rice bran diet produced significantly greater weight gains than the 60% raw rice bran diet (raw RB, 441 g/3 wk vs. heat-treated RB, 568 g/3 wk, $P<0.05$). The quantity of feed required per unit weight gain was significantly ($P<0.05$) less for chickens given heat-treated rice bran (1.59) as compared to raw bran (1.86).

Sayre et al. (1988) and Mujajhid et al. (2004) also observed that processing rice bran by extrusion cooking or roasting improved performance of chicks. Extrusion cooking resulted in the best performance, followed by roasting, while non-significant differences were observed between raw and pelleted bran (weight gain, g/6 wk: extrusion $1991^{a}\pm249$, roasting $1881^{b}\pm310$, pelleting $1787^{c}\pm339$, raw rice bran $1788^{c}\pm347$; lack of a common superscript letter indicates a significant difference, $P<0.05$; Mujajhid et al., 2004). In this study, raw, extruded, roasted, and pelleted rice brans with three inclusions of antioxidants (0, 125, and 250 ppm) were used at 0, 10, 20, 30, 40, and 50% in the diets of broiler chicks. Increasing the amount of rice bran in broiler diets resulted in significantly negative effects on growth performance when rice bran was fed at up to 50% of the diet for 6 wk (0%: $2296^{a}\pm24$, 10%: $2172^{b}\pm61$, 20%: $1949^{c}\pm103$, 30%: $1738^{d}\pm122$, 40%:$1575^{e}\pm121$, 50%:$1442^{f}\pm119$). No significant differences were observed in mortality or dressing percentage due to different processes or concentrations of rice bran in the diet. Organ weights were significantly higher on raw and pelleted rice bran as compared to extruded and roasted bran (liver, g; extrusion, $2.11^{a}\pm0.08$; roasting, $2.12^{a}\pm0.07$; raw, $2.20^{b}\pm0.16$; pelleted, $2.22^{b}\pm0.16$). However, these values were within the normal range. Treating rice bran with antioxidants had no significant effect on broiler performance.

The presence of these heat labile anti-nutritional factors (such as trypsin inhibitors, pepsin inhibitors, and an anti-thiamine factor) is a reason for poor performance of chicks when the content of raw or pelleted rice bran is increased (Kumar and Chaudhuri, 1976; Lu et al., 1991; Tashiro and Ikegami, 1996; Tashiro and Maki, 1986).

Comparison of full-fat and defatted rice bran with wheat and corn

Kahlon et al. (1990) studied the influence of stabilized or parboiled rice brans (full-fat or defatted), oat bran, or a cellulose control on weight gain in 4-wk old hamsters. All diets contained 10% cellulose and 0.5% cholesterol. Weight gain after 3 wk was similar in all groups except the parboiled rice bran group that had less ($P<0.05$) than all other groups (weight gain; control, 2.9; stabilized RB, 2.8; defatted rice bran, 2.8; parboiled rice bran, 2.3; defatted parboiled RB, 2.7; oat bran, 3.1 g/d). No adverse effects of stabilized full-fat or defatted rice bran were observed.

Other studies also reported that rice bran, corn, and other types of brans (oat or wheat bran) and rice bran fiber had comparable weight gains in rats (Ayano et al., 1980; Johnson et al., 1989), mice (Hundemer et al., 1991), geese (Hsu et al., 1996), and

chicks (Sayer et al., 1987). Administration of hemicellulose extracted from rice bran fiber (10% in diet) had no effect on the body weight and relative tissue weight in rats (Takenaka and Itoyama, 1993).

Hematology

Hemicellulose extracted from rice bran fiber increased peripheral blood leukocytes in rats (Takenaka and Itoyama,1993). Wistar male rats were fed 10% RBF or various proportions of a hemicelluloses-containing diet for 2 wk. The number of peripheral blood leukocytes and lymphocytes was increased by 10% in rats fed a 10% hemicellulose diet compared with a control diet ($p < 0.01$). The proportion of each lymphocyte subset was not significantly changed.

2.2. Human Clinical Studies

Numerous human and animal studies examined the health benefits of rice bran (Aoe et al. 1993; Cheng et al. 2009), rice bran fiber (Maeda et al., 2004; Miyoshi et al., 1986; Tomlin and Read, 1988), and cereal fiber (Mozaffarian et al. 2003). Cereal fiber intake has been associated with risk reduction of diabetes (Schulze et al., 2007), heart diseases (Pereira et al., 2004), and obesity (Koh-Banerjee et al., 2004). In Western populations, there are no reports of safety concerns related to inherent cereal fibers including rice bran fiber.

2.2.1. Human studies showing no adverse effects of rice bran fiber

Rice bran fiber has been tested for their hypocholesterolemic, hypoglycemic, gastrointestinal, and immunomodulatory effects in normal human subjects (Table 7; 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/d 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).

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

Subjects	Dose, g/d	Duration	Measurement endpoints	Reference
50 elderly, age 70-95 yr	0.5 g/d 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/d 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

2.2.2. Human studies showing no adverse effects of rice bran

Rice bran has been tested for their hypocholesterolemic and hypoglycemic effects in normal, hypercholesterolemic, or diabetic human subjects (Table 8; 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/d (Hegsted et al., 1993) and the length of the study was up to 12 wk (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.

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

Subjects	Dose, g/d	Duration	Measurement endpoints	Reference
11 subjects with moderately elevated blood cholesterol	100 g RB 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 RB or oat bran vs. rice starch	6 wk	Fasting blood lipid profiles	Gerhardt and Gallo, 1998
24 mildly hypercholesterolemic men	60 g/d RB containing 11.8 g TDF vs. baseline	4 wk	Fasting blood lipid profiles	Kestin et al., 1990
17 moderately hypercholesterolemic and hypertriglyceridemic individuals	Supplementation of 30 g RB and 30 g oat bran vs. usual diet	6 wk	Fasting blood lipid profiles	Ranhotra et al., 1989
20 healthy young men and women	Supplementation of 30 g defatted RB or 33.3 g full-fat RB vs. low fiber period	18 d	Fasting blood lipid profiles	Tsai and Ting, 1992
18 normo-cholesterolemic subjects	15 or 30 g RB vs. 15 g WB	3 wk	Fasting blood lipid profiles	Sanders and Reddy, 1992
6 normolipidemic males	RB diet containing 2.8 g TDF	Single dose	Postprandial lipidemia	Cara et al., 1992
28 subjects with NIDDM	20 g stabilized RB	12 wk	Fasting blood glucose, insulin and lipid profiles, insulin sensitivity	Cheng et al., 2010
11 subjects with NIDDM	RB diet containing 40 g TDF	1 wk	Fasting blood glucose	Rodrigues Silva et al., 2005

Rice bran contains many antioxidants such as phenolic acids (e.g., ferulic acid), vitamin E (alpha-tocopherol, alpha-tocotrienol, gamma-tocopherol, and gamma-tocotrienol) and gamma-oryzanol components (Xu et al., 2001). In addition to fiber, these antioxidants also may contribute to hypoglycemic and hypocholesterolemic effects of rice bran (Jung et al., 2007; Queresi et al., 2002; Xu et al., 2001). No human clinical studies reported adverse effects of rice bran or its fiber fraction.

2.3. 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 (1992) 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 (1994) developed similar symptoms after handling rice at a wedding as well as during handling of raw rice for cooking. It is noteworthy that positive responses to other cereal grains also were observed in these rice-positive women (CIREP, 2006).

C. Safety (Tolerable Upper Intake Levels) of dietary fiber addressed by the Institute of Medicine, the National Academy of Sciences

The IOM (2002) 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. The IOM states that "Although occasional adverse gastrointestinal symptoms were observed with the consumption of dietary and functional fibers, serious chronic adverse effects have not been observed".

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 (Marlett et al., 2002).

IV. CONCLUSIONS

This GRAS determination for rice bran fiber is based on scientific procedures. Rice bran fiber is of natural biological origin and is an isolate of rice bran, a GRAS ingredient, that has been widely consumed for its nutrient properties prior to 1958, without known detrimental effects, and for which no health hazard is known. Numerous human and animal studies examined the health benefits of rice bran, rice bran fiber, cereal brans, and cereal fibers. There are no reports of safety concerns in any of the studies. CJ utilizes a HACCP-controlled manufacturing process and rigorously tests its final production batches to verify adherence to quality control specifications. The literature indicates that rice bran and rice bran fiber offers consumers a safe fiber source.

The information/data provided by CJ Jeiljedang in this report and supplemented by the publicly available literature/toxicity data on rice bran fiber provide a sufficient basis for an assessment of the safety of rice bran fiber for the proposed use as an ingredient in food when prepared according to appropriate specifications and used according to GMP. Key findings are summarized here:

1. Rice bran fiber is well characterized and of consistent quality across lots and free from chemical and microbial contamination.
2. Manufacturing processes for obtaining rice bran fiber have been safely used for many years in the food industry.

3. The safety and nutritional benefits of rice bran fiber are well established by human clinical trials and animal studies of brown rice, rice bran, and rice bran fiber. There are no indications of significant adverse effects related to brown rice, rice bran, and rice bran fiber consumption in the publicly available literature.
4. Increased consumption of dietary fiber has been recommended by the USDA Dietary Guidelines Committee and the IOM. Rice bran fiber is an excellent source of dietary fiber.

Therefore, not only is the proposed use of rice bran fiber 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.

V. 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 bran fiber preparations in foods and beverages, meeting appropriate specifications and used according to GMP, is GRAS.

VI. 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:

CJ America
3500 Lacey Rd, Suite 230
Downers Grove, IL 60515
TEL: 630-241-0112

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Pages 000392-000421 have been removed in accordance with copyright laws. The removed references are:

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AM

Mosley, Sylvester

From: Susan S Cho [susanscho1@yahoo.com]
Sent: Wednesday, March 23, 2011 3:59 PM
To: Mosley, Sylvester
Subject: Re: GRN000373 (Rice bran fiber)

Thank you for your mail.
Answer is NO.
If you want me to further clarify in the text, I am willing to modify it. thanks

Susan Cho

From: "Mosley, Sylvester" <Sylvester.Mosley@fda.hhs.gov>
To: Susan S Cho <susanscho1@yahoo.com>
Sent: Wed, March 23, 2011 12:36:59 PM
Subject: GRN000373 (Rice bran fiber)

Dear Dr. Cho,

I have been assigned to your client's GRAS notice, GRN000373 (Rice bran fiber). I had a clarification question. Is your client including USDA-regulated products or infant formula in the conditions of intended use?

Thanks,
Sylvester

Sylvester L. Mosley, Ph.D.
Consumer Safety Officer
Division of Biotechnology and GRAS Notice Review
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5100 Paint Branch Parkway (HFS-255)
College Park, MD 20740-3835
Phone: 301-436-1333
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Email: Sylvester.Mosley@fda.hhs.gov

AM

Mosley, Sylvester

From: Susan S Cho [susanscho1@yahoo.com]
Sent: Wednesday, March 30, 2011 2:25 PM
To: Mosley, Sylvester
Cc: Robert L Martin
Subject: Re: Regarding the Review of GRN000373 (Rice Bran Fiber)
Attachments: grn000261 oat hull fiber.pdf; GRN000342 oat hull fiber 342.pdf; GRN 116 carrot fiber.pdf

Drs. Mosley and Martin,

I have time on April 6.
I am writing this letter to request your re-consideration. I woudl appreciate it it you would ask us to provide additional information instead of recommending a withdrawal of the GRN 373, rice bran fiber.

I hope you compare the GRN 373, rice bran fiber, with other GRNs related to carrot fiber and oat hull fiber.

Safety data
Rice bran fiber is not much different from the case of carrot fiber for which FDA had no question.
Even oat hull fiber received no question (which did not have safety data).

Rice bran fiber has much more safety data in the literature than oat hull fiber or carrot fiber. Also, rice bran has been widely consumed by Americans in a form of **brown rice** since prior to 1958. Rice bran fiber was isolated from brown rice.
Human did not eat oat hulls prior to 1958.
GRN 261 and 342 on oat hull fibers did not present solid safety data.
Still FDA had no question.

Intended use and exposure estimate
Intended use and exposure estimates for these fiber ingredients were listed as follows:

	Intended use	Exposure estimates
GRN 261; oat hull fiber	-5 g per 50 g food serving; no specific names of food categories	25-28 g /d
GRN 172; Isomalto-oligosaccharide (IMO)	Self limiting level of use	Not mentioned

Rice bran fiber follows a format similar to those which received no question by FDA.
If you want us to be more specific about intended use and exposure estimates, we can provide more detailed data (as of now, we followed the sample of GRN 172).

I would really appreciate it if you would re-consider the rice bran fiber case.
Thanks

Susan
Susan Cho, Ph.D.
NutraSource
6309 Morning Dew Ct
Clarksville, MD 21029
410-531-3336 (O)

From: "Mosley, Sylvester" <Sylvester.Mosley@fda.hhs.gov>
To: Susan S Cho <susanscho1@yahoo.com>
Sent: Wed, March 30, 2011 11:45:42 AM
Subject: Regarding the Review of GRN000373 (Rice Bran Fiber)

Good morning Susan,

The review team for GRN000373 has completed an initial review of GRN000373 (rice bran fiber). As a result of this initial review, a few deficiencies have been found with the notice. Being that you are relatively close in proximity to FDA, we would like to invite you to come in for a discussion on these deficiencies. Would you be available either next Wednesday, April 6, 2011 at 2pm or next Thursday, April 7, 2011 at 10am? With the deficiencies found in the notice, we are doubtful that the meeting will last any more than 30minutes, but we will set aside 1 hour just in case. Please let me know your availability at your earliest convenience.

Sincerely,
Sylvester

Sylvester L. Mosley, Ph.D.
Consumer Safety Officer
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AM

Mosley, Sylvester

From: Susan S Cho [susanscho1@yahoo.com]
Sent: Monday, June 13, 2011 11:09 AM
To: Mosley, Sylvester
Subject: Answer to your Q-Rice bran fiber GRN 373

Dear Dr. Mosley,

In response to your query, the following table has been prepared to compare the composition of various fiber sources. Rice fiber has been well characterized and is composed of glucose (42.3%), arabinose (11.5%), xylose (11.5%), mannose (3.8%), galactose (3.8%), and lignin (26.9%). Fibers have beta linkages of theses sugars. For example, cellulose has beta linkages of glucose and starches have alpha linkages of glucose. Human alimentary enzymes (in upper gastrointestinal tract) can not hydrolyze beta linkages. Thus, fiber escapes the upper gastrointestinal tract to be fermented in the colon. These are common characteristics of fiber.

All of these sugar units are known to be safe. Lignin is a well known fiber component which contributes no health hazard. Other fiber sources containing these sugars and lignin are also known to be safe for human consumption.

Composition of various fibers, %

	Anhydro sugar components						Anhydro uronic acid	Lignin
	Rhamnose	Arabinose	Xylose	Mannose	Galactose	Glucose		
Rice	trace	11.5	11.5	3.8	3.8	42.3	trace	26.9
Corn bran	0.13	13.1	37.3	0.65	5.5	25.5	6.8	5.0
Wheat bran	trace	20.1	36.8	1.1	2.4	24.4	1.6	10.2
Lettuce, iceburg	2.8	4.7	5.1	5.1	2.7	6.3	32.0	10.3
Soy isolate	1.7	3.5	1.7	15.7	5.2	7.0	8.8	56.1
potato	2.1	3.2	2.1	2.1	17.8	54.7	13.7	4.2

From Theander O. and Westerlund E, Determination of individual components of dietary fiber. *In* CRC Handbook of Dietary Fiber in Human Nutrition, GA Spiller (Ed). 1993

If you have further questions, please let me know.

Sincerely,

Susan Cho, Ph.D.

NutraSource

410-531-3336

From: "Mosley, Sylvester" <Sylvester.Mosley@fda.hhs.gov>
To: Susan S Cho <susanscho1@yahoo.com>
Sent: Fri, June 10, 2011 4:57:44 PM
Subject: RE: Rice bran fiber GRN 373

Susan,

That will work. We'll give you a call.

Sylvester

Sylvester L. Mosley, Ph.D.
Consumer Safety Officer
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From: Susan S Cho [mailto:susanscho1@yahoo.com]
Sent: Friday, June 10, 2011 2:15 PM
To: Mosley, Sylvester
Subject: Re: Rice bran fiber GRN 373

How about 9 am?
Look forward to talking to you soon.
Have a nice weekend!

Susan

From: "Mosley, Sylvester" <Sylvester.Mosley@fda.hhs.gov>
To: Susan S Cho <susanscho1@yahoo.com>
Sent: Fri, June 10, 2011 8:27:33 AM
Subject: RE: Rice bran fiber GRN 373

That's quite alright. I am working off-site today. Let's plan to chat on Monday. Are you available at 9:00am, 9:30am or 12:30pm?

Sylvester L. Mosley, Ph.D.
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From: Susan S Cho [mailto:susanscho1@yahoo.com]
Sent: Thursday, June 09, 2011 8:52 PM
To: Mosley, Sylvester
Subject: Re: Rice bran fiber GRN 373

I have been in out of the country starting May 30th
I apoplogize for not checking my mail for the past 3 days.
I am at the airport in Korea and will be back to USA today.
I will be arriving in USA friday late am and will call you in the afternoon of June 10th.

Look forward to talking to you soon.
Please advise me the best number I can talk to you.
Thanks

Susan Cho

From: "Mosley, Sylvester" <Sylvester.Mosley@fda.hhs.gov>
To: Susan S Cho <susanscho1@yahoo.com>
Sent: Tue, June 7, 2011 10:39:47 AM
Subject: RE: Rice bran fiber GRN 373

Good morning Dr. Cho,

At your earliest convenience, the toxicologist supervisor and I, would like to talk with you briefly about GRN000373 (Rice Bran Fiber). If we could talk today or tomorrow before 1, that would be great.

Thanks,
Sylvester

Sylvester L. Mosley, Ph.D.
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From: Susan S Cho [mailto:susanscho1@yahoo.com]
Sent: Thursday, April 21, 2011 4:00 PM
To: Carlson, Susan ; Mosley, Sylvester
Subject: Rice bran fiber GRN 373

Dear Drs. Carlson and Mosley,

We have added some pivotal toxicological data of related compounds (such as wild brown rice and cellulose, a fiber component in rice bran fiber, as well as mutagenicity studies on wheat bran, which has similar composition) to the GRAS self affirmation document. Panelists re-sign the GRAS self affirmation document.

Today, I sent you signed documents of GRN 373 Amendment/supplement by overnight mail. Meanwhile, please take a look at e files.

In the 'Riber GRAS 4-19-2011 amendment-showing changes' doc, blue font indicates changes or new additions.
The portions which were deleted (for example, examples of food application and statement about historic use in the conclusion section) are not shown.

Please let me know if you have further questions or concerns.

Happy Easter!
Sincerely,

Susan
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