Notification for a Health Claim Based on an Authoritative Statement: Whole Grain Brown Rice

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TABLE OF CONTENTS

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I. INTRODUCTION

The USA Rice Federation (USA Rice) intends to make a health claim based on an authoritative statement pursuant to section 403(r)(3)(C) of the Federal Food, Drug, and Cosmetic Act (FFDCA) (21 U.S.C. § 343(r)(3)(C)) regarding the relationship between whole grain rice and reduced risk of coronary heart disease (CHD) and certain cancers in the labeling of whole grain brown rice. This claim will be based on the same authoritative statement that underlies the current whole grain health claims authorized in "Health Claim Notification for Whole Grain Foods" (FDA, 1999[1]) and "Health Claim Notification for Whole Grain Foods with Moderate Fat Content" (FDA, 2003[2]). USA Rice intends to apply this claim to whole grain brown rice despite the fact that this food does not meet the minimum criterion for dietary fiber used as a marker for compliance relative to the existing claims. This position is based on the fact that the authoritative statement supporting these claims does not specify that dietary fiber is obligatory for efficacy, that the benefits of whole grains beyond dietary fiber are well recognized and that brown rice is specifically mentioned as a source of whole grain recommended for frequent consumption by the 2005 Dietary Guidelines for Americans (DGA) (U.S. Department of Health and Human Services, U.S. Department of Agriculture, 2005) and MyPyramid. The rationale and supporting evidence for this notification is presented in detail below.

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[1] http://www.cfsan.fda.gov/~dms/flgrains.html
[2] http://www.cfsan.fda.gov/~dms/flgrain2.html

II. BACKGROUND INFORMATION

A. Increased consumption of whole grains is an important public health priority.

Numerous public health and governmental organizations have recommended increased consumption of whole grain foods, including whole grain forms of rice. For example, current diet and lifestyle recommendations from the American Heart Association (AHA) (Lichtenstein *et. al.*, 2006) recommend, "Choose foods made with whole grains. Common forms of whole grains are whole wheat, oats/oatmeal, rye, barley, corn, popcorn, **brown rice,** wild rice, buckwheat, triticale, bulgur (cracked wheat), millet, quinoa, and sorghum." (Emphasis provided). In addition, these AHA recommendations cite whole grains as a recommended source of antioxidants, "Although antioxidant supplements are not recommended, food sources of antioxidant nutrients, principally from a variety of plant-derived foods such as fruits, vegetables, **whole grains**, and vegetable oils are recommended." (Emphasis provided).

Recently revised recommendations from the American Cancer Society (ACS) (2006) also recommend frequent consumption of whole grain foods, "There's no doubt about it: Eating a diet composed of mostly vegetables, fruits, and **whole grains** is good for your health and can help reduce your cancer risk." (Emphasis provided).

The food intake patterns[3] specified by MyPyramid recommend that minimum daily whole grain consumption should range from one and one-half 3-ounce serving equivalents for persons consuming 1,000 kcal diets to five such servings for persons

[3] http://www.mypyramid.gov/downloads/MyPyramid_Food_Intake_Patterns.pdf

consuming 3,200 kcal diets. In addition, MyPyramid provides the following suggestions to help consumers increase whole grain consumption.

- To eat more whole grains, substitute a whole-grain product for a refined product – such as eating whole-wheat bread instead of white bread or **brown rice** instead of white rice.

- Create a whole grain pilaf with a mixture of barley, wild rice, **brown rice**, broth and pices *(sic)*. For a special touch, stir in toasted nuts or chopped dried fruit.

- For a change, try **brown rice** or whole-wheat pasta. Try **brown rice stuffing** in baked green peppers or tomatoes and whole-wheat macaroni in macaroni and cheese.

(Emphasis provided). Finally, as noted in the introduction, the 2005 DGA (U.S. Department of Health and Human Services, U.S. Department of Agriculture, 2005) and MyPyramid recommend increased consumption of whole grains and mention brown rice as a source of this dietary component. Specifically, the Guidelines state, "Consume 3 or more ounce-equivalents of whole-grain products per day, with the rest of the recommended grains coming from enriched or whole-grain products. In general, at least half the grains should come from whole grains." In addition, Table 7 (Whole Grains

Available in the United States) includes brown rice along with 13 other examples of whole grain foods.

These contemporary dietary recommendations clearly indicate that increased consumption of whole grains is a public health priority in the United States, and that whole grain rice is a recognized source of such whole grains.

B. **More education is needed to help consumers identify whole grain foods and understand their benefits.**

The fact that whole grain consumption in the United States is dramatically below recommended amounts is a clear indication of the need for more consumer education. Specifically, mean consumption of whole grain was only 1.0 serving per day among 9,323 men and women ≥20 years of age who participated in the 1994-96 Continuing Survey of Food Intakes by Individuals (Cleveland *et. al.,* 2000). In addition, McKeown *et. al.* (2004) reported that mean consumption of whole grains among the lowest quintile of members of the Framingham Offspring cohort was 0.13 servings per day (n=566) and 2.9 servings per day among the highest quintile (n=567). Therefore, mean whole grain consumption among this population was less than recommended amounts even among the highest intake group. Finally, data from the 1999-2002 National Health and Nutrition Examination Survey (NHANES) found that only 8% of adults consumed three or more servings of whole grains daily (Cleveland, 2005).

Two of the most frequently cited barriers to increased consumption of whole grain foods are low awareness of their benefits and inability to identify such foods in the marketplace (Adams and Engstrom, 2000; Kantor *et.al.*, 2001). Edge *et. al.* (2005) concluded that increased understanding of exactly what constitutes a whole grain, and why such foods are beneficial to health, are necessary to increase consumers' willingness to increase consumption. Nevertheless, these issues continue to be prevalent among U.S. consumers and health professionals. For example, Chase *et. al.* (2003) reported that only 60% of dietitians who responded to a survey regarding their knowledge and intention to promote whole grain foods correctly identified such products by examining food labels. Marquart *et. al.* (2006) reported that a survey of health professionals and consumers (WIC participants and state fair attendees, respectively) found that the later were unlikely to mention reduced risk of chronic disease as a benefit of increasing whole grain consumption although these individuals had a positive attitude regarding such foods.

USA Rice agrees that additional nutrition education regarding whole grains is necessary to increase their consumption. We believe authorization of a health claim for whole grain rice based on the existing health claims will help accomplish this goal by allowing easy identification of such products in the marketplace and by helping to explain their health benefits. The availability of this claim will also provide an incentive for food manufacturers to develop more products containing whole grain rice, which would furnish additional opportunities for increased consumption.

C. **Brown rice is a whole grain food.**

The American Association of Cereal Chemists (AACC) approved the following definition of "whole grain" in 1999[4],

> Whole grains shall consist of the intact, ground, cracked or flaked caryopsis, whose principal anatomical components - the starchy endosperm, germ and bran - are present in the same relative proportions as they exist in the intact caryopsis.

This definition was used virtually verbatim in an FDA document entitled, "Draft Guidance – Guidance for Industry and FDA Staff**.** Whole Grain Label Statements," issued in February, 2006[5]. In fact, the agency cited brown rice as an example of whole grain foods in the answers to hypothetical questions in this guidance document,

> **1. Question:** What factors should be considered in determining whether a food is a whole grain?
>
> **Answer:** Cereal grains that consist of the intact, ground, cracked or flaked caryopsis, whose principal anatomical components – the starchy endosperm, germ and bran – are present in the same relative proportions as they exist in the intact caryopsis – should be considered a whole grain food.
>
> **2. Question:** What are some examples of cereal grains?
>
> **Answer:** Cereal grains may include amaranth, barley, buckwheat, bulgur, corn (including popcorn), millet, quinoa, **rice**, rye, oats, sorghum, teff, triticale, wheat, and wild rice. (Emphasis provided).
>
> **11. Question:** Can the name of the particular whole grain be substituted for the term "whole grain" in label statements? For example, could the statement "100% **brown rice**" replace the statement "100% whole grains" or "1 ounce whole wheat" replace "1 ounce whole grain?"
>
> **Answer:** The specific name of the whole grain **(e.g., brown rice)** can be used for label statements made under 21 CFR 102.5(b) or 21 CFR

[4] http://www.aaccnet.org/definitions/wholegrain.asp
[5] http://www.cfsan.fda.gov/~dms/flgragui.html

> 101.13(i) (3) as long as the statement is truthful and not misleading. However, "whole grains" is the substance of the health claims established under section 403(r) (3)(C) of the Act and the name of a particular whole grain can not be substituted for the term "whole grain foods" in the health claims. (Emphasis provided).

Although this document is not legally binding, it clearly establishes that brown rice meets FDA's "current thinking" with respect to the definition of whole grain foods. The agency's February 2006 Draft Guidance document has not been superseded by a more recent revision.

As noted earlier, the 2005 DGA (U.S. Department of Health and Human Services, U.S. Department of Agriculture, 2005) and USDA's MyPyramid also cite brown rice as an example of whole grain foods. USA Rice believes that these examples, as well as those noted above, provide indisputable evidence that brown rice is a whole grain food.

D. **The compliance standard for dietary fiber in the existing whole grain health claims serves solely as a marker, and is not mandated by the authoritative statement.**

The authoritative statement upon which the existing whole grain health claims are based was taken from the landmark report entitled, *Diet and Health: Implications for Reducing Chronic Disease Risk* (Food and Nutrition Board (FNB), National Academy of Sciences (NAS), 1989). This statement reads, "Diets high in plant foods--i.e., fruits, vegetables, legumes, and whole-grain cereals--are associated with a lower occurrence of coronary heart disease and cancers of the lung, colon, esophagus, and stomach." The NAS report

notes that dietary fiber is one possible beneficial component of such diets but does not attribute the protective effect to any single dietary element,

> Although the mechanisms underlying these effects are not fully understood, the inverse association with coronary heart disease may be largely explained by the usually low saturated fatty acid and cholesterol content of such diets. Such diets are also low in total fat, which is directly associated with risk of certain cancers, but rich in complex carbohydrates (starches and fiber) and certain vitamins, minerals, trace elements, and nonnutritive constituents, and these factors also confer protection against certain cancers and coronary heart disease.

This statement clearly indicates that NAS did not consider dietary fiber an indispensable component of whole grain necessary for its protective effects. Considerable information that has become available since publication of the *Diet and Health* report supports the premise that protective substances other than dietary fiber are at least partially responsible for its health benefits. This information will be reviewed in detail later in this notification.

The eligibility criteria for the existing health claims specify that foods eligible to bear the claims must contain a minimum of 51% whole grain. The dietary fiber content of whole wheat, the predominant grain in the U.S., was used as a marker of compliance because no analytical method is available to measure whole grains directly. Whole wheat contains 11 grams of dietary fiber per 100 grams; thus, the qualifying amount of dietary fiber required for a food to bear the claim is calculated by the following formula: 11 grams x 51% x RACC/100.

FDA's website authorizations of health claims for whole grain clearly specify that dietary fiber is being used for compliance purposes, and do not suggest that this dietary component is necessary for the health benefits of whole grain. As will be discussed in detail below, USA Rice strongly believes this compliance criterion should not be imposed on whole grain rice to prevent it from qualifying for virtually the same health claim.

III. PROPOSED MODIFICATIONS OF THE EXISTING HEALTH CLAIMS

As noted in the previous section, increased consumption of whole grains is an important public health priority in the U.S.; more education is needed to help consumers identify and understand the benefits of whole grains; brown rice is a whole grain food; and the sole purpose of the minimum dietary fiber criterion for the existing health claims is to allow FDA to easily monitor compliance. USA Rice believes that these observations provide compelling justification to permit whole grain forms of rice to bear the existing claims. We therefore, intend to apply the following modifications to the current health claims for this purpose

A. Eliminate the requirement that whole grain rice contain a minimum of 11 grams of dietary fiber per 100 grams in order to bear the claim.

As noted previously, the minimum dietary fiber requirement for the existing health claims was established solely as a marker for whole grain to help FDA monitor compliance. Therefore, USA Rice intends to eliminate this requirement.

USA Rice believes the elimination of this requirement is warranted because it would allow use of a claim on brown rice which is recommended for increased consumption by U.S. government policy (e.g., DGA. MyPyramid).

The only substantive change USA Rice is making to the existing health claims criteria is removal of the minimum dietary fiber compliance standard. The elimination of this standard is justified by the recognition that the protective effects of whole grains are not contingent on their being a significant source of dietary fiber. This position is well accepted by the nutrition and regulatory communities.

Whole grain foods contain a wide range of potentially cardioprotective and/or anti-cancer phytonutrients in addition to dietary fiber. These components include antioxidants, lignans, phytin, sphingolipids, phytosterols, tocotrienols, unsaturated fatty acids and vitamins and minerals (Slavin, 2003). The antioxidant component of whole grains is composed of water- and fat-soluble antioxidants including vitamins (e.g., tocopherols), minerals (e.g., selenium), phenolic acids, phytic acid, tocotrienols and phyto-ostrogens (Seal, 2006).

The 2005 DGA (U.S. Department of Health and Human Services, U.S. Department of Agriculture, 2005) acknowledged the phytonutrient content of whole grains by referring to “vitamins, minerals, lignans, phytoestrogens, phenolic compounds and phytic acid,” as desirable components of whole grains that are removed during the refining process.

An editorial by Dr. James W. Anderson (Anderson, 2004) recounted the fact that Dr. Hugh Trowell, father of the seminal hypothesis that whole grain consumption protects against CHD, was disappointed that this hypothesis became known as the "fiber hypothesis" because this name ignored the "hundreds of bioactive constituents" in whole grains besides dietary fiber.

Anderson (2004) noted that the relative contribution of the various bioactive substances to the protective effect of whole grains has not been clearly delineated. However multivariate analysis of data from prospective observational studies generally show that whole grains are inversely associated with CHD incidence; and these associations are not greatly affected by adjustments for dietary fiber.

For example, a recent prospective cohort study (Schatzkin *et. al.,* 2007) among 291,988 men and 197,623 women aged 50-71 years found that total dietary fiber intake was not associated with colorectal cancer after adjustment for age, gender, physical activity, smoking, menopausal hormone therapy, red meat intake, dietary calcium and dietary folate (Relative Risk (RR) = 0.99; 95% Confidence Interval (CI), 0.85-1.15)). However, whole grain intake *was* inversely associated with this disease (RR = 0.79; 95% CI, 0.70-0.89).

A review of the biological mechanisms by which whole grains protect against chronic disease (Slavin, 2003) reinforced the notion that the protective effect of whole grains is due to more than dietary fiber,

> Additionally, it is clear that whole-grain consumption is protective beyond what would be predicted if the protection found with these individual compounds [including dietary fiber] was just added up (Slavin *et. al.,* 2001). Thus, there appears to be a synergy among the wide range of protective compounds in whole grains, suggesting that the whole is greater than the sum of the parts.

Furthermore, a letter from the Center for Food Safety and Applied Nutrition to the Grain Foods Foundation dated January 24, 2006[6] contains the statement, "We agree with you that the health benefits of whole grains are based on more than their fiber content." This letter documents the agency's position that the non-dietary fiber components of whole grains contribute to their protective effects.

Finally, a wide range of potentially protective substances have been identified in whole grain forms of rice. Juliano (2003) reported that a whole grain rice sample contained 7.3% protein, 2.2% lipids, 1.4% crude ash and 3.3% dietary fiber (of which 39% was soluble). The majority of bioactive components in rice occur in the bran (i.e., bran plus germ) component (Afinisha *et. al.,* 2007). This component constitutes about six percent of dehulled brown rice (Finocchiaro *et. al.,* 2007) and ranges from 5 - 8% among different varieties (Bergman and Chen 2007).

The potentially protective substances in rice bran occur in the oil component (15-20% by weight) and in the non-lipid faction. The nonsaponifable fraction of rice bran oil contains tocotrienols, tocopherols, phytosterols, gamma-oryzanol compounds, policosanols, and

[6] Letter from Shellee Anderson, Special Assistant, Food Labeling and Standards Staff, Center for Food Safety and Applied Nutrition, to Judi Adams, MS, RD, President, Grain Foods Foundation, dated January 24, 2006. A copy of this letter is provided in Appendix B.
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saponines (Balachandran *et. al.*, 2007). Each of these phytochemical fractions consists of several different compounds. For example, the gamma-oryzanol fraction is composed of ferulic acid esters of triterpene alcohols: the three primary compounds are cycloartenyl ferulate, 24-methylenecycloartanyl ferulate and campesteryl ferulate (Xu and Godber 1999). In total, these investigators reported the gamma-oryzanol fraction to be composed of 10 compounds, while Akhisa et al. (2000) found 12 compounds in this fraction.

The data in Table 1 provide quantitative estimates of the major unsaponifiable constituents found in crude and refined rice bran oil as recently reported by Afinisha Deepam *et. al.* (2007).

Table 1
Unsaponifiable Components (USC) in Crude Rice Bran Oil (CRBO) and Refined Rice Bran Oil (RRBO)

USC	CRBO (mg/g)[a)]	RRBO (mg/g)[b)]
Sterol	11.20 ± 0.19	10.80 ± 0.37
Oryzanol	18.80 ± 0.21	13.80 ± 0.12
Tocols	2.00 ± 0.07	1.40 ± 0.03
Squalene	0.40 ± 0.01	0.48 ± 0.02
Steryl ester	7.20 ± 0.22	7.00 ± 0.30
Wax	13.20 ± 0.24	ND [b)]

a) Mean ± SE, $n = 3$.
b) ND = not detected.

Source: Afinisha Deepam *et. al.* A new method for simultaneous estimation of unsaponifiable constituents of rice bran oil using HPTLC. *J. Sep. Sci.* 30:2786 (2007).

The non-lipid fraction of rice bran also contains many of the polyphenols found in rice bran oil. Devi and Arumughan (2007) reported that defatted rice bran contains 2,204

mg/kg total phenolics, 313 mg/kg oryzanols and 233 mg/kg ferulic acid. Other recent publications that have characterized the phytochemical constituents in whole grain rices and/or rice bran include Adom and Liu (2002), Bergman and Xu (2003), Abdel-Aal *et. al.* (2006), Miller and Engel (2006) and Finocchiaro *et. al.* (2007).

Considerable evidence suggests that many of the phytochemical constituents of rice bran (including rice bran oil) have beneficial effects. For example, Vissers et al. (2000) reported that 2.1 g of rice bran sterols lowered serum total cholesterol (T-C) by 5% and low density lipoprotein cholesterol (LDL-C) by 9% in normolipemic humans. These researchers studied 28 men and 32 women who consumed three types of margarine for three weeks each in a crossover, double-blind study. Concentrates of plant sterols from rice bran oil or triterpene alcohols from sheanut oil were added to make two experimental margarines with the same fatty acid composition as the control margarine. The authors concluded that the effect of rice bran oil sterols was likely due to beta-sitosterol and other 4-desmethylsterols and not to 4,4'-dimethylsterols.

Policosanols are a mixture of primary long-chained alcohols. Sugar cane policosanols (2 to 40 mg per day) have been reported to reduce plasma LDL-C concentrations in several clinical trials of varying duration (Varady *et. al.*, 2003; Chen et. al., 2005). Research designed to evaluate the effect of policosanols from whole grain rice on blood cholesterol concentrations has recently been reported by Reiner et al. (2005). Rice policosanols (10 mg per day) fed to hypercholesterolemic men and women (n = 70) lowered plasma T-C and increased Apo A-I concentrations. This study was a randomized, double-blind,

crossover, placebo-controlled trial. Subjects were placed on a cholesterol-lowering diet for eight weeks prior to being randomly assigned to receive rice policosanol once daily or a placebo for eight weeks.

Recently, a lack of cholesterol-lowering efficacy of sugar cane policosanols was reported from a study with a similar design to those reported above. Thus, some doubt remains as to the association between policosanol consumption and plasma cholesterol reduction. To clarify this situation, future research will need to take into consideration that the specific compounds and amounts of each type in the polycosinal fraction varies both between and within crops and according to the method of extraction. For example, Hwang *et. al.* (2005) reported the policosanol content of two samples of whole grain rice to be 1.9 and 3.7 mg per 100 mg. In the same study, samples of corn contained a mean of 0.2 mg polycosinol per100 mg and whole wheat contained a trace of polycosinol.

Wang *et. al.* (2007) recently reported that sixty Chinese CHD patients aged 45-75 years supplemented with 10 grams per day of black rice pigment fraction for six months experienced enhanced plasma total antioxidant capacity ($p = 0.003$), reduced plasma concentrations of soluble vascular cell adhesion molecue-1 ($p = 0.03$), soluble CD40 ligand ($p = 0.002$) and high sensitive C-reactive protein ($p = 0.002$) compared to a placebo group given a similar amount of white rice pigment fraction. There were no differences between the two groups in plasma total superoxide dismutase activity, lipid concentrations or carotid artery intima-media thickness.

Numerous studies with rodents have reported that the γ-oryzanol fraction from rice bran is able to lower serum cholesterol concentrations in animals fed hypercholesterolemic diets (Cicero and Derosa 2005). The mechanism of action appears to include increased fecal excretion of cholesterol and its metabolites (Wilson *et. al*., 2007). These authors also reported that rice bran ferulic acid showed antiatherogenic properties, but through a different mechanism. The serum cholesterol lowering properties of γ-oryzanol have not been confirmed in humans.

Pure and mixed isoprenoids are known to possess potent anti-cancer activity (Sen *et. al.,* 2007). Whole grain rice contains several different types of isoprenoid compounds. For example, γ-tocotrienol (the tocotrienol that rice has in the largest quantity) has been documented using tissue culture techniques to be the most potent anti-cancer Vitamin E isoform of all the isomers that occur in nature. Numerous studies documenting this observation have shown inhibition of the increase in populations of various breast, prostate and colon cancer cell lines. Work using mice not only supports these results found using cell lines, but when extrapolated to humans indicate that an efficacious dose of tocotrienols could be consumed from the diet (He *et. al.*, 1997).

Other isoprenoids in whole grain rice have been reported to interfere with the colony-forming ability of breast and colon cells (Hudson *et. al*., 2000). Eight phenolic compounds were identified in the extracts studied: protocatechuic acid, p-coumaric acid, caffeic acid, ferulic acid, sinapic acid, vanillic acid, methoxycinnamic acid and tricin. Tricin has received the greatest research attention of these compounds; probably because

it has greater activity in tissue culture experiments at concentrations lower than the other phenolics studied.

Tricin appears to act as a strong inhibitor of cyclooxygenase (COX) enzymes without a marked effect on the COX-2 gene expression in human-derived colon cells and in mice (i.e., ApcMin) that spontaneously develop multiple polyps in the small and large intestine (Cai *et. al*. 2005, Al-Fayez *et. al*. 2006). Elevated synthesis of prostanoids by the enzyme COX-2 has been linked to carcinogenesis, including cell proliferation, apoptosis, angiogenesis, and invasiveness. COX-2 is over-expressed in several malignancies including colon cancer.

A critical early step during tumor metastasis is cell invasion of the basement which allows cells to invade the surrounding tissue. Another isoprenoid fraction from whole grain rice (specifically the anthocyanins cyanidin 3-glucoside and peonidin 3-glucoside) were isolated by Chen *et. al*. (2006). This fraction inhibited the mobility and invasion ability of human hepatocellular carcinoma (SKHep-1) cells. This effect was associated with a reduced expression of several proteinases. In addition, these compounds were fed to mice after subcutaneous inoculation with SKHep-1 cells. Small solid tumors were observed following cell inoculation and a 1.9-fold reduction in tumor volume and a 1.7-fold reduction in tumor weight were reported after feeding the mice the anthocyanin fraction.

In summary, USA Rice believes there is compelling evidence that numerous components in whole grain foods (including rice) contribute to their protective effects, and that dietary fiber has not been shown to be an obligatory component for such benefits. This position is reflected by the fact that whole grain foods (not dietary fiber) were designated as the "substance" of the claims in the current FDAMA notifications – consistent with the authoritative statement. We therefore believe that elimination of the requirement that whole grain foods contain at least 11 grams of dietary fiber per 100 grams is justified as long as compliance can be assessed by other means.

B. **Assessment of compliance**

Assessment of compliance will be obvious because the claim is limited to products that are essentially pure brown rice. The identity of such products can be determined from the product name and its ingredient declaration.

IV. STATUTORY REQUIREMENTS

The information in this section is provided pursuant to section 403(r)(3)(C) of the FFDCA and in accordance with FDA's guidance document, "Guidance for Industry: Notification of a Health Claim or Nutrient Content Claim Based on an Authoritative Statement of a Scientific Body" (June 11, 1998).[7]

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A. **Exact wording of the proposed claim**

USA Rice intends to use the following language for health claims pertaining to whole grain brown rice.

[7] http://www.cfsan.fda.gov/~dms/hclmguid.html

Diets rich in whole grain foods and other plant foods, and low in saturated fat and cholesterol, may help reduce the risk of heart disease and certain cancers.

This statement is a combination of the language provided in FDA's health claim authorization summaries for whole grain foods published in July, 1999 and December, 2003. Wording from the 1999 notification stating that the product bearing the claim is low in total fat is eliminated (pursuant to the 2003 "Whole Grains Foods with Moderate Fat Content" notification) and the phrase, "certain cancers" is retained (pursuant to the 1999 FDAMA notification). The word "may" is used to characterize the relationship between whole grain foods and heart disease and certain cancers so as to indicate that the disease or health-related condition is caused by many factors. The claim is not false or misleading in any particular. Moreover, it is stated in a manner so that the claim is an accurate representation of the authoritative statement referred to and so that the claim enables the public to comprehend the information provided in the claim and to understand the relative significance of such information in the context of a total daily diet.

USA Rice believes this language is appropriate because it reflects the authoritative statement, current public health policy with respect to dietary fat and the totality of scientific evidence regarding the association of whole grains and chronic disease. Specifically, there is consensus in the nutrition and public health communities, as discussed in the 2005 DGA, that moderate fat diets (up to 35% of total energy) are nutritionally appropriate as long as they are low in saturated and *trans* fat. Furthermore, FDA has repeatedly adopted the position that foods need not be low in fat to be eligible

to bear a cardiovascular health claim. Specifically, the agency initially proposed that foods eligible to make the soy-CHD claim be required to be low in fat, but eliminated this requirement because total fat intake is not directly related to CHD, and because the inherent fat content of soybeans would have prevented many products made from whole beans from making the claim (64 FR 57700, 57717, October 26, 1999). In addition, the agency chose not to impose a low-fat criterion on products eligible to make the sterol/stanol ester health claim because fat is the only vehicle capable of delivering these cardioprotective substances, which were deemed to have important public health significance (65 FR 54686, 54708, September 8, 2000). This position was subsequently embraced with respect to qualified health claims for nuts and CHD, walnuts and CHD, monounsaturated fatty acids from olive oil and CHD, unsaturated fatty acids from canola oil and CHD and corn oil and CHD.

USA Rice also believes that language regarding reduced risk of certain cancers, as specified in the 1999 Whole Grains notification, should be retained. Evidence published since this notification has provided additional evidence that whole grain consumption is associated with reduced incidence of certain cancers. This evidence is summarized later in this notification (see page 33).

B. Basis for determining qualification as an authoritative statement.

Section 403(r)(3)(C)(ii) of the FFDCA requires persons submitting FDAMA notifications to provide, "…a concise description of the basis upon which such person relied for determining that the requirements of subclause (i) have been satisfied." This subclause,

in turn, requires that authoritative statements be made by, "…a scientific body of the United States Government with official responsibility for public health protection or research directly related to human nutrition (such as the National Institutes of Health or the Centers for Disease Control and Prevention) or the National Academy of Sciences…". This subclause also requires that authoritative statements be "currently in effect" and be "about a [substance] and a disease or health-related condition to which the claim refers".

USA Rice concludes that use of the authoritative statement cited above in the two previous FDAMA whole grain notifications provides indisputable evidence that this statement is from an appropriate source (i.e., the National Academies) and that it meets the contextual parameters noted. The National Academy of Sciences is a scientific body expressly recognized in FDAMA. The authoritative statement is about the relationship between a substance and a disease or health-related condition, published by the scientific body, currently in effect, and not merely a statement of an employee of the scientific body made in the individual capacity of the employee. Rather, the authoritative statement reflects a consensus within the scientific body and is based on a deliberative review by the scientific body of the relevant scientific evidence.

In addition, we believe that the multiple current public health recommendations advising increased consumption of whole grains as well as a comprehensive review of the recent literature supporting the benefits of whole grain consumption provided below, shows that

the authoritative statement is current. It is therefore concluded that the statutory requirements for an authoritative statement supporting the proposed claim are fulfilled.

C. Copy of the proposed authoritative statement

A copy of the authoritative statement is provided in Appendix A

D. Summary of the recent literature on whole grains and cancer and cardiovascular disease.

Section 403(r)(3)(C)(ii) of the FFDCA also requires persons submitting FDAMA notifications to provide a balanced representation of the scientific literature in the area relating to the proposed claim. Scientific evidence submitted to FDA in the two prior whole grain notifications fulfilled this requirement for cardiovascular disease up to approximately 2003 and for cancer until approximately 1999. Therefore, this section provides a comprehensive review of the subsequently published human observational and intervention studies that are germane to the proposed claim. Animal studies are not included in this review because FDA does not consider them relevant to the evaluation of health claims. Meta-analyses and review papers are included in this section. It is understood that these publications do not contribute original data to the literature, and that they do not provide sufficient evidence for FDA to evaluate the individual studies they discuss. Nevertheless, USA Rice believes these publications place the individual studies in perspective and document the significant scientific agreement that exists among scientific experts that a diet rich in whole grain foods may help reduce the risk of cardiovascular disease and certain cancers.

1. Studies pertaining to cardiovascular disease

The relevant studies pertaining to cardiovascular disease are discussed in chronological order in this section.

a) Observational studies

Mozaffarian *et. al.* (2003) conducted a prospective cohort study among 3,588 men and women 65 years of age or older to assess associations between dietary fiber intake from cereal as well as from fruits and vegetables on risk of CVD during a mean follow-up period of 8.6 years. CVD incidence was inversely associated with intake of cereal fiber (RR = 0.79; 95% CI, 0.62-0.99) after multivariate adjustment for age, gender, education, diabetes, smoking, daily physical activity, exercise intensity, alcohol intake and cereal fruit and fiber intake (total fiber intake not adjusted for the specific fiber types). There were no significant associations between CVD incidence and intake of total fiber or fiber from fruit or vegetables. This study did not report the intake of whole grains *per se*, however fiber from cereals is largely from whole grains and provides indirect support for the conclusion that whole grain intake is inversely associated with CHD. The authors concluded, "Our results suggest that dietary habits may affect cardiovascular risk beyond the earlier development and progression of disease in young adulthood and middle-age, supporting recommendations for increased consumption of dietary fiber from cereal and whole grain sources among older adults."

The Atherosclerosis Risk in Communities (ARIC) Study was conducted among 15,792 adults aged 45-65 years living in the United States (Steffen *et. al.*, 2003). Whole grain

consumption was inversely associated with coronary artery disease (CAD) (RR = 0.72; 95% CI, 0.53-0.97) and all-cause mortality (RR = 0.77; 95% CI, 0.61-0.97) after adjustment for age, race, gender, energy intake, smoking status, pack-years of smoking, physical activity, alcohol intake, hormone replacement in women, BMI, waist-to-hip ratio, systolic blood pressure, use of antihypertensive medications and plasma HDL and LDL concentrations (CAD only). The mean follow-up period was 11 years. The authors concluded, "These study conclusions support the US *Dietary Guidelines for Americans*: 'choose a variety of fruits and vegetables daily' and 'choose a variety of grains daily, especially whole grains.' Our data specifically suggest that whole-grain foods are more healthful than are refined-grain foods."

Jensen *et. al.* (2004) reported data from 42,850 members of the Health Professionals Follow-Up study. The subjects were men (40-75 years of age) who were free of CHD, cancer and diabetes at baseline. Whole grain intake was inversely associated with CHD (RR = 0.82; 95% CI, 0.70-0.96) after adjustment for bran intake, added germ intake, age, energy intake, smoking, alcohol intake, physical activity, family history of myocardial infarction, use of vitamin E supplements and intake of fats (saturated, polyunsaturated and *trans*), fruit, vegetables and fish. This association remained significant after further adjustment for BMI (RR = 0.84; 95% CI, 0.71-0.98). Intake of bran was also inversely associated with CHD incidence in these models. The authors concluded, "The study supports the reported beneficial association of whole-grain intake with CHD and suggests that the bran component of whole grains could be a key factor in this relation."

A cross-sectional analysis of members of the Framingham Offspring Study cohort consisting of 2,834 subjects (mean age = 54 years) was conducted by McKeown *et. al.* (2004). The presence of metabolic syndrome was significantly lower among those in the highest quintile of whole grain intake compared to subjects in the lowest quintile after adjustment for numerous potentially confounding variables (RR = 0.678; 95% CI, 0.48-0.91). Metabolic syndrome was defined as the presence of three or more components related to waist circumference, low serum HDL-C concentration, hypertriglyceridemia, hypertension and fasting glucose concentration. The authors concluded, "Given that the metabolic syndrome is an identifiable and potentially modifiable risk state for both type 2 diabetes and cardiovascular disease, increasing whole-grain cereal fiber may reduce the potential untoward effects of carbohydrate on risk of these diseases. However, more longitudinal studies are required to ascertain which aspects of carbohydrate nutrition are linked to development of the metabolic syndrome milieu."

A prospective study of 229 postmenopausal (mean age ~65 years) women with coronary artery disease was reported by Erkkilä *et. al.* (2005). Whole grain intake of more than six servings per week was associated with smaller decline in minimum coronary artery diameter (-0.1 vs. -0.6 mm, $p<0.04$) compared to lower intakes after a mean follow-up period of 3.2 years. The results were adjusted for age, a wide variety of CVD risk factors and dietary intakes of saturated and polyunsaturated fat, cholesterol and alcohol. The authors concluded, "Higher intakes of cereal fiber and whole-grain products are associated with less progression of coronary atherosclerosis in postmenopausal women with established CAD."

A cross-sectional study of 827 adults (18-74 years) living in Tehran (Esmaillzadeh *et. al.,* 2005) found that whole grain consumption was inversely associated with incidence of the metabolic syndrome (RR = 0.68; 95% CI, 0.60-0.78) after correction for age, energy intake, energy from fat, use of blood pressure medication, use of estrogen, smoking, physical activity and consumption of meats and fish, fruit and vegetables. Metabolic syndrome was defined as three or more abnormal measures of abdominal adiposity, serum HDL-C concentration, serum TG concentration, blood pressure or fasting plasma glucose level. Whole grain consumption was also inversely associated with four of these parameters: abdominal adiposity (RR = 0.90; 95% CI, 0.79-0.96), serum TG concentration (RR = 0.53; 95% CI, 0.42-0.68), elevated blood pressure (RR = 0.79; 95% CI, 0.70-0.85) and abnormal glucose homeostasis (RR = 0.75; 95% CI, 0.63-0.90). The authors concluded that whole grain intake is inversely associated with incidence of the metabolic syndrome and that increased whole grain consumption may reduce this risk.

Jensen *et. al.* (2006) conducted a cross-sectional study on the association of whole grain intake with a variety or cardiovascular risk factors among 938 healthy men and women who were members of the Health Professionals' Follow-Up Study and Nurses' Health Study, respectively and had provided blood samples. Subjects in the upper quintile of whole grain intake had mean T-C concentrations 2.9% lower than subjects in the lowest quintile ($p = 0.02$) after adjustment for age, gender, total energy intake and a wide variety of potentially confounding lifestyle and dietary variables. Serum LDL-C was also lower in the high whole grain group (-2.1%, $p = 0.10$) as were HDL-C concentrations (-5.3%, $p = 0.05$). Whole grain consumption was also inversely associated with markers of

glycemic control in this population. The authors concluded, "The results suggest a lower risk of diabetes and heart disease in persons who consume diets high in whole grains."

A cross-sectional study among 535 healthy residents of the Boston area aged 60-98 years was conducted by Sahyoun *et. al.* (2006). Subjects in the upper quartile of whole grain intake were significantly less likely to have died from CVD than those in the lowest quartile (RR = 0.48; 95% CI, 0.25-0.96). The incidence of metabolic syndrome was also inversely associated with whole grain intake in this population (RR = 0.46; 95% CI, 0.27-0.79). The authors concluded, "Whole-grain intake is a modifiable dietary risk factor, and older and young adults should be encouraged to increase their daily intake to ≥3 servings per day."

A cross-sectional analysis of baseline data from the Multi-Ethnic Study of Atherosclerosis (Lutsey *et. al.*, 2007) among 5,496 men and women free of CHD found no association between whole grain intake and serum lipids, blood pressure or sub-clinical markers of atherosclerosis (i.e., carotid intima-media thickness (IMT), coronary artery calcification) after adjustment for age, gender, race, site and energy intake. Whole grain intake was very low among this population (less than 1% of participants consumed the recommended three servings per day) which may explain the lack of an association. In addition, the authors speculated that the sub-clinical markers of CHD measured may be "too loosely connected to the whole body burden of atherosclerosis to detect this influence". Finally, the cross-sectional nature of this analysis makes it considerably less robust than studies that follow participants prospectively.

Mellen *et. al.* (2007) studied the association between whole grain intake and carotid artery IMT in a prospective study of 1,178 men and women (mean age at baseline = 55.2 years) living in California, Colorado or Texas during a five-year follow-up period. Whole grain intake was inversely associated with common carotid artery (CCA) IMT ($\beta \pm SE$: -0.043 ± 0.013; $p = 0.005$) and internal carotid artery (ICA) IMT ($\beta \pm SE$: $- 0.13 \pm 0.014$; $p = 0.05$) at baseline after adjustment for age, gender, ethnicity and numerous physiological and life-style risk factors. There was also a protective trend for whole grain consumption and progression of CCA IMT ($\beta \pm SE$: -0.019 ± 0.011; $p = 0.09$) but not for progression of ICA IMT ($\beta \pm SE$: $- 0.013 \pm 0.014$; $p = 0.35$) in the fully-adjusted model. The authors concluded, "Whole-grain intake is inversely associated with CCA IMT, and this relation is not attributable to individual risk intermediates, single nutrient constituents, or larger dietary patterns."

Djoussé and Gaziano (2007) studied the association between breakfast cereal consumption and heart failure (as defined by the Framingham criteria of Ho *et. al.* (1993)) among 21,376 participants of the Physicians' Health Study after a mean follow-up period of 19.6 years. Consumption of whole grain breakfast cereals was inversely associated with heart failure (RR = 0.72; 95%; 95% CI, 0.59-0.88) after adjustment for age, smoking, alcohol consumption, vegetable consumption, multivitamin use and history of atrial fibrillation, left ventricular hypertrophy and valvular heart disease. The intake of refined cereals was not associated with heart failure in this population (RR = 0.83; 95% CI, 0.58-1.18). The authors concluded, "Our data demonstrate that a higher intake of whole grain breakfast cereals is associated with a lower risk of heart failure. Additional

studies are warranted to confirm these findings and determine specific nutrients that are responsible for such a protection."

Jacobs *et. al.* (2007) studied the association between whole grain intake and mortality among 41,836 women (age 55-69 years at baseline) in the Iowa Women's Study cohort after an average follow-up period of 17 years. Subjects in the upper quintile of whole grain intake experienced significantly lower incidence of CVD death (0.73; 95% CI, 0.62-0.86), CHD death (RR = 0.72; 95% CI, 0.57-0.90) and total death (RR = 0.79; 95% CI, 0.72-0.87) compared to women in the lowest quintile. The authors speculated that reduction in oxidative stress due to components in whole grains could contribute to the putative protective effects.

b) Intervention studies

No controlled intervention studies published since 2003 were identified that examined the effect of whole grain on CVD using disease incidence as an endpoint.

Several intervention studies that provided various forms of whole grain to human subjects and employed one or more CVD-related biomarkers as endpoints were published since this time, however these studies were not designed to examine the effect of whole grain *per se* and conclusions that can be drawn from them are limited. Nevertheless, the majority of these studies provide indirect support for the premise that whole grains have beneficial effects on CVD biomarkers. These studies will not be discussed in detail, but are enumerated below.

- Keenan *et. al.* (2002) showed that a whole oat cereal (exact identity not provided) reduced serum T-C, LDL-C and blood pressure among 18 healthy men and women with borderline hypertension living in Minnesota.
- Pins *et. al.* (2002) reported that whole grain oat-based cereal reduced the need for antihypertensive medication among 88 U.S. men and women with hypertension.
- Li *et. al.* (2003) reported that a diet containing 30% whole grain barley decreased plasma T-C, LDL-C and TG concentrations (but not that of HDL-C) among 10 young subjects living in Japan.
- Behall *et. al.* (2006) found that whole grain diets from a combination of wheat and rice or wheat, rice and barley lowered systolic blood pressure among 25 mildly hypercholesterolemic men and women living in Maryland.
- Andersson *et. al.* (2007) reported that a diet rich in whole grain (primarily from wheat) did not affect serum lipids or blood pressure compared to a similar diet with refined grains among 30 healthy, moderately overweight Swedish subjects.

2. **Studies pertaining to cancer**

a) Observational studies

Jain *et. al.* (1999) conducted a retrospective case-control study among 617 prostate cancer patients and 636 population-based controls living in Canada. The controls were matched on the basis of age, body weight and daily energy intake. Whole grain intake from breads and cereals was not associated with prostate cancer (upper vs. lower quintile) after multivariate adjustment for age, energy intake, vasectomy, smoking, marital status, study area, BMI, education, multivitamin use and a variety of dietary factors (RR = 1.13;

95% CI, 0.82-1.56). However, whole grain from breakfast cereals was positively associated with prostate cancer in this study (RR = 1.41; 95% CI, 1.05-1.88) while the intake of total grains was not (RR = 0.83; 95% CI, 0.61-1.14). The intake of total fruit, citrus fruit and fruit other than citrus was also positively associated with prostate cancer. The authors noted the possibility that confounding factors affected the intake of whole grains in this population.

A case-control study among colon cancer (n=119) and rectal cancer (n=104) patients and 491 age and gender matched, hospital-based controls was reported by Levi *et. al.* (1999). Whole grain was inversely associated with colorectal cancer (upper vs. lower tertile) among this population (RR = 0.54; 95% CI, 0.34-0.85) after adjustment for age, gender, education, smoking, alcohol intake, BMI, physical activity and total energy intake. An increase of one serving of whole grains per day was associated with reduced risk of colorectal cancer (RR = 0.85; 95% CI, 0.75-0.97). The authors concluded that the data support recommendations to substitute whole grains for refined grains in the diet.

Levi *et. al.* (2000) studied 156 subjects with cancer of the oral cavity and pharynx, 101 patients with oesophageal cancer and 40 subjects with cancer of the larynx compared to 349 hospital-based controls. Subjects who consumed whole grains more than 10 times per week had significantly lower incidence of oesophageal cancer (RR = 0.30; 95% CI, 0.1-0.6) than subjects with no or rare consumption. Non-significant inverse associations were seen for cancer of the oral cavity and pharynx (RR = 0.6; 95% CI, 0.30-1.2) and total cancer incidence (RR = 0.50; 95% CI, 0.3-1.0). The results were adjusted for age,

gender, education, smoking, fruit and vegetable intake, alcohol intake and total daily energy intake. The authors concluded that whole grain intake is favorably associated with the risk of upper aerodigestive and respiratory tract neoplasms.

Kasum *et. al.* (2001) studied the association between whole grain intake and endometrial cancer among 23,014 members of the Iowa Women's Study cohort among users and never-users of hormone replacement therapy (HRT). The incidence of cancer decreased significantly (p for trend = 0.05) from the lowest to the highest quintile of whole grain consumption among never-users of HRT: RR = 1.0, 0.77, 0.70, 0.66, 0.63 (95% CI, 0.39-1.01), respectively after adjustment for age, energy intake, education, BMI, smoking, vitamin use, fruit and vegetable intake, red meat intake, refined grain intake, total- and saturated fat intake, age at menarche, age at menopause and number of live births. The mean follow-up period was 13 years. No such association was observed for women who had used HRT. The authors concluded, "Whole grain intake may protect against endometrial cancer among never-users of hormone replacement therapy."

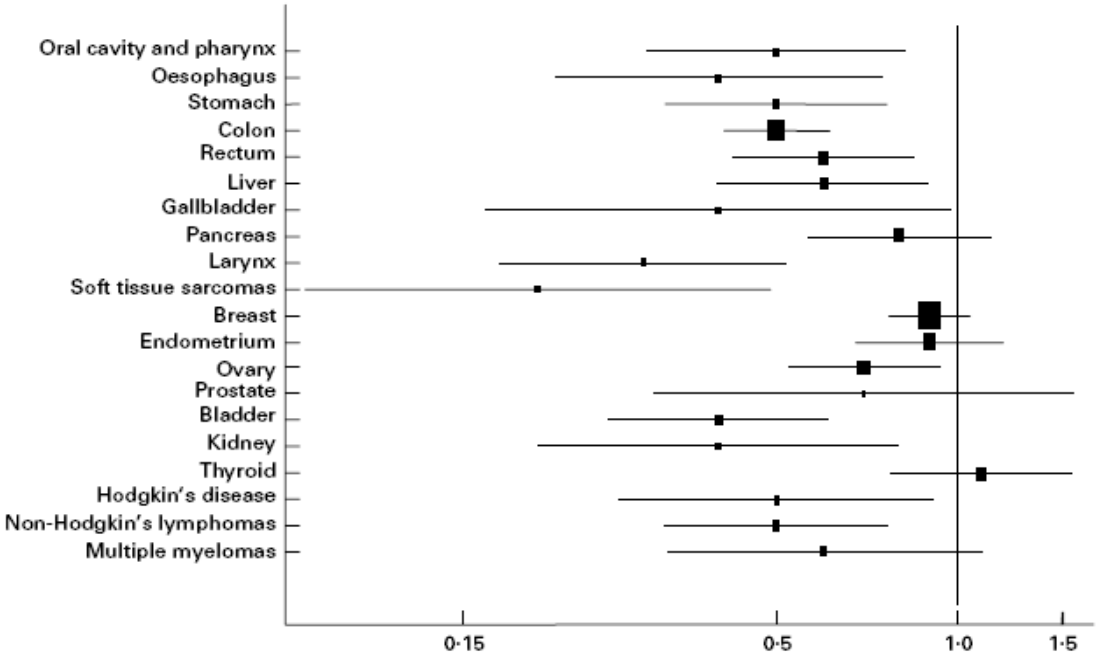
La Vecchia *et. al.* (2003) have published results from a series of case-control studies among cancer and CVD patients in Italy[8]. The studies included the following incident histologically-confirmed neoplasms: oral cavity and pharynx (n = 524), oesophagus (n = 410), stomach (n = 745), colon (n = 955), rectum (n = 625), liver (n = 435), gallbladder (n = 65), pancreas (n = 402), larynx (n = 388), soft tissue sarcomas (n = 217), breast (n = 3,412), edometrium (n = 750), ovary (n = 971), prostate (n = 127), bladder (n = 431),

[8] Data from this series of studies has been published elsewhere: LaVecchia *et. al.,* (2001); La Vecchia (2004).

kidney (n = 190), thyroid (n = 428), Hodgkin's disease (n = 201), non-Hodgkin's lymphomas (n = 529) and multiple myelomas (n = 185). The study also included 10,058 hospital-based controls. The data presented in Figure 1 show that whole grain consumption was associated with significantly lower incidence of the following cancers: oral cavity and pharynx, oesophagus, stomach, colon-rectum, liver, larynx, soft tissue sarcomas, ovary, bladder, kidney, Hodgkin's disease and non-Hodgkin's lymphomas. The data were adjusted for age, gender (when required) residence, education, smoking and alcohol intake. The authors concluded, "In this population whole-grain food consumption is an indicator of reduced risk of several neoplasms."

Figure 1

Odds ratios for high score of intake of whole-grain foods in data from case-control studies in Milan, Italy 1983-97.



Points are odds ratios with 95% confidence intervals represented by horizontal bars.
Source: La Vecchia *et. al.,* (2003)

A prospective, case-control study among 439 female and 910 male stomach cancer victims from the 1.2 million member Cancer Prevention Study (CPS) II cohort was reported by McCullough *et. al.* (2001). Whole grain consumption was inversely associated (upper vs. lower tertile) with stomach cancer mortality in men (RR = 0.77; 95% CI, 0.66-0.90) after adjustment for age, but not after further adjustment for education, smoking, BMI, multivitamin- and vitamin C use, aspirin use, race and family history (RR = 0.90; 95% CI, 0.77-1.06). The mean follow-up period was 14 years. No such associations were seen among women. The consumption of "plant foods" (a sum of vegetables, citrus fruit and whole grains) was also inversely associated with stomach cancer death in men (RR = 0.79; 95% CI, 0.67-0.93) after adjustment for potentially confounding variables, but not among women. The authors concluded that a diet pattern high in vegetables, citrus fruit and whole grains is associated with a modestly lower risk of stomach cancer in men.

Nicodemus *et. al.* (2001) studied the association between grain intake and breast cancer incidence in a prospective case-control study among the Iowa Women's Health Study cohort during a mean follow-up period of nine years. There were 977 breast cancer cases diagnosed during the follow-up period from a cohort of 27,588 women who met the inclusion criteria. There was a significant (p=0.03) trend for a *positive* association between whole grain intake and incidence of breast cancer among women who had received a screening mammography prior to baseline, however none of the RRs between the lowest and other quintiles were significant at the 95% significance level. The greatest

RR occurred between the first and fourth quintile (RR = 1.24; 95% CI, 0.95-1.6). These results were adjusted for age, energy intake, estrogen use, personal history of benign breast disease, family history of breast cancer, mammography status, age at first live birth, number of live births, current weight, waist-to-hip ratio, vitamin use, education, vitamin A and refined grain intake. There were no such associations among women who had never had a screening mammography (RR first vs. fifth quintile = 1.11; 95% CI, 0.74-1.7; p-for trend = 0.62). The authors noted that habitual whole grain consumers had a healthier lifestyle, including higher likelihood of prior screening mammography, and concluded, "…the apparent increase in risk was therefore likely due to increased use of screening mammography."

Kasum *et. al.* (2002) used the Iowa Women's Study cohort to examine the association between dietary factors and incidence of aerodigestive tract cancers during a 14-year follow-up period. There were 169 cases of upper aerodigestive tract cancers diagnosed during the follow-up period among 34,651 members of the initial cohort of postmenopausal, cancer-free women. Whole grain consumption was inversely associated with incidence of these cancers between the lowest and highest tertiles (RR = 0.53; 95% CI, 0.34-0.81). Fiber intake from whole grains was also inversely associated with cancer incidence (RR = 0.56; 95% CI, 0.37-0.84). The authors concluded, "These findings confirm previous observations that high intake of fruits and vegetables and that intake of whole grains and the fiber derived from them may reduce risk of upper aerodigestive tract cancers."

A case-control study among 310 breast cancer victims and 353 age-matched, hospital-based controls living in Heidelberg, Germany was reported by Adzersen *et. al.* (2003). Whole grain consumption was inversely associated with breast cancer (RR = 0.57; 95% CI, 0.34-0.95) after adjustment for age, energy intake, age at menarche, age at first birth, age at menopause, family history of breast cancer, smoking, personal history of benign breast disease, BMI, alcohol intake, current HRT and HRT during the past year. The authors concluded, "…our study suggests that although numerous single micronutrients and dietary components of plant foods may be related to risk, directly or as surrogate indicators, high raw vegetable and high whole-grain consumption may contribute to risk reduction."

Slattery *et. al.* (2004) studied data from 952 cases of rectal cancer and 1,205 population-based controls living in Utah or enrolled in the Kaiser Permanente Medical Care Program in northern California. Whole grain intake (lowest vs. highest quintile) was inversely associated with rectal cancer (RR = 0.69; 95% CI, 0.51-0.94) among all subjects after adjustment for age, BMI, physical activity, smoking calcium intake and energy intake. This association was also significant among men (RR = 0.67; 95% CI, 0.46-0.98), but not among women (RR = 0.74; 95% CI, 0.43-1.27). The authors concluded, "The results suggest that plant foods may be important in the etiology of rectal cancer in both men and women."

Fung *et. al.* (2005) studied the association of a prudent dietary pattern (i.e., high in fruits, vegetables, whole grains, low-fat dairy products, fish and poultry) with postmenopausal

breast cancer incidence among 3,026 cases from the Nurses' Health Study cohort during a 16-year follow-up period. This dietary pattern was not associated with total postmenopausal breast cancer incidence, however such a pattern was inversely associated with estrogen receptor-negative cancer (RR = 0.62; 95% CI, 0.45-0.88) after adjustment for numerous potentially confounding variables. Whole grain intake *per se* was not associated with estrogen receptor-negative breast cancer incidence (RR = 1.04; 95% CI, 0.63-1.69). The RR for this disease of one additional serving of whole grains was 0.99 (95% CI, 0.91-1.17). The authors observed, "…a prudent diet may protect against estrogen receptive-negative tumors."

Larsson *et. al.* (2005) studied the association between whole grain intake and colorectal cancer among 61,433 members of the Swedish Mammography Cohort during a follow-up period of 14.8 years. There were 805 incident cases diagnosed during this period. Whole grain consumption was inversely associated with colon cancer (lowest vs. upper quintile) (RR = 0.67; 95% CI, 0.47-0.96) after adjustment for age, BMI, education, energy intake as well as intake of saturated fat, calcium, red meat, fruits and vegetables. There was no significant association between whole grain intake and rectal cancer. The authors concluded, "Our findings suggest that high consumption of whole grains may decrease the risk of colon cancer in women."

Murtaugh *et. al.* (2006) studied the association of vitamin D receptor (VDR) gene polymorphisms and dietary factors on colorectal cancer in a case-control study of 1,698 cases and 1,861 controls for colon cancer and 752 cases and 960 controls for rectal

cancer. The subjects were residents of northern California, Utah and Minneapolis-St. Paul, Minnesota. Whole grain intake was significantly higher among healthy controls for both colon cancer ($p=0.01$) and rectal cancer ($p<0.01$) in this population. There were no significant interactions between whole grain consumption and the VDR genotype with respect to colon cancer risk.

A retrospective case-control study among 1,723 Canadian colon cancer patients and 3,097 population-based controls was reported by Hu *et. al.* (2007). Controls were matched to cases on the basis of age and gender. Whole grain consumption was not associated with proximal or distal colon cancer among women or men in this study after adjustment for age, geographic location, BMI, physical activity and total energy intake. The study reported significant associations between colon cancer and intake of red meat and dairy products among men and between total meat and processed meat among women. Data on the potential association of whole grains after correction for these dietary constituents was not reported.

A case-control study among 532 pancreatic cancer patients and 1,701 age- and gender-matched community-based controls reported protective trends between whole grain and brown rice consumption (Chan *et. al.*, 2007). Persons who consumed ≥2 servings of whole grains per day had a lower risk of pancreatic cancer than persons who consumed <1 serving per day (RR = 0.60; 95% CI, 0.31-1.2; p for trend = 0.04) after correcting for age, gender, total energy intake and numerous physiological and life-style risk factors. Analogous data for brown rice were RR = 0.72; 95% CI, 0.44-1.2; p for trend = 0.02.

The authors concluded that these data provide some evidence that consuming more whole-grain or high-fiber products may reduce the risk of pancreatic cancer.

Schatzkin *et. al.* (2007) studied the association between whole grain consumption and colorectal cancer among 197,623 female and 291,988 male members of the National Institutes of Health – AARP cohort during a five year follow-up period. There were 2,974 incident colorectal cancer cases diagnosed during this period. Whole grain consumption was inversely associated with colorectal cancer (RR = 0.79; 95% CI, 0.70-0.89) for the entire population after adjustment for age, gender, physical activity, smoking, menopausal hormone therapy, intake of red meat, dietary calcium, dietary folate and total energy. Dietary fiber from grains was also associated with reduced risk of colorectal cancer (RR = 0.86; 95% CI, 0.76-0.98) but total dietary fiber was not (RR = 0.99; 95% CI, 0.85-1.15). The authors concluded, "In this large prospective cohort study, total dietary fiber intake was not associated with colorectal cancer risk, whereas whole-grain consumption was associated with a modest reduced risk."

b) Intervention studies

No controlled intervention studies published since 1999 were identified that examined the effect of whole grain on cancer using disease incidence or validated cancer biomarkers as endpoints.

3. Review papers

The first major review paper on the potential benefits of whole grains and chronic disease was published by Thompson (1994). This paper concluded that whole grain intake has been associated with protective effects against hormone-related diseases such as cancer of the breast and prostate as well as coronary heart disease. It was also concluded that lignans, phytoestrogens, antioxidants and other compounds in whole grain foods, in addition to dietary fiber, may be responsible for its beneficial effects.

Numerous literature reviews on the relationship between whole grains and chronic diseases have been published since the Thompson paper. The conclusions from reviews on cancer and cardiovascular disease published since 1999 that were identified are provided below.

Kushi *et. al.* (1999) concluded, "Overall, there is substantial epidemiologic evidence that dietary fiber and whole grains are associated with decreased risk of coronary artery disease and some cancers, whereas the role of legumes in these diseases appears promising but as yet inconclusive."

A review on mechanisms of the protective effects of whole grains (Slavin *et. al.,* 1999) noted, "Clearly, the range of protective substances in whole grains is impressive and advice to consume additional whole grains is justified. Further study is needed regarding the mechanisms behind this protection so that the most potent protective components of

whole grains will be maintained when developing whole grains into acceptable food products for the public."

A subsequent review by Slavin *et. al.* (2001) concluded, "Whole-grain foods are valuable sources of nutrients that are lacking in the American diet, including dietary fiber, B vitamins, vitamin E, selenium, zinc, copper and magnesium. Whole-grain foods also contain phytochemicals, such as phenolic compounds, that together with vitamins and minerals play important roles in disease prevention."

Hallmans *et. al.* (2003) published a review paper entitled, "Rye, lignans and health." This review paper was the only publication identified that provided a null conclusion regarding whole grains and cancer – possibly because of the narrow focus of the publication. The paper stated, "At present, evidence from studies in human subjects does not warrant the conclusion that rye, whole grains or phyto-oestrogens protect against cancer. Some studies, however, have pointed in that direction, especially in relation to cancers of the upper digestive tract. A number of prospective epidemiological studies have clearly shown a protective effect of whole grain cereals against myocardial infarctions."

Hu (2003) concluded, "In conclusion, substantial evidence indicates that plant-based diets including whole grains as the main form of carbohydrate, unsaturated fats as the predominate form of dietary fat, an abundance of fruits and vegetables, and adequate n-3 fatty acids can play an important role in preventing CVD. Such diets – which have other

health benefits, including the prevention of other chronic diseases – deserve more emphasis in dietary recommendations."

Pereira and Liu (2003) concluded, "Similar to findings for fruits and vegetables, whole grain intake has been found to be consistently associated with a reduction in risk of coronary heart disease (CHD)."

A review paper by Slavin (2003) concluded, "Whole grains are rich in many components, including dietary fiber, starch, fat, antioxidant nutrients, minerals, vitamins, lignans and phenolic compounds that have been linked to reduced risk of CHD, cancer, diabetes, obesity and other chronic diseases. Most of the components are found in the germ and bran, which are reduced in the gain-refining process. The most potent protective components of whole grains need identification so that efforts can be directed to minimizing the losses of physiologically-important constituents of grains during processing. There is also a need to educate the public to increase their intake of whole grains to the recommended levels."

Anderson (2004) stated, "Nevertheless, the take-home message is that consumption of generous amounts of whole grains, cereal fiber, total fiber, fruit, or vegetables decreases the risk of CHD by ≥30%, irrespective of other lifestyle behaviors. These observations encourage us to recommend that ≥3 servings of whole grains be consumed daily."

A review on dietary determinants of epithelial ovarian cancer (EOC) (Schulz *et. al.,* 2004) concluded, "We identified 7 cohort studies and 27 case-control studies of consumption of major food groups (fruits and vegetables, meats, eggs, fish, dairy products, grains, fats and oils) and EOC risk…A protective effect on risk of EOC for whole-grain food consumption as well as for consumption of low-fat milk is suggested by the results of the studies."

Slavin (2004) stated, "Based on epidemiological studies and biologically plausible mechanisms, the scientific evidence shows that the regular consumption of wholegrain foods provides health benefits in terms of reduced rates of CHD and several forms of cancer."

Seal (2006) concluded, "There is an increasing body of evidence, including that from prospective population studies and epidemiological observational studies, suggesting a strong inverse relationship between increased consumption of wholegrain foods and reduced risk of CVD…Well-controlled intervention studies are needed to provide more detailed mechanistic evidence to support the health claims and findings which can be used to develop effective public health strategies to promote whole-grain consumption."

E. Conclusions from the summary of recent literature on whole grains and cancer and cardiovascular disease

The totality of scientific literature published since authorization of the existing whole grain health claims in 1999 and 2003 clearly shows that the authoritative statement

underpinning these claims remains valid and that a plethora of constituents in whole grains in addition to dietary fiber are likely responsible for its protective properties.

All of the studies identified that examined the association between incidence of CVD and whole grain intake provided direct or suggestive evidence of an inverse association. The strongest evidence was provided by four prospective cohort studies (Steffen *et. al.,* 2003; Jensen *et. al.,* 2004; Djoussé and Graziano, 2007; Jacobs *et. al.,* 2007) that reported significant, inverse associations between whole grain intake and CVD incidence after correction for potentially confounding variables. A fourth prospective cohort study (Mozaffarian *et. al.,* 2003) provided suggestive evidence of such an association but measured cereal fiber intake rather than that of whole grain intake *per se.* A cross-sectional study that used CVD incidence as an endpoint also provided direct evidence of a protective association for whole grains (Sahyoun *et. al.,* 2006). Five additional studies that measured metabolic syndrome (McKeown *et. al.,* 2004; Esmaillzadeh *et. al.,* 2005), atherosclerotic plaque (Erkkilä *et. al.,* 2005), carotid IMT (Mellen *et. al.*, 2007) or serum lipids (Jensen *et. al.,* 2006) also provided direct evidence of protective associations between whole grain intake and CVD. One study (Lutsey *et. al.*, 2007) found no association between carotid IMT and whole grain consumption, but the conclusions that can be drawn from this cross-sectional study are limited.

No randomized, controlled dietary intervention studies were identified that examined the effect of whole grain intake on CVD morbidity or mortality in healthy humans. However five such studies (Keenan *et. al.,* 2002; Pins *et. al.,* 2002; Li *et. al.,* 2003; Behall *et. al.,*

2006; Wang *et. al.*, 2007) showed that whole grain-containing diets significantly reduced serum lipids and/or blood pressure while only one experiment (Andersson *et. al.,* 2007) found no such effect. These studies provide suggestive evidence that whole grains reduce the risk of CVD, but are not conclusive with respect to the proposed claim because they were not designed to examine the effect of whole grain intake *per se*.

The majority of the recent scientific evidence also shows that whole grains may reduce the risk of certain cancers in healthy humans. The evidence is strongest for colorectal cancer where two prospective studies (Larsson *et. al.,* 2005; Schatzkin *et. al.,* 2007) and four case-control studies (Levi *et. al.,* 1998; Slattery *et. al.,* Murtaugh *et. al.,* 2006; Hu *et. al.,* 2006) reported direct or suggestive evidence of a protective effect. The recent evidence for breast cancer is less persuasive. A case-control study found a protective association between whole grain intake and breast cancer incidence (Adzersen *et. al.,* 2003). However one prospective study (Fung *et. al.,* 2005) found no such association (although a prudent dietary pattern including whole grains was inversely associated with estrogen receptor-negative cancer) and another prospective study (Nicodemus *et. al.,* 2001) found a *positive* association (although this result appeared to be due to increased detection with mammography among high whole grain consumers). The recent literature also does not provide compelling evidence of a protective association between whole grain intake and prostate cancer (Jain *et. al.,* 1999) or stomach cancer (McCullough *et. al.,* 2001); however there is direct or supportive evidence for aerodigestive cancers (Levi *et. al.,* 2000; Kasum *et. al.,* 2002), endometrial cancer (Kasum *et. al.,* 2001) and pancreatic cancer (Chan *et. al.*, 2007).

No controlled intervention studies with cancer or a commonly accepted biomarker of this disease were identified.

In conclusion, the recent evidence provides strong, consistent support for a protective association between whole grain consumption and CVD. The evidence for such an association with cancer is less consistent, however the bulk of the evidence provides direct or suggestive evidence; especially for cancers of the digestive tract. These conclusions are expressed eloquently in ten of the eleven review papers cited above (Thompson, 1994; Kushi *et. al.,* 1999; Slavin *et. al.,* 1999, 2001; Hallmans *et. al.,* 2003; Hu, 2003; Pereira and Liu, 2003; Slavin, 2003; Anderson, 2004; Schulz *et. al.,* 2004; Seal, 2006). USA Rice, therefore, strongly believes the scientific literature published since the existing FDAMA notifications continues to support the authoritative statement that underlies these claims.

V. SUMMARY AND CONCLUSIONS

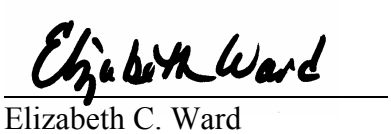
USA Rice strongly believes that expanding the existing whole grain health claims to include whole grain brown rice is in the best interest of all stakeholders. Brown rice meets the definition of whole grain broadly accepted by the professional community – including FDA. Increased consumption of whole grain is a current public health priority as evidenced by the 2005 DGA, MyPyramid and other public health policy. Whole grain forms of rice contain a wide variety of bioactive constituents that are thought to contribute to their beneficial properties, and the authoritative statement upon which the current health claims are based does not specify dietary fiber as an obligatory component

for the efficacy of whole grains. In other words, there is no reason to exclude whole grain forms of rice from making a health claim based on the authoritative statement. On the other hand, whole grain consumption in the U.S. continues to be well below recommended amounts and many consumers have difficulty identifying such foods in the grocery store. Availability of the health claim for brown rice will encourage increased consumption by helping consumers identify this nutritious food and by explaining its beneficial effects.

In conclusion, USA Rice believes use of the existing whole grain health claims on brown rice is justified from a scientific and regulatory perspective and has the potential to contribute to U.S. nutritional objectives and improve public health. We sincerely appreciate the agency's consideration in this matter and look forward to using the proposed claim after 120 days.

Respectfully submitted,

USA RICE FEDERATION

By 

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