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2012 MAR 12 P 1:56

Food and Drug Administration
Office of Nutrition, Labeling and Dietary Supplements
HFS-800
5100 Paint Branch Parkway
College Park, MD 20740

To Whom It May Concern:

On behalf of the ConAgra Foods Inc. we are submitting the enclosed health claim petition pursuant to section 403 (r)(4) of the Federal Food, Drug, and Cosmetic Act with the respect to whole grain consumption and the reduced risk of Type II diabetes. We request this petition be reviewed as a qualified health claim, and waive review under the Significant Scientific Agreement standard. An original and one copy of the petition are enclosed, as well as, duplicate sets of the references cited.

If you have any questions, please feel free to contact me. Thank you for your consideration of this matter.

Sincerely,

Mark Benson Andon

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FDA-2012-Q-0242

QHC

PETITION FOR HEALTH CLAIM

WHOLE GRAIN CONSUMPTION

AND

REDUCED RISK OF DIABETES MELLITUS TYPE 2

SUBMITTED TO THE

FOOD AND DRUG ADMINISTRATION

January 25, 2012

PETITIONER:

CONAGRA FOODS INC.

Whole Grains and Diabetes Health Claim Petition

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I. INTRODUCTION

A. Overview of Petition

Pursuant to section 403(r)(4) of the Federal Food, Drug and Cosmetic Act (FFDCA) ConAgra Foods believes that there is ample scientific evidence for the authorization of a health claim about the relationship between whole grain consumption and a reduced risk of diabetes mellitus type 2 (DMT2). Therefore, this petition requests that the Food and Drug Administration (FDA) authorize a qualified health claim based on the scientific evidence about the relationship between the consumption of whole grains and the reduced risk of DMT2 on the label or in the labeling of whole grains and certain whole grain-containing products. We request this petition be reviewed as a qualified health claim, and waive review under the significant scientific agreement standard.

B. Background

The FDA has been moving forward to reach stated public health objectives with relation to food and nutrient consumption. Authorization of health claims is one way FDA can contribute to public health goals. Epidemiological and clinical trial evidence clearly identifies a metabolic health benefit associated with whole grain consumption. The following examples of existing health claims set the current backdrop for whole grains consumption and reduced risk of chronic disease:

Two **FDA Modernization Act of 1997 (FDAMA) Claims** are examples of whole grains and their health benefits:

1. Whole Grain Foods and Reduced Risk of Coronary Heart Disease and Certain Cancers

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

2. Whole Grain Foods with Moderate Fat Content and Reduced Risk of Coronary Heart

Disease and Certain Cancers

The Claim: *"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."*

To qualify for these FDAMA claims, the foods must contain a minimum of 51% whole grains (using dietary fiber as a marker) among other qualifications. While whole grains were included in the specified FDAMA health claims mentioned above, this petition asks FDA to consider the relationship of whole grains and the reduced risk of DMT2. We believe there is consistent scientific evidence to suggest an inverse relationship of whole grain consumption and the incidence of DMT2.

II. PRELIMINARY REQUIREMENTS

A. Diabetes mellitus type 2 is a disease for which the U. S. population is at risk, meeting requirements of 21 CFR 101.14(b)(i).

DMT2 has reached epidemic proportions in the United States and more recently worldwide. The morbidity and mortality associated with diabetes is anticipated to account for a substantial proportion of health care expenditures (FDA, 2008). From 1980 through 2007, the number of Americans with diabetes tripled from 5.6 million to 17.4 million (CDC, 2009). We conclude that DMT2 meets the requirements of 21 CFR 101.14(b)(i) to be a disease which affects public health.

B. Whole grains are foods that provides nutritive value and complies with the requirements of [21 CFR 101.14(b)(3)(i)]

Whole grains are a food that provides nutritive value and complies with the requirements of 21 CFR 101.14(b)(3)(i). A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance is defined as a specific food or component of food (21 CFR 101.14(a)(2)). In the preamble to the final rule on general principles for health claims, FDA stated that a phrase such as "eat apples to..." would constitute a reference to a substance and would satisfy the first element of a health claim. Whole grains are a particular food and the substance in the petition. For the purpose of the petition, whole grains are defined as in 2006, where FDA issued the *Whole Grain Label Statements* to "provide guidance to the industry about what FDA considers to be whole grains and to assist manufacturers in labeling their products" (U.S. Food and Drug Administration, 2006). In that document FDA specified that, "*whole grains 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*". Within the following discussion of the science of whole grains and DMT2, an expanded definition of whole grain foods is indicated when a food or treatment with whole grains included additional bran and/or germ.

1. Whole Grains Composition

A whole grain is the fruit (also known as the seed, caryopsis, or kernel) of plants belonging to the *Poaceae* (or *Gramineae*) family also known as grasses. Some examples of whole grains are wheat, rice, barley, corn, rye, oats, millets, sorghum, teff, triticale, canary seed, Job's tears, fonio, and wild rice. The seed is composed of three parts: 1) the endosperm which comprises approximately 80-90% of the grain, 2) the bran which is the outer layers of the whole grain, and 3) the germ or embryo that is located at the base of the grain. Although all grains contain the three anatomical parts, there is variability among the various whole grains in their content of macronutrients, micronutrients and bioactive components, including components thought to have a role in disease prevention, such as, fiber, folate, phenolic compounds, lignan, and sterols. For example, the total fiber content of bulgur and barley is approximately 5-fold higher than that of brown rice. Rye contains the highest amount of lignan and sterols (other than phenolic acids and phenolic lipids) compared to wheat, oats, and barley. Furthermore, some nutrients are absent in some grains, but present in high amounts in other grains as in the case of vitamin A, β-carotene, lutein and zeaxanthin that are present in high levels in corn but absent in brown rice, oats, and sorghum. The nutritive values of whole grains are shown in Table 1.

Table I. Nutrient Content (*per* 100g) of a Variety of Grains[1,2]

Nutrient	Barley (hulled)	Brown Rice	Bulgur	Corn (yellow)	Oats	Rye	Sorghum	Wheat	Wild Rice
Proximate analyses									
Energy, Kcal	354	362	342	365	389	335	339	327	357
Protein, g	12.5	7.5	12.3	9.4	16.9	14.8	11.3	12.6	14.7
Total lipid, g	2.3	2.7	1.3	4.7	6.9	2.5	3.3	1.5	1.1
Carbohydrate[5], g	73.5	76.2	75.9	74.3	66.3	69.8	74.6	71.2	74.9
Fiber, total dietary, g	17.3	3.4	18.3	7.3	10.6	14.6	6.3	12.2	6.2
Minerals									
Calcium, mg	33	33	35	7	54	33	28	29	21
Iron, mg	3.6	1.8	2.5	2.7	4.7	2.67	4.4	3.2	2.0
Magnesium, mg	133	143	164	127	177	121	-	126	177
Phosphorus, mg	264	264	300	210	523	374	287	288	433
Potassium, mg	452	268	410	287	429	264	350	363	427
Sodium, mg	12	4	17	35	2	6	6	2	7
Zinc, mg	2.8	2.0	1.9	2.2	4.0	3.7	-	2.6	6.0
Copper, mg	0.50	0.28	0.34	0.31	0.63	0.45	-	0.43	0.52
Manganese, mg	1.9	3.7	3.05	0.48	4.92	2.68	-	3.98	1.33
Selenium, µg	37.7	-	2.3	15.5	-	35.3	-	70.7	2.8
Vitamins[3]									
Thiamin, mg	0.65	0.41	0.23	0.38	0.76	0.32	0.24	0.38	0.12
Riboflavin, mg	0.28	0.04	0.12	0.20	0.14	0.25	0.14	0.12	0.26
Niacin, mg	4.60	4.3	5.1	3.6	1.0	4.3	2.9	5.5	6.7
Pantothenic acid, mg	0.28	1.50	1.04	0.42	1.35	1.46	-	0.95	1.07
Vitamin B6, mg	0.32	0.51	0.34	0.62	0.12	0.29	-	0.30	0.39
Folate, µg	19	20	27	19	56	60	-	38	95
Choline, total, mg	-	-	28.1	-	-	30.4	-	31.2	35.0
Vitamin A, IU	22	0	9	214	0	11	0	9	19
Vitamin E [4], mg	0.57	-	0.06	0.49	-	1.3	-	1.01	0.82
Vitamin K, µg	2.2	-	1.9	0.3	-	5.9	-	1.9	1.9
Other									
Beta-carotene, µg	13	-	5	97	-	7	-	5	11
Lutein + Zeaxanthin, µg	160	-	220	1355	-	210	-	220	220

Data source: USDA National Nutrient Database for Standard Reference, Release 20 (U.S. Department of Agriculture, 2008).

[1]Nutrient values and weights are for edible portion.

[2]Scientific names and specifications of grains (top row, from left to right): Barley hulled (*Hordeum vulgare L.*), Rice (*Oryza sativa L.*), brown and medium-grain raw; Bulgur (*Triticum*) dry; Corn, yellow (*Zea mays L.*); Oats (*Avena sativa L.*); Rye (*Secale cereale L.*); Sorghum (*Sorghum spp.*); Wheat (*Triticum aestivum L.*), hard red winter; Wild rice, raw (*Zizani spp.*).

[3]The values for vitamin C and vitamin B_{12} for all the grains listed above were (0.0 mg/100 g).

[4]Vitamin E values are for α-tocopherol. Dash (-) represents the nutrients not listed in the USDA database for the respective grains.

[5]The sum of available and non-available carbohydrate.

C. Whole grains are safe and lawful, meeting requirements of 21 CFR 101.14(b)(3)(ii).

Whole grains have a long history of use as human food. Whole grains have been a component of diets in numerous cultures dating back thousands of years and many species are mentioned in the Bible. Domestication of whole grains appears to be an early event. Evidence suggests, for example, that hunter-gatherers in the Near East first cultivated rye fields as early as 13,000 years ago. But for centuries thereafter, they continued to hunt wild game and gather an ever-decreasing range of wild plants, only becoming dedicated farmers living in populous villages by 8500 B.C (Pringle, 1998). Remains of barley (*Hordeum vulgare*) grains found at archaeological sites in the Fertile Crescent indicate that about 10,000 years ago the crop was domesticated there from its wild relative *Hordeum spontaneum* (Badr et al., 2000). Today, whole grains and whole grain products are used in a large variety of breakfast cereals, breads, snacks, drinks, and bakery products.

Currently, there is a strong demand for whole grains worldwide. However, Americans eat more refined grain and less whole grain than is recommended by public health agencies. During 1994-96 and 1998, Americans consumed 6.7 ounces of total grains per day, or 106 percent of the recommendation. However, whole grain consumption was only 34 percent of the amount of whole grains recommended in the 2005 Dietary Guidelines (Lin & Yen, 2007).

The US currently produces nearly 500 million metric tons of grains annually and US consumption is estimated at about 330 million metric tons. Approximately 20% of US grain production is exported. The world produces approximately 2,700 million metric tons of grains and consumes about 2,230 metric tons (USDA, 2012).

The aforementioned whole grains when used as a food or food ingredients at levels necessary to justify the petition claim are safe and lawful under FFDCA. (21 CFR 101.14(b)(ii)). As has been discussed in this section, whole grains have a long history

of use and current production data demonstrate a wide use worldwide and are generally recognized as safe (21 CFR 170.30(d)).

D. Conclusion of Preliminary Requirements

Based on information above, we conclude that DMT2 is a disease affecting significant numbers of Americans, whole grains meet the definition of a substance, and whole grains are safe and lawful, thus fulfilling requirements of 21 CFR 101.14(b)(i), 101.14(b)(3)(i), and 101.14(b)(3)(ii).

III. SUMMARY OF SCIENTIFIC EVIDENCE

A. Background

The 2010 Dietary Guidelines for Americans recommend different amounts of calories and foods according to age and activity level. Overall, the Dietary Guidelines recommend that all Americans make half or more of their grains whole grains. For everyone age 9 and up, this means eating 3 to 5 servings or more of whole grains every day. The 2010 recommendation for whole grain intake is identical to that made in the 2005 Dietary Guidelines for Americans which was in part based on the conclusion by the scientific advisory committee to the Dietary Guidelines for Americans that "consuming at least 3 servings (3 ounce equivalents) of whole grains per day can reduce the risk of diabetes and coronary heart disease (CHD) and helps with weight maintenance" (Dietary Guidelines Advisory Committee Report on the Dietary Guidelines for Americans, 2005)

The 2010 Dietary Guidelines for Americans states that "Limited evidence also shows that consuming whole grains is associated with a reduced incidence of type 2 diabetes (Dietary Guidelines for Americans, 2010). This conclusion was based the **USDA's 2010 Dietary Guidelines Advisory Committee** asking the following question and offering a subsequent conclusion and implications based on Nutritional Evidence Library evidence-based systematic review:

"What is the Relationship between *Whole Grain* Intake and Selected Health Outcomes?"

Conclusion: "Limited evidence shows that consumption of whole grains is associated with a reduced incidence of type 2 diabetes in large prospective cohort studies."

Implications: "Currently most Americans are not consuming adequate amounts of whole grains, which are an important source of dietary fiber and other nutrients. Enriched and fortified grains provide important nutrients; hence, individuals are encouraged to consume grains as both fiber-rich whole grains and enriched grains. To ensure nutrient adequacy, especially for folate, individuals who consume all of their grains as whole grains should include some that have been fortified with folic acid."

This systematic review was based on published literature reviews and meta-analyses of prospective cohort trials discussed later in the petition.

In addition, a number of professional societies and/or medical institutions have historically promoted greater intakes of whole grains in the context of reduced risk or control of DMT2.

The **American Diabetes Association** makes numerous references to whole grains in their publications. An example is: "High-fiber foods like beans, peas, ***whole grains,*** bran cereals, vegetables, and low glycemic index fruits are very healthy for diabetics and are definitely recommended as part of the American Diabetic Association diet." In 2008, a position statement of the **American Diabetes Association** concluded "individuals at high risk for type 2 diabetes should be encouraged to achieve the U.S. Department of Agriculture (USDA) recommendation for dietary fiber (14 g fiber/1,000 kcal) and foods containing whole grains (one-half of grain intake)". The evidence rating for this statement was "B" meaning that there is supportive evidence from well-conducted cohort studies (Position Statement of the American Diabetes Association, 2008).

The **American Medical Association** in their AMA *Healthier Life Steps*^{TM} - "a physician-patient alliance for a longer, healthier life" states that one of the goals is "eat mostly whole grains". Later in the same program information, it is stated, "Eating healthier can help you: prevent and control chronic diseases, such as high blood pressure, heart disease, stroke, diabetes, cancer, and osteoporosis."

The Mayo Clinic website in their diabetes prevention section states "Although it's not clear why, whole grains may reduce your risk of diabetes and help maintain blood sugar levels. Try to make at least half your grains whole grains. Many foods made from whole grains come ready to eat, including various breads, pasta products and many cereals. Look for the word "whole" on the package and among the first few items in the ingredient list." This information was accessed on line on 10-20/2011 (http://www.mayoclinic.com/health/diabetes-prevention/DA00127).

B. Process for Review of the Literature for Whole Grains and Reduced Risk of Diabetes

In order to include all relevant scientific studies, a search was conducted using PubMed with the following search terms:

a) "whole grain and diabetes"
b) "[individual whole grain] and diabetes"
c) "whole grain and glucose"
d) "[individual whole grain] and glucose"
e) "whole grains and insulin"
f) "[individual whole grain] and insulin"
g) "whole grains and glycemic index"
h) "[individual whole grain] and glycemic index"

Inclusion criteria for clinical studies were as follows:

1. whole grains were clearly identified
2. conducted in healthy populations (i.e., intervention studies in subjects with chronic diseases were excluded)
3. included an outcome measure of incidence of DMT2 or, in an attempt to identify potential mechanisms of actions, fasting levels of glucose and/or measures of insulin, insulin resistance and/or insulin sensitivity
4. minimized confounding by including factors such as: age, BMI, smoking, alcohol, physical activity, and family history in prospective cohort studies
5. must have been randomized and implemented an appropriate control or made comparisons to baseline levels in randomized control studies

In total, 123 abstracts and articles were scanned for relevance or exclusion for this evaluation. Based on the initial abstract review and subsequent review of individual articles, 95 studies were excluded from consideration for use in this project for not

meeting the inclusion criteria. The remaining 28 studies were categorized to type of research and whether the FDA definition or an expanded definition of whole grains was used. Eight studies used the FDA whole grain definition and the remaining 20 included treatments or criteria that essentially expanded that definition to added bran and/or germ. The two categories of research used for this review were observational studies (prospective cohort or cross-sectional – 8 studies) and randomized controlled trials (20 studies).

In 2006, FDA issued the *Whole Grain Label Statements* to "provide guidance to the industry about what FDA considers to be whole grains and to assist manufacturers in labeling their products" (U.S. Food and Drug Administration, 2006). In that document FDA specified that, "*whole grains 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*". An expanded definition of whole grain foods was indicated when a food or treatment with whole grains included added bran and/or germ.

C. Overview of Scientific Data

The scientific data presented in this section summarizes relevant human studies and the relationship between consumption of whole grains and the reduced risk of DMT2 incidence.

Eight qualified observational (prospective cohort) trials conducted in the United States provide scientific evidence suggesting that consumption of whole grains reduces the incidence of DMT2 (Liu et al., 2000; Meyer et al., 2000; Fung et al., 2002; van Dam et al., 2002; van Dam et al., 2006; de Munter et al., 2007; Kochar et al., 2007; Sun et al., 2010). The twenty randomized controlled studies are summarized in table form in Appendix A based on whether the study was an acute or chronic study and whether whole grain definition was based on the current FDA definition or whether was based on an expanded definition including additional bran/germ. Of the randomized controlled studies reviewed, seven high quality randomized, controlled, crossover studies deserve

particular mention. Overall these studies provide evidence suggesting that the mechanism by which whole grain consumption reduces incidence of DMT2 is, at least in part, through modifying the surrogate endpoints of blood glucose, insulin, or insulin resistance. (Behall et al., 2005; Nilsson et al., 2008a,b; Pereira et al., 2002; Priebe et al., 2010; Rosen et al., 2009; Wolever & Bolognesi, 1996).

D. Whole Grains Reduce Risk of DMT2

1. Epidemiological Evidence: An Inverse Association between Whole Grain Consumption and DMT2

Large observational trials (e.g., Iowa Women's Health Study, Nurses Health Studies I & II, Physicians Health Study, Health Professionals Follow-up Study, and the Black Women's Health Study) support an inverse association between whole grains (may include added bran and/or germ) consumption and DMT2 morbidity and mortality (see observation trial summary, Table 2). Whole grains consumption reduced the relative risk of DMT2 incidence. Overall, the data indicate that there is an independent and favorable effect of whole grain intake on DMT2 risk, such that eating multiple servings of whole grains (may include added bran and/or germ) daily was associated with significant risk reduction in DMT2.

Table 2. Comparison of DMT2 incidence, lowest versus highest intake of whole grains (may include added bran and/or germ)

Study or Subgroup	Population[1]	Relative Risk[2]	95% CI[3]
Liu, 2000	NHS I	0.73	0.63, 0.85
Meyer, 2000	IWHS	0.79	0.65, 0.96
Fung, 2002	HPFS	0.70	0.57, 0.85
van Dam, 2002	HPFS	0.84	0.70, 1.00
van Dam, 2006	BWHS	0.73	0.63, 0.85
de Munter, 2007	NHS I	0.75	0.68, 0.83
de Munter, 2007	NHS II	0.86	0.72, 1.02
Kochar, 2007	PHS I	0.69	0.60, 0.79
Sun, 2010	HPFS, NHS I, NHS II (pooled)	0.73	0.68, 0.78

[1] NHS, Nurses health study; IWHS, Iowa women's health study; HPFS, Health professional followup study; BWHS, black women's health study; PHS, Physician's health study
[2] Multivariate analyses including body mass index (BMI), values below 1.00 suggest reduced incidence of type 2 diabetes at highest level of whole grains intake
[3] Confidence interval which includes 1.00 or greater is non-significant

Eight prospective cohort whole grain studies were identified for the purposes of this review (Table 3). Quantification of whole grains within the diets of the subject populations was slightly variable, depending upon the extent of the food frequency questionnaire used for each study. Subject populations were variable between studies based on the original objectives of each study, but consisted mainly of health professionals. The relative risk (RR, 8 cohorts) or hazard ratio (HR, 1 cohort) for the lowest population quintile or quartile of whole grain intake is designated as a value of "1.00", which is compared to the RR (or HR) of the highest population quintile or quartile of whole grain intake to estimate risk of becoming a type 2 diabetic. Any highest quintile

RR that is reported as lower than 1.00 would indicate that whole grains may be protective and RR greater than 1.00 would indicate whole grains may be associated with DMT2 onset in the population. The RRs reported for dietary whole grains in these studies vary from 0.69 to 0.86, indicating protective effects. One study reported values for two population cohorts. The frequency of reported RRs is: one <0.70, six between >0.70 and <0.80, and two between >0.80 and <0.90, indicating that whole grain inclusion in diets of various subject populations may be protective of onset of DMT2. Highest mean intakes of whole grains (that may include added bran and/or germ) to achieve the reported RRs ranged from greater than 1 to 3.2 servings per day and ~16 to 51.2 g whole grains per day.

TABLE 3. Summary of Observational (prospective cohort) Studies' Risk Ratios for Type 2 Diabetes at Highest Level of Intake of Whole Grain Intake (may include added bran and/or germ)

Study	Sample Size	Whole Grain[1] Intake, average g/d	Risk Ratios (CI)	P for trend
Kochar et al., 2007	21,152	≥ 16 (≥ 1 serv.)	0.69 (0.60-0.79)	< 0.0001
van Dam et al., 2006	41,186	20.6 (1.29 serv.)	0.73 (0.63-0.85)	< 0.0001
de Munter et al., 2007	73,327	31.2 (1.95 serv.)	0.75 (0.68-0.83)	< 0.001; NHS I
van Dam et al., 2002	42,504	32 (2 serv.)	0.84 (0.70-1.00)	< 0.20
Liu et al., 2000	75,521	43.2 (2.7 serv.)	0.73 (0.63-0.85)	< 0.0001
Meyer et al., 2000	35,988	46.4 (2.9 serv.)	0.79 (0.65, 0.96)	0.0089
Sun et al., 2010	197,228	39 (2.44 serv.)	0.73 (0.68-0.78)	< 0.0001
de Munter et al., 2007	88,410	39.9 (2.49 serv.)	0.86 (0.72-1.02)	< 0.03; NHS II
Fung et al., 2002	42,898	51.2 (3.2 serv.)	0.70 (0.57-0.85)	< 0.0006

[1] One serving of whole grains = 16 grams

2. **Supportive Epidemiological Meta-Analyses and Reviews**

Two recent studies' results were highlighted by the 2010 Dietary Guidelines Advisory Committee evidence-based review that mirror results of this petition's analysis. De Munter (2007), in addition to conducting the NHS I & II cohort studies, performed a meta-analyses of six prospective cohorts including the two NHS cohorts. Only one of the included prospective cohort studies (Montonen, 2003, conducted in Finland) was not included in this review. The de Munter (2007) authors stated in their conclusion:

> "Based on pooled data for six cohort studies including 286,125 participants and 10,944 cases of type 2 diabetes, a two-serving-per-day increment in whole grain consumption was associated with a 21% (95% CI 13%–28%) decrease in risk of type 2 diabetes after adjustment for potential confounders and BMI."

Priebe (2008) conducted a Cochrane-type systematic review of studies from Europe and the United States that examined the effect of whole grain foods on prevention of DMT2. The literature included in that study was published prior to May 2006. Inclusion criteria for the cohort studies specified at least five years in duration and evaluated the relationship between whole-grain foods or cereal fiber intake on incidence of DMT2. Eleven prospective cohort studies met their inclusion criteria; however the data were not pooled due to methodological differences. Three studies examined whole grain intake, four studied cereal fiber intake, and two studied both whole grain and cereal fiber intake. The five studies that examined the effect of whole grain foods consistently found an inverse association with DMT2 at the higher consumption levels. The RR ranged between 0.67 (95% CI 0.32 to 1.38) and 0.79 (95% CI 0.65 to 0.96). When studies were excluded that did not correct for family history of diabetes (Meyer 2000; Montonen 2003) and physical activity (Montonen 2003), the observed effect was very similar in the rest of the studies (RR of 0.70, 0.73 and 0.73). Four of the eleven studies included in Priebe (2008) were included in this petition's analysis. Although the results of the cohort studies were consistent in observing an inverse relationship between whole grains intake risk of developing DMT2, the authors conservatively stated that evidence from

only prospective cohort-type studies was considered too weak to draw definite conclusions about the effect of whole grain foods on the development of DMT2. Authors' implications for future research were:

> "Properly designed long-term randomized controlled trials are needed to establish whether whole grain foods are protective for the development of type 2 diabetes. To facilitate this, further mechanistic research should focus on finding a set of relevant intermediate endpoints for type 2 diabetes and on identifying genetic subgroups of the population at risk that are most susceptible to dietary intervention."

This circumstance (consistent, reproducible, high quality, large prospective cohort studies in the absence of precise mechanistic evidence from RCTs) is analogous to some other diet and chronic disease risk reduction relationships for which mechanisms of actions may be multifactorial and the disease endpoint, due to the long-term nature of its development, does not lend itself to randomized, controlled diet based interventions. For example, the FDAMA health claim for whole grain foods and reduced risk of coronary heart disease and certain cancers, with the exception of limited number of soluble fiber containing whole grains and their effects on blood cholesterol, is without a defined mechanism of action. Similarly, the health claim for dietary fats and cancer states in the section pertaining to the relationship between dietary fat and cancer that the mechanism by which total fat affects cancer has not yet been established" (21 CFR 101.73).

3. Descriptions of Prospective Cohort Studies

STUDY 1: de Munter JSL, Hu FB, Spiegelman D, Franz M, van Dam RM. **2007.** Whole grain, bran, and germ intake and risk of type 2 diabetes: A prospective cohort study and systematic review. PLoS Med 4(8): e261. doi:10.1371/journal.pmed. 0040261.

They evaluated intakes of whole grain, bran, and germ in relation to risk of type 2 diabetes in prospective cohort studies. They followed 161,737 US women of the Nurses' Health Studies (NHSs) I and II, without history of diabetes, cardiovascular disease, or cancer at baseline. The age at baseline was 37–65 y for NHS I and 26–46 y for NHS II.

Dietary intakes and potential confounders were assessed with regularly administered questionnaires. They documented 6,486 cases of type 2 diabetes during 12–18 y of follow-up. Other prospective cohort studies on whole grain intake and risk of type 2 diabetes were identified in searches of MEDLINE and EMBASE up to January 2007, and data were independently extracted by two reviewers. The median whole grain intake in the lowest and highest quintile of intake was, respectively, 3.7 and 31.2 g/d for NHS I and 6.2 and 39.9 g/d for NHSII. After adjustment for potential confounders, the relative risks (RRs) for the highest as compared with the lowest quintile of whole grain intake was 0.63 (95% confidence interval [CI] 0.57–0.69) for NHS I and 0.68 (95% CI 0.57–0.81) for NHS II (both: p-value, test for trend <0.001). **After further adjustment for body mass index (BMI), these whole grain RRs were 0.75 (95% CI 0.68–0.83; p-value, test for trend, 0.001) and 0.86 (95% CI 0.72–1.02; p-value, test for trend 0.03) respectively.** Associations for bran intake were similar to those for total whole grain intake, whereas no significant association was observed for germ intake after adjustment for bran. Based on pooled data for six cohort studies including 286,125 participants and 10,944 cases of type 2 diabetes, **a two-serving-per-day increment in whole grain consumption was associated with a 21% (95% CI 13%–28%) decrease in risk of type 2 diabetes after adjustment for potential confounders and BMI. Whole grain intake is inversely associated with risk of type 2 diabetes**, and this association is stronger for bran than for germ. Findings from prospective cohort studies consistently support increasing whole grain consumption for the prevention of type 2 diabetes.

STUDY 2: Fung TT, Hu FB, Pereira MA, Liu S, Stampfer MJ, Colditz GA, Willett WC. **2002**. Whole-grain intake and the risk of type 2 diabetes: a prospective study in men. Am J Clin Nutr 2002;76:535–40.

They prospectively examined the associations between whole- and refined-grain intake and the risk of type 2 diabetes in a large cohort of men. Men from the Health Professionals Follow-up Study without a history of diabetes or cardiovascular disease in 1986 (n = 42,898) were followed for ≤ 12 y. Intakes of whole and refined grains, measured every 4 years by use of food-frequency questionnaires, were used to predict subsequent type 2 diabetes risk through multivariate analysis. They determined 1197 cases of incident type 2 diabetes. After adjustment for age; physical activity; cigarette smoking; alcohol consumption; family history of diabetes; and fruit, vegetable, and energy intakes, the relative risk of type 2 diabetes was 0.58 (95% CI: 0.47, 0.70; *P* for trend < 0.0001) comparing the highest with the lowest quintile of whole-grain intake. **The association with whole grains was moderately attenuated when additionally adjusted for body mass index (relative risk: 0.70; 95% CI: 0.57, 0.85; *P* for trend = 0.0006).** Intake of refined grains was not significantly associated with risk of type 2 diabetes. After further adjustment for magnesium intake, cereal fiber intake, and glycemic load, the association between whole grains and type 2 diabetes was attenuated and the trend no longer significant. **In men, a diet high in whole grains is associated with a reduced risk of type 2 diabetes in men that may be mediated by cereal fiber.**

STUDY 3: Kochar J, Djousse' L, Gaziano JM. **2007.** Breakfast cereals and risk of type 2 diabetes in the Physicians' Health Study I. Obesity 15: 3039 –3044.

They examined the association between breakfast cereal consumption and the risk of type 2 diabetes. They prospectively analyzed data from 21,152 male participants of the Physicians' Health Study I. Consumption of breakfast cereals was estimated using an abbreviated food questionnaire, and incident diabetes mellitus was determined through yearly follow-up questionnaires. The average age was 53.6 ± 9.4 years (range, 39.7 to 85.9) during the initial assessment of cereal intake (1981 to 1983). During a mean follow-up of 19.1 years, 1958 cases of diabetes mellitus occurred. The crude incidence rates of diabetes mellitus were 57.7, 53.8, 43.5, and 35.4 cases/10,000 person-years for people reporting breakfast cereal intake of 0, ≤1, 2 to 6, and ≥7 servings/wk, respectively. In a Cox regression model adjusting for age, cigarette smoking, BMI, physical activity, vegetable consumption, and alcohol intake, hazard ratios (95% confidence interval) for diabetes mellitus were 1.0 (reference), 0.89 (0.79 to 1.00), 0.76 (0.67 to 0.86), and 0.63 (0.55 to 0.72) from the lowest to the highest category of cereal consumption, respectively (*P* for trend < 0.0001). **In secondary analyses, the inverse association between cereal intake and DM was stronger with whole-grain than refined cereals at 0.69 (0.60-0.79); *P* for trend < 0.0001.** These results suggest that intake of breakfast cereals might confer a lower risk of DM. **Consumption of whole-grain products may help lower the risk of diabetes mellitus**.

STUDY 4: Liu S, MD, Manson JE, Stampfer MJ, Hu FB, Giovannucci E, Colditz GA, Hennekens CH, Willett WC. **2000**. Am J Public Health. 2000;90:1409–1415.

This was a prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women. This study examined the association between intake of whole vs refined grain and the risk of type 2 diabetes mellitus. They used a food frequency questionnaire for repeated dietary assessments to prospectively evaluate the relation between whole-grain intake and the risk of diabetes mellitus in a cohort of 75,521 women aged 38 to 63 years without a previous diagnosis of diabetes or cardiovascular disease in 1984. At the 10-year follow-up, they confirmed 1879 incident cases of diabetes mellitus. **When the highest and the lowest quintiles of intake were compared, the age and energy-adjusted relative risks were 0.62 (95% confidence interval [CI] = 0.53, 0.71, *P* for trend < .0001) for whole grain,** 1.31 (95% CI=1.12, 1.53, *P* trend=.0003) for refined grain, and 1.57 (95% CI=1.36, 1.82, *P* for trend <.0001) for the ratio of refined- to whole-grain intake. **These findings remained significant in multivariate analyses, 0.73 (0.63-0.85; *P* for trend < 0.0001).** The findings were most evident for women with a body mass index greater than 25 and were not entirely explained by dietary fiber, magnesium, and vitamin E. **These findings suggested that substituting whole- for refined- grain products may decrease the risk of diabetes mellitus.**

STUDY 5: Meyer KA, Kushi LH, Jacobs DR Jr, Slavin J, Sellers TA, Folsom AR. **2000.** Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. Am J Clin Nutr 71:921–30.

They examined the relationship of baseline intake of carbohydrates, dietary fiber, dietary magnesium, and carbohydrate-rich foods and the glycemic index with incidence of diabetes. This was a prospective cohort study of 35,988 older Iowa women initially free of diabetes. At 6 years of follow-up, 1141 incident cases of diabetes were reported. Total grain, whole-grain, total dietary fiber, cereal fiber, and dietary magnesium intakes showed strong inverse associations with incidence of diabetes after adjustment for potential non-dietary confounding variables. **Multivariate-adjusted relative risks of diabetes were 1.0, 0.99, 0.98, 0.92, and 0.79 (P for trend: 0.0089) across quintiles of whole-grain intake**; 1.0, 1.09, 1.00, 0.94, and 0.78 (P for trend: 0.005) across quintiles of total dietary fiber intake; and 1.0, 0.81, 0.82, 0.81, and 0.67 (P for trend: 0.0003) across quintiles of dietary magnesium intake. Intakes of total carbohydrates, refined grains, fruit and vegetables, and soluble fiber and the glycemic index were unrelated to diabetes risk. **These data support a protective role for grains (particularly whole grains)**, cereal fiber, and dietary magnesium in the development of diabetes in older women.

STUDY 6: Sun Q, Spiegelman D, van Dam RM, Holmes MD, Malik VS, Willett WC, Hu FB. **2010.** White rice, brown rice, and risk of type 2 diabetes in US men and women. Arch Intern Med.170(11):961-969

They examined white and brown rice consumption in relation to type 2 diabetes risk prospectively in the Health Professionals Follow-up Study and the Nurses' Health Study I and II. They prospectively determined and updated diet, lifestyle practices, and disease status among 39,765 men and 157,463 women in the cohorts. After multivariate adjustment for age and other lifestyle and dietary risk factors, higher intake of white rice (≥5 servings per week vs <1 per month) was associated with a higher risk of type 2 diabetes: pooled relative risk (95% confidence interval [CI]), 1.17 (1.02-1.36). In contrast, **high brown rice intake (≥2 servings per week vs <1 per month) was associated with a lower risk of type 2 diabetes: pooled relative risk, 0.89 (95% CI, 0.81-0.97).** They estimated that replacing 50 g/d (uncooked, equivalent to one-third serving per day) intake of white rice with the same amount of brown rice was associated with a 16% (95% CI, 9%-21%) lower risk of type 2 diabetes, whereas the same **replacement with whole grains as a group was associated with a 36% (30%-42%) lower diabetes risk.** Substitution of whole grains, including brown rice, for white rice may lower risk of type 2 diabetes. **These data support the recommendation that most carbohydrate intake should come from whole grains rather than refined grains to help prevent type 2 diabetes.**

STUDY 7: van Dam RM, Rimm EB, Willett WC, Stampfer MJ, Hu FB. **2002**. Dietary patterns and risk for type 2 diabetes mellitus in U.S. men. Ann Intern Med.136:201-209.

They examined the association between major dietary patterns and risk for type 2 diabetes mellitus. This was a prospective cohort study conducted in the United States with 42,504 male health professionals, 40 to 75 years of age, without diagnosed diabetes, cardiovascular disease, or cancer at baseline. They used a factor analysis based on data from food frequency questionnaires; they identified and validated two major dietary patterns labeled "prudent" (characterized by higher consumption of vegetables, fruit, fish, poultry and whole grains) and "western" (characterized by higher consumption of red meat, processed meat, French fries, high-fat dairy products, refined grains, and sweets and desserts). Relative risks and 95% CIs were adjusted for potential confounders, including body mass index (BMI), physical activity, and cigarette smoking. At 12 years of follow-up (466,508 person-years), they documented 1321 cases of type 2 diabetes. **The prudent dietary pattern (2 servings of whole grains daily) score was associated with a modestly lower risk for type 2 diabetes (relative risk for extreme quintiles, 0.84 [CI, 0.70 to 1.00])**. In contrast, the western dietary pattern score was associated with an increased risk for type 2 diabetes (relative risk, 1.59 [CI, 1.32 to 1.93]; P < 0.001 for trend). A high score for the western dietary pattern combined with low physical activity (relative risk comparing extreme quintiles of dietary pattern score and physical activity, 1.96 [CI, 1.35 to 2.84]) or obesity (relative risk for BMI > 30 kg/m2 vs. <25 kg/m2, 11.2 [CI, 8.07 to 15.6]) was associated with a particularly high risk for type 2 diabetes. Their findings suggest that a western dietary pattern is associated with a substantially increased risk for type 2 diabetes in men.

STUDY 8: van Dam RM, Hu FB, Rosenberg L, Krishnan S, Palmer JR. **2006**. Dietary calcium and magnesium, major food sources, and risk of type 2 diabetes in U.S. black women. Diabetes Care 29:2238–2243.

They examined magnesium, calcium, and major food sources in relation to type 2 diabetes in African-American women. This is a prospective cohort study that included 41,186 participants of the Black Women's Health Study, without a history of diabetes, who completed validated food frequency questionnaires at baseline. At 8 years of follow-up (1995–2003), they documented 1,964 newly diagnosed cases of type 2 diabetes. The multivariate-adjusted hazard ratio of type 2 diabetes for the highest compared with the lowest quintile of intake was 0.69 (95% CI 0.59–0.81; *P* trend <0.0001) for dietary magnesium and 0.86 (0.74–1.00; *P* trend < 0.01) for dietary calcium. After mutual adjustment, the association for calcium disappeared (hazard ratio 1.04 [95% CI 0.88 –1.24]; *P* trend < 0.88), while the association for magnesium remained. Daily consumption of low-fat dairy (0.87 [0.76 –1.00]; *P* trend < 0.04) and whole grains (0.69 [0.60 – 0.79]; *P* trend <0.0001) were associated with a lower risk of type 2 diabetes compared with a consumption less than once a week. After mutual adjustment, the hazard ratio was 0.81 (0.68–0.97; *P* trend < 0.02) for magnesium and **0.73 (0.63– 0.85; P trend <0.0001) for whole grains**. Findings indicated that **diets high in magnesium-rich foods, particularly whole grains, is associated with a substantially lower risk of type 2 diabetes in U.S. black women.**

4. Evidence from Randomized Controlled Clinical Trials

DMT2 is a chronic disease which develops over a long periods of time and has multiple risk factors. In the absence of large, long-term randomized, controlled studies with development of DMT2 as the endpoint (which are impractical for food based interventions), the FDA has identified surrogate endpoints for identifying risk reduction: fasting blood glucose concentrations, oral glucose tolerance tests (OGTT), and/or measures of insulin resistance (FDA, 2009).

Other risk factors or modifying surrogates are believed to be part of the multifactorial nature of the long-term development of DMT2 including overweight and obesity, inflammatory state, and central adiposity. There is evidence from both observation cohort studies and randomized controlled trials that whole gains modify these intermediate factors and may account for the observed reduction in DMT2 incidence in population cohorts with greater intake of whole grains. For example, the Dietary Guidelines for Americans 2010 scientific advisory committee concluded from an evidence-based systematic review that there is moderate evidence showing that intake of whole grains and grain fiber is associated with lower body weight and that abdominal fat have been demonstrated to be lower and/or decrease more in those consuming greater amounts of whole grains (USDA Nutrition Evidence Library, 2010)

The above additional intermediate disease vectors are potentially important for understanding the mechanism by which whole grains are protective against DMT2. However, as the FDA does not currently recognize them as viable surrogate endpoints related to the development of DMT2, the literature review for this petition with respect to variables other than the primary endpoint of incidence of DMT2 which could assist in identifying a mechanism of action for whole grains is focused on randomized, controlled, studies in which the primary measured variables were blood glucose and insulin concentrations or measures of insulin resistance. The following section summarizes the results from high quality randomized trials providing supporting evidence that the

mechanism of action by which whole grains reduce the risk for developing DMT2 is, at least in part, related to surrogate endpoints currently recognized by the FDA as useful for the purpose of health claim evaluations.

STUDY 1: Behall KM et al. 2005. Comparison of hormone and glucose responses of overweight women to barley and oats. J Am Coll Nutr. 24(3):182-8.

Study 1 Table: Glucose and insulin responses to different particle sizes in oat and barley whole grain meals (Randomized, Controlled, Crossover)

	Surrogate Endpoints		
Treatment[1]	**OGTT Blood Glucose AUC, mmol x min/l**	**HOMA Index of Insulin Resistance**	**OGTT Plasma Insulin, µU/ml x min/L**
Glucose (control)	171 ± 16[a]§	1.9 ± 0.5	2141 ± 201[a]
Oatmeal (74g CHO)	122 ± 16[b]	1.9 ± 0.5	1873 ± 201[a]
Oat flour (74g CHO)	109 ± 16[bc]	1.9 ± 0.5	2007 ± 201[a]
Barley flakes (76g CHO)	**61 ± 16[d]**	1.9 ± 0.5	**937 ± 201[b]**
Barley flour (76g CHO)	**70 ± 16[cd]**	2.2 ± 0.5	**1204 ± 201[b]**
[1]All treatment meals 0.67g CHO/kg BW from whole grain			

STUDY 2: Nilsson AC et al., 2008a. Effect of cereal test breakfasts differing in glycemic index and content of indigestible carbohydrates on daylong glucose tolerance in healthy subjects. Am J Clin Nutr 87: 645-654.

Study 2 Table: Postprandial blood glucose incremental areas under the curve (IAUCs; 0 –120 min) after a test breakfast and the following standardized lunch and dinner, respectively, and total blood glucose IAUCs (breakfast + lunch + dinner) after different test breakfasts[1] (Randomized, Controlled, Crossover)

	GLUCOSE IAUC (0 –120 min)			
Test meal	**Breakfast**	**Lunch**	**Dinner**	**Total[2]**
	mmol · min/L			
White wheat bread (WWB)	145.4 ± 22.4	192.5 ± 28.9	360.6 ± 36.3	698.5 ± 70.7[a]
Barley porridge	134.6 ± 20.6	157.0 ± 17.8	366.9 ± 23.9	658.5 ± 41.8[a,b]
WWB + barley dietary fiber	116 ± 14.8	156.2 ± 21.9	379.7 ± 17.6	651.9 ± 42.0[a,b]
Oat kernels	105.0 ± 15.1	137.1 ± 17.0	372.6 ± 34.7	614.7 ± 49.3[a,b,c]
Wheat kernels	100.4 ± 17.5	127.4 ± 14.2	361.0 ± 33.5	588.8 ± 40.5[a,b,c]
Rye kernels	80.6 ± 11.3	130.7 ± 21.2	345.8 ± 36.0	557.1 ± 58.2[b,c]
Barley kernels	68.2 ± 11.8	107.7 ± 14.4	309.6 ± 25.6	485.5 ± 40.1[c]

[1] All values are mean ± SEM; n = 12 healthy subjects. Significant effects of treatment (type of breakfast) ($P < 0.001$) and of time ($P < 0.0001$) were found along the test day, whereas no treatment × time interaction was seen. Means in a column not sharing the same superscript letter are significantly different, $P < 0.05$ (ANOVA followed by Tukey's test).
[2] The combined blood glucose IAUCs after the breakfast, lunch, and dinner.

STUDY 3: Nilsson AC et al., 2008b. Including indigestible carbohydrates in the evening meal of healthy subjects improves glucose tolerance, lowers inflammatory markers, and increases satiety after a subsequent standardized breakfast. J. Nutr. 138: 732–739.

Study 3 Table: Blood-glucose and serum-insulin of subjects after they consumed the standardized breakfast following cereal-based test evening meals[1] (Randomized, Controlled, Crossover)

	B-Glucose		S-Insulin	
Evening meal	**IAUC (0 - 120)**	**Peak[2]**	**IAUC (0 - 120)**	**Peak[2]**
	mmolxmin/L	*Δmmol/L*	*pmolxmin/L*	*Δpmol/L*
White wheat bread (WWB)	211.6 ± 23.8[a]	4.0 ± 0.3[a]	17.3 ± 2.9[a]	0.29 ± 0.05
WWB + resistant starch (RS)	167.2 ± 21.3[a,b]	3.5 ± 0.2[a,b]	12.5 ± 1.3[a,b]	0.24 ± 0.02
1/2 OB	160.6 ± 16.4[a,b]	3.2 ± 0.2[a,b]	13.3 ± 1.5[a,b]	0.25 ± 0.03
WWB + RS + barley dietary fiber	156.8 ± 17.0[b]	3.3 ± 0.3[a,b]	14.8 ± 1.7[a,b]	0.29 ± 0.04
Ordinary barley (OB)	**152.1 ± 17.0[b]**	**3.0 ± 0.3[b]**	**11.6 ± 1.3[b]**	0.23 ± 0.03
High β-glucan barley	**149.9 ± 19.3[b]**	**2.7 ± 0.3[b]**	12.2 ± 2.3[a,b]	0.22 ± 0.06
Cut OB[3]	**142.2 ± 14.1[b]**	**3.0 ± 0.2[b]**	12.2 ± 1.3[3a,b]	0.24 ± 0.03
High amylose barley	**135.5 ± 11.6[b]**	**2.9 ± 0.2[b]**	12.6 ± 1.2[a,b]	0.25 ± 0.03

[1] Values are means 6 SEM, n 1⁄4 15. Means in a column with superscripts without a common letter differ, P < 0.05 (ANOVA followed by Tukey's test).
[2] Glucose and insulin peak values are based on the mean of the individual peaks.
[3] CutOB vs. WWB, P < 0.05.

STUDY 4: Pereira MA et al., 2002. Effect of whole grains on insulin sensitivity in overweight hyperinsulinemic adults. Am J Clin Nutr 75: 848-855.

Study 4 Table: Blood glucose and insulin responses after six weeks on the refined or whole grain diets. (Randomized, Controlled, Crossover)

	Surrogate Endpoints		
Treatment	**Fasting Blood Glucose mmol/l**	**HOMA Insulin Resistance Index**	**Fasting Plasma Insulin µU/ml**
Refined grain diet (Control)	5.3 ± 0.1	6.2 ± 0.2[a]	22.5 ± 0.6[a]
Whole grain diet	5.2 ± 0.1	5.4 ± 0.2[b]	20.3 ± 0.6[b]
Means within a column not containing the same superscript are significantly different (p < 0.05)			

STUDY 5: Priebe MG et al., 2010. Factors related to colonic fermentation of non-digestible carbohydrates of a previous evening meal increase tissue glucose uptake and moderate glucose-associated inflammation. Am J Clin Nutr 91: 90–7.

Study 5 Table: Response of plasma glucose and insulin to a 50g oral-glucose-tolerance test in the morning after a barley kernel or white bread evening meal[1] (Randomized, Controlled, Crossover)

				IAUC[2]	
	Fasting value	**Time to peak (min)**	**Peak value**	**0-2 h**	**0-4 h**
Glucose (mmol/L)					
Barley kernel	5.1 ± 0.1	40.5 ± 3.2	**8.5 ± 0.3**[3]	**167.1 ± 18.9**[3]	**170.2 ± 21.1**[3]
White bread	5.0 ± 0.1	39.0 ± 2.5	9.1 ± 0.4	234.9 ± 29.9	241.4 ± 30.9
Insulin (mU/L)					
Barley kernel	6.3 ± 0.7	40.5 ± 3.9	72.5 ± 11.4	3035 ± 417	3121 ± 431
White bread	5.5 ± 0.6	43.5 ± 3.5	70.1 ± 6.5	3753 ± 392	4057 ± 481

[1] All values are means ± SEMs; n = 10 healthy men. iAUC, incremental area under the curve.
[2] Units of the 0–2-h and 0–4-h iAUC for glucose, insulin are the unit of per 2 or 4 h, respectively.
[3] Significantly different from white bread, $P < 0.05$ (univariate general linear model).

STUDY 6: Rosén LAH et al., 2009. Endosperm and whole grain rye breads are characterized by low post-prandial insulin response and a beneficial blood glucose profile. Nutr J 8:42-53.

Study 6 Table: Blood glucose and insulin responses after the various rye test meals. (Randomized, Controlled, Crossover)

Meals	Glucose	Glucose	Insulin	Insulin
	IAUC (0-30 min)	**IAUC (0-120 min)**	**IAUC (0-30 min)**	**IAUC (0-120 min)**
	min·mM	min·mM	min·nM	min·nM
White wheat bread	34.6 ± 4.1[a]	167.5 ± 17.8[a]	1.42 ± 0.15[a,b]	8.35 ± 0.50[a,b]
White wheat porridge	34.2 ± 4.7[a]	119.0 ± 13.0[a,b]	1.96 ± 0.32[a]	**7.19 ± 0.66[b,c]**
Endosperm rye bread	**17.0 ± 3.2[c]**	**104.0 ± 15.9[b]**	**0.76 ± 0.12[c]**	**4.99 ± 0.57[d]**
Endosperm rye porridge	25.7 ± 3.0[a,b,c]	**103.1 ± 7.6[b]**	1.49 ± 0.24[a,b]	5.77 ± 0.55
Whole grain rye bread	**22.1 ± 3.6[b,c]**	118.9 ± 21.8[a,b]	1.03 ± 0.16[b,c]	**6.06 ± 0.59[c,d]**
Whole grain rye bread w/lactic acid	**17.9 ± 3.1[c]**	**113.6 ± 11.0[b]**	0.91 ± 0.20[a,b]	**5.98 ± 0.70[c,d]**
Whole grain rye porridge	31.5 ± 3.8[a,b]	110.0 ± 14.4[b]	**1.93 ± 0.31[a]**	7.31 ± 0.69[b,c,d]
Rye bran bread	33.5 ± 3.0[a]	147.2 ± 23.1[a,b]	1.87 ± 0.22[a]	10.45 ± 1.06[a]
Values are means ± SEM, n = 12 (WGRP: n = 11). Products not sharing the same letters were significantly different, $p < 0.05$ (ANOVA, followed by Tukey's test).				

STUDY 7: Wolever TM, Bolognesi C. 1996. Source and amount of carbohydrate affect postprandial glucose and insulin in normal subjects. J Nutr Nov;126(11):2798-806.

Study 7 Table: OGTT responses to different foods in healthy volunteers, including whole grain pearled barley. (Randomized, Controlled, Crossover)

Treatment[1]	OGTT Blood Glucose AUC, mmol x min/l	OGTT Plasma Insulin, µU/ml x min/L
White bread (control)	151 ± 21[a]	1305 ± 321[ab]
Cooked pearled barley	**73 ± 10[b]**	348 ± 60[a]
Cooked spaghetti	102 ± 11[b]	662 ± 154[ab]
Instant potatoes	169 ± 16[a]	1378 ± 281[b]
[1]Test (25, 50, 100g carbohydrate portions) meals averaged 58.3g)		

E. No Significant Adverse Effects

None of the studies summarized for this petition have provided any evidence of significant adverse effects related to the intake of whole grains and whole grain products and gastrointestinal disturbances, choking or vitamin-mineral malabsorption.

1. Whole grain as a Food Allergen

The FDA requires, under the Food Allergen Labeling and Consumer Protection Act of 2004, a listing of all major food allergens on packaging. According to the FDA, the term "major food allergen" includes any of the following foods, or a food ingredient that contains protein derived from the following foods: milk, eggs, fish, crustacean shellfish, tree nuts, wheat, peanuts, and soybeans[1]. We support appropriate allergen labeling of foods that contain whole grains.

[1] Food Allergen Labeling and Consumer Protection Act of 2004; U.S. Food and Drug Administration, Office of Regulatory Affairs, www.fda.gov/ora/compliance_ref/rpm/chapter2/ch2-2.html

IV. NATURE OF THE SUBSTANCE AND FOODS ELIGIBLE TO BEAR THE CLAIM

ConAgra requests that the FDA authorize a qualified health claim for whole grains and whole grain products on the basis of the criteria outlined in 21 CFR 101.14.

A. Establishment of Daily Amount of Whole Grains

The data presented in this petition suggests that consumption of 3 servings (48 g) per day of whole grains may lead to reduced incidence of DMT2, perhaps in part, through the mechanisms of modifying fasting blood glucose, OGTT parameters, and insulin resistance. The chronic effects on incidence of DMT2 of consuming whole grain levels such as those tested in relatively acute randomized, controlled studies that use surrogate measures is largely unknown. Therefore, whole grain intake recommendations for this petition are based upon whole grain intake levels observed in large prospective cohort studies conducted in the United States that show reduced incidence of DMT2. In Table 4, we provide a summation of prospective cohort trial support for this intake level of whole grains to be defined as the daily amount regarding authorization of a health claim about the relationship between consumption of whole grains and the reduced risk of DMT2. The recommended level of daily whole grain consumption of 48 g may be translated to 4 daily servings, each containing 12 g of whole grains. Using the same approach FDA has adopted for two other health claims pertaining to the consumption of whole grains, compliance can be assessed by reference to the dietary fiber content of whole wheat, the predominant grain in the U.S. diet. Whole wheat contains 11 grams of dietary fiber per 100 grams; thus, the minimum absolute compliance level of dietary fiber required for a food to bear the prospective claim is 11 grams dietary fiber/100 grams X 12 grams = 1.3 grams dietary fiber which in turn, would round to a minimum compliance level of dietary fiber of 1.5 grams per RACC for food labeling purposes.

Table 4. Summary of Highest Whole Grain Intake Levels in Prospective Cohort Studies Observing Whole Grain Effect on DMT2 Incidence

Study	Whole Grain Intake, average g/d	Whole Grain Servings[1]
Kochar et al., 2007	≥ 16	≥ 1
van Dam et al., 2006	20.6	1.29
de Munter et al., 2007	31.2	1.95
van Dam et al., 2002	32	2
Liu et al., 2000	43.2	2.7
Meyer et al., 2000	46.4	2.9
Sun et al., 2010	39	2.44
de Munter et al., 2007	39.9	2.49
Fung et al., 2002	51.2	3.2
Average	**> 35.5**	**>2.22**
Recommendation	**48**	**3**
[1] One serving of whole grains = 16 grams		

B. Products Eligible to Bear the Claim

The petitioners request that the FDA allow the following group of products to be eligible for the proposed health claim:

1. "Whole grains" defined as "*consisting 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" and may contain added bran and/or germ.*

2. "Whole grain-containing products" are all other whole grain-containing foods that do not meet the definition of "whole grains" above. These include the many products in the food supply that contain whole grains in varying amounts in combination with significant amounts of other ingredients.
    a) Must provide at least (12) g of whole grains per RACC (one-quarter daily amount)
    b) Must meet the nutrient content requirements in §101.62 for a "low saturated fat" and "low cholesterol"; and
    c) Must meet the nutrient compositional requirement in §101.14

Table 5. Representative Foods that Would be Candidates Eligible to Bear the Claim.

Name of Food and (RACC)	MPED Food Code*	MPED Whole Grain Content per RACC (g)*	Fiber per RACC (g)**
Pita Bread, whole wheat toasted (50 g)	51201160	39	4.0
Bagel, whole wheat toasted (55 g)	51208010	37	5.5
Pita Bread, whole wheat (50 g)	51201150	35	3.7
Bagel, whole wheat (55 g)	51208000	34	5.1
Pasta, whole wheat, cooked, with tomato sauce, meatless (1 cup)	58146310	34	9.2
Macaroni, whole wheat, cooked (140 g)	56102010	32	3.9
English muffin, whole wheat, toasted (50 g)	51202020	32	3.6
Oatmeal - quick cooking, cooked (1 cup)	56202970	32	3.7
Oatmeal – instant, cooked (1 cup)	56203030	32	4.4
Cream of rye, cooked (1 cup)	56209000	32	4.3
Rye crisp bread (30 g)	54322000	30	5.0
Bread, whole wheat, toasted (50 g)	51201020	30	3.7
Cracker, whole wheat, reduced fat (30 g)	54337050	29	3.9
Roll, whole wheat (50 g)	51220000	29	3.8
Noodles, whole wheat, cooked (140 g)	56113010	28	3.9
Brown rice cooked, with tomato sauce (1 cup)	58161310	28	4.1
Puffed wheat cake (30 g)	54319200	28	2.8
Bread, whole wheat (50 g)	51201010	27	3.4
Wheat Chex ready to eat cereal (55 g)	57411000	27	6.0
English muffin, whole wheat, (50 g)	51202000	27	3.4
Wheat and malt barley ready to eat cereal (e.g. Grape-Nuts) (55 g)	57230000	27	4.8
Oatmeal/multigrain cereal, cooked (1 cup)	56203610	26	5.4
English muffin, pumpernickel (55 g)	51404550	23	5.2
Brown rice, cooked (140 g)	56205110	23	2.5
Tortilla, whole wheat (55 g)	52215260	23	3.9
Popcorn, air-popped (30 g)	54403010	20	4.4
Bread, Boston brown (55 g)	52401000	18	3.8

Table 5 - continued. Representative Foods that Would be Candidates Eligible to Bear the Claim.

Name of Food and (RACC)	MPED Food Code*	MPED Whole Grain Content per RACC (g)*	Fiber per RACC (g)**
Toasted whole grain flakes, sweetened, ready to eat cereal (e.g. Wheaties) (30 g)	57418000	14	3.0
Whole grain wheat, corn and rice flakes, ready to eat cereal (e.g. Just Right) (55 g)	57244000	13	2.8
*MPED: MyPyramid Equivalent Database version 2.0 is the database used by USDA ARS to translate food intake data collected from the dietary interview portion (What We Eat in America) of the National Health and Nutrition Examination Survey into the corresponding food group amounts consistent with the USDA recommended eating pattern. http://www.ars.usda.gov/Services/docs.htm?docid=17558			
**Fiber values correspond to the respective food codes from MPED which are in the USDA's Food and Nutrient Database for Dietary Studies 2.0. These data are derived from analytical data within the USDA Nutrient Database for Standard Reference database. The USDA Nutrient Database for Standard Reference uses AOAC methods 985.29 or 991.43 to determine total dietary fiber content. http://www.ars.usda.gov/Services/docs.htm?docid=12089			

C. Model Health Claims

The following are proposed model health claims consistent with the data presented in this petition:

a. Scientific evidence suggests, but does not prove, that diets low in saturated fat and cholesterol that include three servings (48 grams) of whole grains per day may reduce the risk of diabetes mellitus type 2

b. Scientific evidence suggests, but does not prove, that whole grains (three servings or 48 grams per day), as part of a low saturated fat, low cholesterol diet, may reduce the risk of diabetes mellitus type 2

D. Projected Impact of Authorized Health Claim on Food Consumption

While we might expect an increase in whole grain consumption associated with authorization of this health claim, we are not aware of any credible method to estimate the expected increase. That said, we are not aware of any concerns that may arise from an increase in whole grain consumption. To the contrary, increased whole grain consumption has been a goal of the Dietary Guidelines for Americans for the past 30 years and may actually lead to increases in fiber and potassium consumption in the population (fiber and potassium were identified in the 2010 Dietary Guidelines as a nutrient of concern for most adults).

V. ENVIRONMENTAL IMPACT

ConAgra claims a categorical exclusion under 21 CFR 25.32(p) for an environmental assessment (EA) and an environmental impact statement (EIS). Under the environmental impact consideration regulations, actions involving the issuance of a health claim does not individually or cumulatively have a significant effect on the human environment, thus this process does not require the development of an EA or EIS.

VI. CONCLUSION

A. Overview of Scientific Data:

Eight large prospective cohort trials (e.g., Iowa Women's Health Study, Nurses Health Studies I & II, Physicians Health Study, Health Professionals Follow-up Study, and the Black Women's Health Study) support an inverse association between whole grains consumption and DMT2 incidence. Whole grains consumption reduced the relative risk of DMT2 onset. Overall, these data indicate that there is an independent and favorable effect of whole grain intake on DMT2 risk, such that eating multiple servings of whole grains daily, that may include added bran and/or germ, was associated with significant risk reduction in DMT2. Demonstrating the mechanism(s) through which whole grains confer their long-term effect on DMT2 risk is not a requirement for a health claim. Nevertheless, seven high quality acute random controlled studies demonstrated successful reductions in glucose and/or insulin by offering whole grains daily. In addition, a small, but well-controlled six week study found that substituting whole grains (~80% from wheat) daily for refined grains in the diet increased daily dietary fiber intake by 10 g and reduced fasting blood glucose concentrations and insulin resistance. Thus, the large epidemiological studies that showed reduced incidence of DMT2 agreed conceptually with the randomized, controlled studies of DMT2 surrogate measures (reduced glucose and/or insulin) when whole grains were consumed daily. Moreover, although not a focus of the literature review for this petition, example citations were introduced demonstrating the complexity of understanding the mechanisms involved in the protective effects of whole grains such as favorably modifying other factors associated with the development of DMT2 including body weight and abdominal adiposity.

B. Conclusions Based on the Scientific Overview:

1) Qualified prospective cohort studies consistently demonstrate that consuming three servings (48 g) daily of whole grains, that may include added bran and/or germ, may reduce the incidence of DMT2.

2) Quality randomized controlled trials have shown reduced blood glucose and/or insulin concentrations, which conceptually agrees with the reduced incidence of DMT2 noted in the prospective cohort studies and thus may contribute to the overall mechanism through which whole grains reduced incidence of DMT2.

The information presented provides scientific evidence that suggests that whole grain consumption may reduce the incidence of DMT2 in the U.S. population. Since DMT2 is a leading health problem for adults in the U. S., dietary strategies that incorporate increased consumption of whole grains and whole grain products are likely to have a significant and substantially positive public health outcome to the U.S. consumer without any negative health implications.

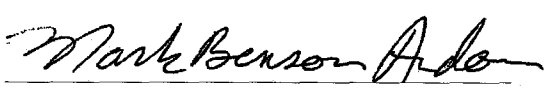
Therefore, ConAgra requests that the Agency authorize a qualified health claim for whole grains and whole grain products for reducing the risk of DMT2.

VII. CERTIFICATION

The scientific studies cited in this petition have been sent electronically in a separate set of files to accompany this petition. To the best of the Petitioner's knowledge, all non-clinical studies relied upon in this petition were conducted in compliance with FDA's good laboratory practices regulations (21CFR Part 58) and all clinical investigations relied upon were either conducted in compliance with the requirements of institutional review set forth at 21CFR. Part 56 or were not subject to such requirements by operation of 21CFR §§ 56.104 or 56.105. To the best of the Petitioner's knowledge, the clinical trials relied upon in the petition were conducted in compliance with the requirements for informed consent set forth in 21CFR Part 50.

On behalf of the Petitioner, we hereby certify that, to the best of our knowledge, this petition is a representative and balanced submission that includes unfavorable information as well as favorable information, known by us to be pertinent to evaluation of the proposed health claim.

Respectfully submitted,



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APPENDIX A

Appendix Table 1. Acute Randomized Controlled Studies Using FDA Whole Grain Definition

Study	Sample Size	Study Type and Duration	Treatment	Results
Alminger et al., 2008	13	Randomized block design, 2-hour postprandial	Glucose solution vs. tempe fermented whole grain barley and oats (All meals 25g available CHO)	↓ glucose & insulin for fermented barley kernels, ↓ insulin for fermented oat kernels
Behall et al., 2005	10	Randomized crossover, 3-hour postprandial	Glucose (control); oatmeal (74g CHO); oat flour (74g CHO); barley flakes (76g CHO); barley flour (76g CHO) (All meals 0.67g test CHO/kg BW from WG)	↓ glucose & insulin for barley flakes and flour
Granfeldt et al., 2000	10	Randomized crossover, 2-hour postprandial	White wheat bread (control); thin roasted oat flakes; thin roasted/steamed oat flakes; thick raw oat flakes; thick roasted oat flakes; thick steamed oat flakes White wheat bread (control); thick steamed barley flakes; thin steamed barley flakes (Each test meal 50g starch)	↓ glucose & insulin for thin roasted or steamed oat flakes and ↓ insulin for thin steamed barley flakes
Hlebowicz et al., 2008	13	Randomized crossover, 2-hour postprandial	Wheat whole-kernel, whole wheat breads vs white wheat bread (All treatments 50g available CHO with 28g white wine vinegar)	↔ glucose
Hlebowicz et al., 2009	10	Randomized crossover, 90-min postprandial	Rye whole-meal bread containing whole kernels vs white wheat bread (Available CHO per meal, 63 and 52g, respectively)	↔ glucose
Priebe et al., 2010	10	Randomized crossover, 2-hour postprandial	White bread (control), cooked barley kernels (Each meal 50g available CHO)	↓ glucose for cooked barley kernels

Appendix Table 2. Acute Randomized Controlled Studies Using Expanded Whole Grain Definition

Study	Sample Size	Study Type and Duration	Treatment	Results
Behall et al., 1999	26	Randomized Latin square design, 3-hour postprandial	Glucose solution vs. breads white, whole-grain wheat, or ultra-fine whole-grain wheat flour (1g CHO/kg BW per treatment)	↔ glucose and insulin compared to white bread control
Liljeberg et al., 1996	9	Randomized crossover design, 3-hour postprandial	Whole-meal porridges (oats, common barley or high β-glucan barley mixed w/common barley (50:50, wet weight basis); whole-meal breads from whole-meal high β-glucan barley and common barley, mixed in ratios of 50:50 or 80:20 (All test meals provided 30g available starch)	↔ glucose & insulin for any treatment & white bread
Najjar et al., 2009	10	Randomized crossover design, 3-hour postprandial	Breads: white wheat (control), sourdough, ultra-fine whole wheat, ultra-fine wheat barley (50g CHO/each treatment)	↔ glucose and insulin vs. white bread
Nilsson et al., 2008a	12	Randomized crossover design, breakfast or dinner, 2-hour postprandial	Porridges made from whole grains (wheat, rye, oats, barley kernels and whole-grain barley flour; white-wheat bread enriched with barley dietary fiber (All test meals provided 50g available starch)	↓ glucose for cooked barley & rye kernel meals for total day
Nilsson et al., 2008b	15	Randomized crossover design, 3-hour postprandial	Cereal-based bread evening meals (barley kernel breads - ordinary, high-amylose- or β-glucan-rich or white wheat flour enriched with barley fiber and resistant starch vs. unenriched white wheat flour (All test meals provided 50g available starch)	↓ glucose & insulin for ordinary barley kernel bread, ↓ glucose for cut, high-amylose & β-glucan-rich barley kernel breads vs control white bread
Rosen et al., 2009	12	Randomized crossover design, 2-hour postprandial	White wheat bread control; white wheat, endosperm rye, and whole grain rye porridges; endosperm rye, whole grain rye w/ or w/o lactic acid, and rye bran breads (All test meals provided 40g available starch)	↓ glucose and insulin for whole grain rye bread w/lactic acid, ↓ glucose for whole grain rye porridge, ↓ insulin for whole grain rye bread
Wolever & Bolognesi, 1996	7	Randomized crossover design, 2-hour postprandial	White bread control; cooked pearled barley; cooked spaghetti; instant potatoes (test meals average 58.3g CHO)	↓ glucose and ↔ insulin for cooked pearled barley

Appendix Table 3. Chronic Randomized Controlled Studies Using FDA Whole Grain Definition

Study	Sample Size	Study Type and Duration	Treatment	Results
Andersson et al., 2007	30	Randomized crossover, 6 weeks per diet	Habitual diet with refined grains (145g CHO/d) vs. diet with substituted whole grains (143g CHO/d)	↔ glucose & insulin or insulin sensitivity
Giacco et al., 2010	15	Randomized crossover, 3 weeks per diet	Refined wheat products (74g soluble CHO) vs whole meal wheat products (77g soluble CHO)	↔ glucose & insulin or insulin sensitivity

Appendix Table 4. Chronic Randomized Controlled Studies Using Expanded Whole Grain Definition

Study	Sample Size	Study Type and Duration	Treatment	Results
Brownlee et al., 2010	266	Randomized parallel design, 16 weeks per diet	Refined grains @ 60g/d (16 wks, control) and Whole grains @ 60g/d (1st 8 wks) & 120g/d (2nd 8 wks)	↔ glucose & insulin and insulin sensitivity
Juntunen et al., 2003	20	Randomized crossover, 8 weeks per diet	Rye bread vs. white wheat bread	↔ glucose & insulin and insulin sensitivity
Pereira et al., 2002	11	Randomized crossover, 6 weeks per diet	Diets with either whole grains (bran, germ, considerable fiber ground to flour; ~ 80% of whole grains was wheat, remainder oats, rice, corn, barley, and rye) vs. diets with refined grains	↔ glucose, ↓ insulin, ↓ insulin resistance
Rave et al., 2007	31	Randomized crossover, 4 weeks per diet	Hypo-caloric diet containing meal replacements (Slim Fast) vs. whole grain double-fermented wheat (Equal energy per treatment)	↓ insulin and insulin resistance after adjusting for weight loss
Saltzman et al., 2001	43	Randomized parallel design, 6 weeks per diet	Hypo-caloric diets with oats (hot cereal or breads, casseroles and snacks) or without oats (refined grains).	↔ glucose & insulin or insulin resistance