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RE: Petition for a Qualified Health Claim for Whole Grains and Reduced Risk of Diabetes Mellitus Type 2 (Docket No. FDA-2012-Q-0242)

Dear Dr. Andon:

This letter responds to the qualified health claim petition received from ConAgra Foods Inc. by the Food and Drug Administration (FDA or the agency) on January 27, 2012. The petition was submitted pursuant to section 403(r)(4) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 343(r)(4)) and in accordance with FDA's guidance on the procedures for the submission of qualified health claim petitions ("qualified health claim procedures guidance").[1] The petition proposed a qualified health claim characterizing the relationship between the consumption of whole grains and a reduction in the risk of diabetes mellitus type 2 (type 2 diabetes).

The petition proposed the following model claims to be used on the labels or in the labeling of whole grains and whole grain-containing products:

> 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.
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> 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.

FDA filed the petition for comprehensive review on March 12, 2012 and posted the petition on the FDA website for a 60-day comment period, consistent with the qualified health claim procedures guidance. The petitioner also subsequently submitted an additional publication in support of the petition.

The agency received a total of eleven comments in response to the petition. Comments were from industry, academia, food and health organizations, and individual consumers. FDA considered all eleven comments in its evaluation of the petition.

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[1] FDA, "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements," July 10, 2003 [http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm053832.htm].

Out of the eleven comments, there were three comments opposed to the qualified health claim proposed in the petition. One of these comments asserted that the excessive consumption of all grain products, including whole grains, is a probable contributing cause of type 2 diabetes. The comment argued that the health claim should describe the relationship between diets low in carbohydrates (defined as no more than 10% of total calories from carbohydrates including whole grains, fruits, vegetables, and legumes) and risk of type 2 diabetes instead. A second comment objected to the proposed health claim as vague and confusing and recommended the same substituted claim for low-carbohydrate diets as the first comment. The third comment in opposition to the petition argued that the proposed health claim should be denied because it was vague and confusing.

Of the remaining eight comments, seven comments strongly supported the claim as proposed by the petitioner, stating that the petitioner had provided adequate scientific evidence to justify the claim. The last comment took issue with the scientific evidence cited by the petition, and recommended modifications to the proposed claim. These recommended modifications were related to the level of scientific support conveyed in the claim, the definition of whole grains, and criteria for dietary fiber content.

Some comments provided references in support of their position. FDA reviewed these references to identify additional relevant human studies that evaluated the relationship between whole grain consumption and risk of type 2 diabetes.

This letter sets forth the results of FDA's scientific review of the evidence for the qualified health claims requested in the petition. As explained in this letter, FDA has determined that the current evidence supports a qualified health claim in the labeling of whole grain-containing conventional foods concerning the relationship between whole grains and type 2 diabetes. Accordingly, this letter discusses the factors that FDA intends to consider in the exercise of its enforcement discretion for a qualified health claim with respect to consumption of whole grains and a reduction in the risk of type 2 diabetes.

I. Overview of Data and Eligibility for a Qualified Health Claim

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). The substance must be associated with a disease or health-related condition for which the general U.S. population, or an identified U.S. population subgroup is at risk (21 CFR 101.14(b)(1)). Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease or health-related condition.[2] In a review of a qualified health claim, the agency first identifies the substance and

[2] See *Whitaker v. Thompson*, 353 F.3d 947, 950-51 (D.C. Cir.) (upholding FDA's interpretation of what constitutes a health claim), *cert. denied*, 125 S. Ct. 310 (2004).

disease or health-related condition that are the subject of the proposed claim and the population to which the claim is targeted.[3]

FDA considers the data and information provided in the petition, in addition to other written data and information available to the agency, to determine whether the data and information could support a relationship between the substance and the disease or health-related condition.[4] The agency then separates individual reports of human studies from other types of data and information. FDA focuses its review on reports of human intervention and observational studies.[5]

In addition to individual reports of human studies, the agency also considers other types of data and information in its review, such as meta-analyses,[6] review articles,[7] and animal and *in vitro* studies. These other types of data and information may be useful to assist the agency in understanding the scientific issues about the substance, the disease, or both, but cannot by themselves support a health claim relationship. Reports that discuss a number of different studies, such as meta-analyses and review articles, do not provide sufficient information on the individual studies reviewed for FDA to determine critical elements, such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. Therefore, FDA uses meta-analyses, review articles, and similar publications[8] to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship.[9] If additional studies are identified, the agency evaluates them individually.

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an

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[3] See FDA, "Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims - Final," January 2009 ("guidance on scientific evaluation of health claims") [http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm073332.htm].

[4] For brevity, "disease" will be used as shorthand for "disease or health-related condition" in the rest of this letter except when quoting or paraphrasing a regulation that uses the longer term.

[5] In an intervention study, subjects similar to each other are randomly assigned to either receive the intervention or not to receive the intervention, whereas in an observational study, the subjects (or their medical records) are observed for a certain outcome (i.e., disease). Intervention studies provide the strongest evidence for an effect. See *supra* note 3.

[6] A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).

[7] Review articles summarize the findings of individual studies.

[8] Other examples include book chapters, abstracts, letters to the editor, and committee reports.

[9] Although FDA does not generally use meta-analyses in its health claim evaluations for the reasons discussed in the text, the agency will include a meta-analysis in its scientific evaluation if the meta-analysis was conducted with pooled data from all the publicly available studies from which scientific conclusions can be drawn (based on the criteria in FDA's guidance on scientific evaluation of health claims) and the statistical analyses were properly conducted. See *supra*, note 3 [Section III.B, "Research Synthesis Studies"].

artificial environment and cannot account for a multitude of normal physiological processes, such as digestion, absorption, distribution, and metabolism, which affect how humans respond to the consumption of foods and dietary substances (Institute of Medicine (IOM), 2005). Animal and *in vitro* studies can be used to generate hypotheses or to explore a mechanism of action but cannot adequately support a relationship between the substance and the disease.

FDA evaluates the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. The absence of critical factors, such as a control group or a statistical analysis, means that scientific conclusions cannot be drawn from the study (Spilker et al., 1991; Federal Judicial Center, 2000). Studies from which FDA cannot draw any scientific conclusions do not support the health claim relationship, and these are eliminated from further review.

Because health claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim, FDA considers evidence from studies in individuals diagnosed with the disease that is the subject of the health claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. If such evidence is not available, the agency cannot draw any scientific conclusions from studies that use diseased subjects to evaluate the substance-disease relationship.

Next, FDA rates the remaining human intervention and observational studies for methodological quality. This quality rating is based on several criteria related to study design (e.g., use of a placebo control versus a non-placebo controlled group), data collection (e.g., type of dietary assessment method), the quality of the statistical analysis, the type of outcome measured (e.g., disease incidence versus validated surrogate endpoint), and study population characteristics other than relevance to the U.S. population (e.g., selection bias and whether important information about the study subjects – e.g., age, smoker vs. non-smoker – was gathered and reported). For example, if the scientific study adequately addressed all or most of the above criteria, it would receive a high methodological quality rating. Moderate or low quality ratings would be given based on the extent of the deficiencies or uncertainties in the quality criteria. Studies that are so deficient that scientific conclusions cannot be drawn from them cannot be used to support the health claim relationship, and these are eliminated from further review.

Finally, FDA evaluates the results of the remaining studies. The agency then rates the strength of the total body of publicly available evidence.[10] The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of studies of each type and study sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results

[10] See *supra*, note 3 [Section III.F].

supporting the proposed claim have been replicated,[11] and the overall consistency[12] of the total body of evidence.[13] Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support a qualified health claim for the substance/disease relationship, and, if so, considers what qualifying language should be included to convey the limits on the level of scientific evidence supporting the relationship or to prevent the claim from being misleading in other ways.

A. Substance

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of food regardless of whether the food is in conventional form or in the form of a dietary supplement (21 CFR 101.14(a)(2)). The petition identified whole grains as the substance that is the subject of the proposed claim. In determining what foods should be considered to be whole grains, FDA is guided by its 2006 draft guidance entitled "Whole Grain Label Statements."[14] In that draft guidance, FDA described whole grains as cereal grains that consist of the intact, ground, cracked or flaked caryopsis,[15] and whose principal anatomical components (the starchy endosperm, germ and bran) are present in the same relative proportions as they exist in the intact caryopsis. The draft guidance listed the following examples of cereal grains: amaranth, barley, buckwheat, bulgur, corn (including popcorn), millet, quinoa, rice, rye, oats, sorghum, teff, triticale, wheat, and wild rice.

The definition of whole grains used in the draft guidance is widely accepted. It is consistent with the federal government definition of whole grains in the *Dietary Guidelines for Americans, 2010*,[16] as well as with the definitions of industry groups, such as the Whole Grains Council and AACC International,[17] and international organizations such as the European Food Information

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[11] Replication of scientific findings is important for evaluating the strength of scientific evidence (An Introduction to Scientific Research, E. Bright Wilson Jr., pages 46-48, Dover Publications, 1990).

[12] Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill A.B., The environment and disease: association or causation? Proc R Soc Med 1965;58:295-300); See also Agency for Healthcare Research and Quality, "Systems to rate the scientific evidence" (March 2002) [http://archive.ahrq.gov/clinic/epcsums/strengthsum.pdf], defining "consistency" as "the extent to which similar findings are reported using similar and different study designs."

[13] See *supra*, note 3 [Section III.F].

[14] See FDA, "Draft Guidance: Whole Grain Label Statements," February 17, 2006 [http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm059088.htm].

[15] "Caryopsis," a synonym for "grain," is the term used in botany to refer to the specialized type of dry, one-seeded fruit characteristic of the cereal grasses. "Caryopsis," Encyclopædia Britannica Online. http://www.britannica.com/EBchecked/topic/97667/caryopsis (accessed June 19, 2013). In plants that produce a caryopsis, the fruit and seed are fused in a single grain. "Caryopsis," Merriam-Webster.com, http://www.merriam-webster.com/dictionary/caryopsis (accessed June 19, 2013).

[16] Dietary Guidelines for Americans 2010, p. 36 [http://www.cnpp.usda.gov/Publications/DietaryGuidelines/2010/PolicyDoc/PolicyDoc.pdf].

[17] See, e.g., http://www.aaccnet.org/initiatives/definitions/Pages/WholeGrain.aspx; http://wholegrainscouncil.org/whole-grains-101/definition-of-whole-grains (accessed July 23, 1013).

Council.[18] Moreover, your petition adopts this same definition.[19] Accordingly, for the purpose of this health claim evaluation, FDA is defining whole grains as cereal grains that consist of the intact, ground, cracked or flaked caryopsis and whose principal anatomical components -- the endosperm, germ, and bran -- are present in the same relative proportions as they exist in the intact grain. Under this definition, a grain ingredient containing only a part (e.g., bran) or only some of the parts (e.g., germ and endosperm without the bran) of the grain would not consist of the intact, ground, cracked or flaked caryopsis and would not have anatomical components present in the same relative proportions as they exist in the intact caryopsis. Therefore, such a grain would not have all of the necessary components to be considered "whole."

Cereal grains, including whole grains, are widely distributed throughout the food supply. The agency concludes that whole grains, the substance identified in the petition, are foods and meet the definition of a substance in the health claim regulation (21 CFR 101.14(a)(2)).

B. Disease or Health-Related Condition

A disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly, or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)). The petition has identified type 2 diabetes as the disease that is the subject of the proposed claims.

Diabetes is a disorder of metabolism resulting from the body's impaired ability to use blood glucose (sugar) for energy.[20] In type 1 diabetes, the pancreas no longer makes insulin, and therefore blood glucose cannot enter the cells to be used for energy. In type 2 diabetes, either the pancreas does not make enough insulin or the body is unable to use insulin effectively (i.e., insulin resistance). A diagnosis of type 2 diabetes can be made after positive results on any one of three tests, with confirmation from a second positive test on a different day: 1) random (taken any time of day) plasma glucose value of 200 mg/dL or more, along with the presence of diabetes symptoms; 2) a plasma glucose value of 126 mg/dL or more after a person has fasted for

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[18] European Food Information Council, "Whole Grain Fact Sheet" [http://www.eufic.org/article/en/expid/Whole-grain-Fact-Sheet (accessed July 23, 2013)].

[19] Specifically, your petition states:

> 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 . . . ." 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."

Your petition goes on to say, however, "Within the following discussion of the science of whole grains and [type 2 diabetes], an expanded definition of whole grain foods is indicated when a food or treatment with whole grains included additional bran and/or germ." Thus, although your petition states that it "defin[es]" whole grains consistent with FDA's 2006 draft guidance, your petition also relies on scientific evidence that uses an "expanded definition." FDA interprets this to mean that you expressly adopt the meaning for whole grains from the 2006 draft guidance, but that you have chosen to include in your petition scientific studies that examine "additional bran and/or germ."

[20] National Institutes of Health (NIH), "Diabetes Overview" [http://diabetes.niddk.nih.gov/dm/pubs/overview/index.htm#what (accessed July 23, 2013)].

8 hours; or 3) an oral glucose tolerance test plasma glucose value of 200 mg/dL or more in a blood sample taken 2 hours after a person has consumed a drink containing 75 g of glucose dissolved in water. Elevated or abnormally high blood glucose levels (fasting blood glucose of > 100 mg/dL and < 126 mg/dL)[21] and insulin resistance[22] are considered risk factors for type 2 diabetes.[23] The agency concludes that type 2 diabetes meets the definition of a disease under 21 CFR 101.14(a)(5) because, in persons with this condition, the glucose metabolism systems of the body have been damaged such that the body is not functioning properly.

C. Safety Review

Under 21 CFR 101.14(b)(3)(ii), if the substance is to be consumed at other than decreased dietary levels, the substance must be a food, food ingredient, or food component whose use at the levels necessary to justify the claim has been demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Act.

FDA evaluates whether the substance is "safe and lawful" under the applicable food safety provisions of the Act. For conventional foods, this evaluation involves considering whether the ingredient that is the source of the substance is generally recognized as safe (GRAS), approved as a food additive, or authorized by a prior sanction issued by FDA (21 CFR 101.70(f)).

Whole grains are the substances that are the subject of the health claims requested in the petition. Whole grains are foods of natural biological origin that have been widely consumed for their nutrient properties prior to January 1, 1958, without known detrimental effects, and for which no known safety hazard exists. Whole grains that have been subject only to conventional processing, as practiced prior to January 1, 1958, are consistent with FDA's definition of food ingredients ordinarily regarded as GRAS (21 CFR 170.30(d)). Thus, FDA concludes, under the preliminary requirements of 21 CFR 101.14(b)(3)(ii), that the use of whole grains that have been subject only to conventional processing as practiced prior to January 1, 1958, as foods or food ingredients is safe and lawful.

II. The Agency's Consideration of a Qualified Health Claim

FDA identified the following endpoints, including three surrogate endpoints of type 2 diabetes, to use in identifying type 2 diabetes risk reduction for purposes of a health claim evaluation: incidence of type 2 diabetes, fasting blood glucose level, oral glucose tolerance test (OGTT) results, and insulin resistance. Therefore, to evaluate the potential effects of whole grain consumption on type 2 diabetes risk, FDA considered these four endpoints as indicators or

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[21] National Diabetes Education Program, "Diabetes Risk Factors" [http://ndep.nih.gov/am-i-at-risk/DiabetesRiskFactors.aspx (accessed July 23, 2013)].

[22] Insulin resistance is a condition in which the cells of the body become resistant to the effects of insulin. As a result, higher levels of insulin are needed for glucose to enter the cells and to achieve normal blood glucose concentration. See NIH, National Diabetes Information Clearinghouse, "Insulin Resistance and Prediabetes" [http://diabetes.niddk.nih.gov/dm/pubs/insulinresistance/index.aspx (accessed July 23, 2013)].

[23] NIH, National Diabetes Information Clearinghouse, "Insulin Resistance and Prediabetes" [http://diabetes.niddk.nih.gov/dm/pubs/insulinresistance/index.aspx (accessed July 23, 2013)].

predictors of type 2 diabetes. Insulin resistance is assessed by various measurements of insulin sensitivity,[24] including the euglycemic hyperinsulinemic clamp method, homeostasis model assessment (HOMA), and quantitative insulin sensitivity check index (QUICK1).

The petition cited 55 publications as evidence to substantiate the risk reduction relationship for the proposed claims (see Docket # FDA-2012-Q-0242), including 19 human intervention studies evaluating the relationship between whole grain intake and risk of type 2 diabetes[25] and 23 publications[26] examining 24 observational studies to evaluate this relationship. In addition to these individual studies, the petition cited four articles on the history or consumption of whole grains, history of agriculture, or world agriculture supply and demand (Badr et al., 2000; Lin et al., 2007; Pringle, 1998; USDA, 2012); five government documents (DGAC, 2005; DGA, 2010; FDA, 2008; FDA, 2009;[27] USDA NEL, 2010); one article on diabetes data and trends (CDC, 2009); one position statement (ADA, 2008); two meta-analyses (de Munter et al., 2007; Sun et al., 2010);[28] and one systematic review (Priebe et al., 2008a).

In addition to the publications cited in the petition, comments supporting or opposing the petition identified 21 human intervention studies[29] and 17 observational studies[30] evaluating the relationship between whole grain intake and risk of type 2 diabetes. References cited in comments during the public comment period also included one meta-analysis (Nettleton et al., 2010); one comment to the 2010 Dietary Guidelines Advisory Committee (McKeown et al., 2009); one comment on phytochemical-rich dietary patterns (McKeown et al., 2010); one article on the development of a whole grain database (Franz et al., 2006); two articles on trends in dietary fiber consumption and modeling (King et al., 2012, Nicklas et al., 2011); four review articles (De Moura et al., 2009, Gil et al., 2011, Liu et al., 2002, McKeown et al., 2011); one

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[24] Insulin sensitivity is the degree to which cells respond to a particular dose of insulin by lowering blood glucose levels. Reduced insulin sensitivity means increased resistance to insulin.

[25] Alminger et al., 2008; Andersson et al., 2007; Behall et al., 1999, 2005; Brownlee et al., 2010; Giacco et al., 2010; Granfeldt et al., 2000; Hallfrisch et al., 2003; Hlebowicz et al., 2008, 2009; Juntunen et al., 2003; Liljeberg et al., 1996; Nilsson et al., 2008a, 2008b; Pereira et al., 2002; Priebe et al., 2010; Rave et al., 2007; Rosen et al., 2009; Saltzman et al., 2001.

[26] de Munter et al., 2007; Esmaillzadeh et al., 2005; Fung et al., 2002; Kochar et al., 2007; Liu et al., 2000; Lutsey et al., 2007; Masters et al., 2010; Meyer et al., 2000; McKeown et al., 2002, 2004; Montonen et al., 2003; Newby et al., 2007; Sahyoun et al., 2006; Salmeron et al., 1997a, 1997b; Schulze et al., 2004; Steffen et al., 2003; Steven et al., 2002 ; Sun et al., 2010; Valachovicova et al., 2006; van Dam et al., 2002, 2006; Wolever et al., 1996.

[27] See *supra*, note 3.

[28] The publication by de Munter et al., 2007 that included a meta-analysis also reported individually on two observational studies, the Nurses' Health Study I (NHS I) and Nurses' Health Study II (NHS II). Similarly, the publication by Sun et al., 2010 included both a meta-analysis and individual reports on three observational studies, the NHS I, NHS II, and Health Professionals Follow-Up Study (HPFS). Therefore, FDA counted each of these publications in both the meta-analysis category and the observational studies category.

[29] Adamsson et al., 2011; Anderson et al., 2010; Casiraghi et al., 2006; d'Emden et al., 1987; Holt et al., 1994; Ito et al., 2005; Jang et al., 2001; Jenkins et al., 1986, 1988; Karupaiah et al., 2011; Kim et al., 2009; Lakshmi et al., 1996; Liljeberg et al., 1992, 1994; Losso et al., 2009; Noriega et al., 1993; Oosthuizen et al., 2005; Panlasigui et al., 2006; Priebe et al., 2008b; Rosen et al., 2011; Thondre et al., 2012.

[30] Anderson et al., 2012; Azadbakht et al., 2006; Deshmukh-Taskar et al., 2009; Fisher et al., 2009; Fung et al., 2001; Ghattas et al., 2008; Hsu et al., 2008; Hur et al., 2012; Jacobs et al., 1998; Jensen et al., 2006; Liese et al., 2003; Liu et al., 2009; McGeoch et al., 2011; McIntosh et al., 2003; Nettleton et al., 2008a, 2008b; Steemburgo et al., 2009.

study that evaluated the effects of whole grain intake on risk of a different disease (coronary heart disease) than identified in the proposed claim (Jensen et al., 2004); and one study that evaluated short-term glycemic response to whole-grain bread in people with type I (insulin dependent) diabetes (Rasmussen et al., 1991).[31] The petitioner also submitted an additional meta-analysis article to supplement the petition (Ye et al., 2012).

In addition to the above publications, FDA identified one relevant intervention study (Tighe et al., 2010) through a literature search for studies evaluating the relationship between whole grain intake and risk of type 2 diabetes. FDA also considered the USDA Nutrition Evidence Library review on whole grain consumption and incidence of type 2 diabetes (USDA NEL, 2010) that was conducted for the 2010 Dietary Guidelines for Americans Advisory Committee and summarized in the Committee's report (DGAC, 2010), and the discussion of the whole grains - type 2 diabetes relationship in the 2010 Dietary Guidelines for Americans (DGA, 2010).

A. Assessment of Review Articles and Meta-analysis

Although useful for background information, review articles and meta-analyses do not contain sufficient information on the individual studies reviewed and, therefore, FDA could not draw any scientific conclusions from this information. For example, FDA could not determine factors such as the study population characteristics or the composition of the products used (e.g., how "whole grain" was defined) from the review articles or meta-analyses submitted with the petition or during the comment period. Similarly, the lack of detailed information on studies summarized in the review articles and meta-analyses[32] prevented FDA from determining whether the studies were flawed in critical elements such as design, conduct, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. As a result, the review articles and meta-analyses did not provide information from which scientific conclusions can be drawn regarding the substance-disease relationship claimed by the petitioner.

B. Assessment of Intervention Studies

FDA evaluated 41 reports of intervention studies that were designed to evaluate the relationship between whole grain intake and type 2 diabetes risk.[33] Some of these studies evaluated the

[31] FDA did not include this study in its review of evidence relevant to the proposed claim because the study evaluated the effects of whole grain intake on glycemic response in subjects with type 1 diabetes and provided no data as to possible effects on risk of type 2 diabetes.

[32] Two of the meta-analyses also reported on individual studies. The meta-analysis by de Munter et al, 2007 analyzed pooled data from six observational studies. Two of these studies, NHS I and NHS II, were reported on and analyzed individually in the same publication by de Munter et al, 2007. These individual analyses met FDA's criteria and were included in our evaluation (see Sections II.C and III below). The meta-analysis by Sun et al., 2010 analyzed pooled data from three observational studies, NHS I, NHS II, and HPFS. The article by Sun et al., 2010 also reported on and analyzed these three studies individually. Like the analyses of individual studies in the article by de Munter et al., these individual analyses by Sun et al. met FDA's criteria and were included in our evaluation (see Sections II.C and III below).

[33] Adamsson et al., 2011; Alminger et al., 2008; Andersson et al., 2007; Anderson et al., 2010; Behall et al., 1999, 2005; Brownlee et al., 2010; Casiraghi et al., 2006; d'Emden et al., 1987; Giacco et al., 2010; Granfeldt et al., 2000;

effects of whole grains as a category of food, while others were limited to single forms of whole grains (e.g., brown rice, oats). Of the 41 intervention studies reviewed, scientific conclusions could not be drawn from 35 studies. For 31 of the studies,[34] the study duration was too short, approximately 90 minutes to 12 hours, to provide any information about the long-term effect of whole grains consumption on risk of type 2 diabetes.[35] Such short-term studies are designed to assess the glycemic index[36] of foods. The glycemic index is a function of the food's immediate effect on blood glucose levels rather than the long-term effect of whole grain consumption on the body's ability to metabolize glucose such that lower blood glucose levels may result in increased insulin sensitivity. Therefore, the agency could not draw scientific conclusions from these studies.

As discussed in Section I.A, FDA considers whole grains to be cereal grains that consist of the intact, ground, cracked or flaked caryopsis, and whose principal anatomical components (the starchy endosperm, germ and bran) are present in the same relative proportions as they exist in the intact caryopsis. The addition of individual parts of a whole grain, such as bran, to a food does not make the food "whole grain" because such ingredients do not contain the entire grain with all its components. One longer-term intervention study (Juntunen et al., 2003) studied rye bread made with added rye bran to increase the bread's dietary fiber content. A second longer-term intervention study (Pereira et al., 2002) did not specify the composition of the foods studied clearly enough for FDA to determine whether they were actually whole grain.[37] Another long-term intervention studied legumes, seeds, and vegetables in addition to whole grains (Jang et al., 2001). A fourth long-term intervention study investigated the effects of the Nordic diet, which is rich in fish, low-fat milk products, and rapeseed oil as well as in whole grains and other high-fiber plant foods like fruits, berries, nuts, and vegetables (Adamsson et al., 2011). Because these four studies evaluated or may have evaluated the addition of substances other than whole grains to the diet, no scientific conclusions about whether whole grains may reduce the risk of type 2 diabetes could be drawn from them.

Hallfrisch et al., 2003; Hlebowicz et al., 2008, 2009; Holt et al., 1994; Ito et al., 2005; Jang et al., 2001; Jenkins et al., 1986, 1988; Juntunen et al., 2003; Karupaiah et al., 2011; Kim et al., 2009; Lakshmi et al., 1996; Liljeberg et al., 1992, 1994, 1996; Losso et al., 2009; Nilsson et al., 2008a, 2008b; Noriega et al., 1993; Oosthuizen et al., 2005; Panlasigui et al., 2006; Pereira et al., 2002; Priebe et al., 2008b, 2010; Rave et al., 2007; Rosen et al., 2009, 2011; Saltzman et al., 2001; Thondre et al., 2012; Tighe et al., 2010.

[34]Alminger et al., 2008; Anderson et al., 2010; Behall et al., 1999, 2005; Casiraghi et al., 2006; d'Emden et al., 1987; Granfeldt et al., 2000; Hallfrisch et al., 2003; Hlebowicz et al., 2008, 2009; Holt et al., 1994; Ito et al., 2005; Jenkins et al., 1986, 1988; Karupaiah et al., 2011; Kim et al., 2009; Lakshmi et al., 1996; Liljeberg et al., 1992, 1994, 1996; Losso et al., 2009; Nilsson et al., 2008a, 2008b; Noriega et al., 1993; Oosthuizen et al., 2005; Panlasigui et al., 2006; Priebe et al., 2008b, 2010; Rosen et al., 2009, 2011; Thondre et al., 2012.

[35] See *supra*, note 3 [Section III. D].

[36] The glycemic index is a marker used to quantify the relative blood glucose response to consumption of foods. The glycemic index measures the increase in blood glucose during the two hours after ingestion of a set amount of carbohydrate in a test food, compared to the same amount of carbohydrate from a reference food (white bread or glucose solution) tested in the same individual and under the same conditions, using the initial blood glucose concentration as a baseline (DGAC, 2010).

[37] Specifically, Pereira et al., 2002 does not make clear whether the foods studied contained intact whole grains or individual components of whole grains (bran, germ and/or fiber) that were separately added to the food.

Based on the above discussion, there were six intervention studies available from which scientific conclusions could be drawn about the relationship between whole grain intake and risk of type 2 diabetes (Andersson et al., 2007; Brownlee et al., 2010; Giacco et al., 2010; Rave et al., 2007; Saltzman et al., 2001; Tighe et al., 2010). Each of these studies is discussed in turn below. Andersson et al. (2007) conducted a randomized cross-over intervention study[38] of high methodological quality in 30 Swedish overweight and obese (body mass index (BMI) 28 $\pm$ 2 kg/m^2) men (n =8)[39] and women (n =22) with one or more of the following symptoms: high serum insulin, high fasting blood glucose, high triglycerides level, low high-density lipoprotein (HDL), or borderline hypertension. The subjects continued with their habitual diets but were advised to incorporate a fixed amount (112 g/day, or about 7 servings/day) of whole grain foods (for the experimental group) or refined grain foods (for the control group) for a period of 6 weeks on each diet. The whole grain products used were defined as foods for which whole grains (including the bran, germ, and starchy endosperm), mainly in milled form, made up 50% of the dry weight of the product. Both whole grains and refined grains were provided to the subjects by the researchers. Compliance with the dietary intervention was monitored by diaries, including a structured list to verify daily portions eaten, and subjects adhered to their prescribed diets. In this study, subjects did not lose weight. Insulin sensitivity was directly measured by the euglycemic hyperinsulinemic clamp method.[40] Results showed that insulin sensitivity and fasting blood glucose levels were not significantly different[41] between the whole grains and refined grains groups.

Brownlee et al. (2010) conducted a 16-week parallel intervention study[42] of high methodological quality in 266 overweight men and women (BMI > 25 kg/m^2) at two centers in the United Kingdom. The subjects were randomly divided into three groups: group 1 (control group) (n = 100; no dietary changes); group 2 (n = 85; 60 g of whole grains/day for 16 weeks); and group 3 (n = 81; 60 g of whole grains/day for 8 weeks followed by 120 g of whole grains/day for 8 weeks). Whole grain foods were provided to the subjects, and they were instructed to substitute the prescribed amount of whole grain foods for an equivalent amount of refined grain foods. Seven day food frequency questionnaires were used for assessing compliance. On average, the subjects adhered to their assigned diets. Fasting blood glucose and serum insulin were measured in order to calculate insulin resistance based on the QUICK1[43] method. There was no significant

[38] In a cross-over intervention study, all subjects in the intervention group "cross over" to the control group, and vice versa, after a defined time period. See *supra*, note 3 [Section III. B]. In other words, during the second phase of the study, the groups switch so that the subjects who had been in the intervention group follow the control diet, and the subjects who had been on the control diet receive the intervention.

[39] The abbreviation "n" refers to the number of subjects.

[40] See *infra*, notes 43 and 44.

[41] Statements in this letter about the significance of a difference, association, or other finding refer to statistical significance.

[42] Intervention studies with a parallel design involve two groups of subjects, the test group (also called the intervention group) and the control group, which simultaneously receive the substance or serve as the control, respectively. See *supra*, note 3 [Section III. B].

[43] The QUICK1 method of estimating insulin resistance relies on calculated values using fasting blood glucose and insulin rather than direct measurement such as with an euglycemic hyperinsulinemic clamp, which is a more reliable measure of insulin resistance than QUICK1. However, according to endocrinology specialists in FDA's Center for Drug Evaluation and Research, QUICK1 is considered to be an acceptable method for estimating insulin resistance where clamp procedures are not feasible.

difference in fasting blood glucose or insulin resistance between either of the intervention groups as compared to the control group.

Giacco et al. (2010) was a randomized cross-over study of moderate methodological quality that was conducted in 15 healthy overweight/obese (BMI 27.4 $\pm$ 3.0 kg/m^2) Italian men (n = 12) and women (n =3). After a two-week run-in period, the subjects were randomly assigned to follow two isocaloric (same amount of calories) diets in random order for three weeks each. The subjects were advised not to modify their habitual intake of non-grain foods (meats, dairy products, eggs, fish, fruits, and vegetables) during the study. The only difference between the two diets was the inclusion of a fixed amount of whole-wheat (i.e., whole grain) foods or refined wheat foods as the main carbohydrate sources at all meals. All grain foods (both whole grains and refined grains) were provided to the subjects. Compliance with the diets was evaluated using a 7-day food record at the start of the study, during the study, and at the end of the study. The subjects' compliance with both diets was good. Fasting blood glucose and insulin levels were measured in order to calculate insulin resistance using HOMA.[44] There was no significant difference in fasting blood glucose or insulin resistance between the whole grain and refined grain groups.

Rave et al. (2007) was a randomized cross-over design study of moderate methodological quality in which the effects of hypocaloric (reduced calorie) diets on fasting blood glucose and insulin resistance were investigated. Study subjects in the whole grains group consumed a diet containing whole-grain double fermented wheat for four weeks, and those in the control group consumed a diet containing a nutrient-dense, high-fiber meal replacement product that contained no whole grains (the "reference meal") for four weeks. Thirty-one obese (BMI 33.9 $\pm$ 2.7 kg/m^2) German men (n =13) and women (n = 18) with elevated fasting blood glucose (meaning that they were at high risk for type 2 diabetes) were instructed to replace at least two daily meals with either the double fermented wheat or the reference meal, with a target consumption of 200 g of the assigned product per day. Both whole-grain and reference meals were provided in a powder form and were prepared in portions equivalent in calorie content. Subjects in the whole-grain group were instructed to dissolve the whole-grain powder in water, skim milk, or yogurt; subjects in the reference meal group were instructed to dissolve the powder in skim milk. All subjects were interviewed by a dietitian during the first, second and third week of the study for compliance with the study diet, body weight changes, and any potential adverse events. In addition, they recorded their daily food intake daily using a standardized questionnaire. Based on the questionnaire responses, the authors reported that the subjects adhered to their prescribed diets. After four weeks, there was a loss in body weight, lower fasting blood glucose levels, and improved insulin resistance (calculated by HOMA) in each group, but there were no significant differences between the two groups. However, after statistical adjustment for body weight reduction, insulin resistance was significantly reduced in the whole grain group compared to the

[44] The HOMA method of estimating insulin resistance relies on calculated values using fasting blood glucose and insulin rather than direct measurement such as with an euglycemic hyperinsulinemic clamp, which is a more reliable measure of insulin resistance than HOMA. However, according to endocrinology specialists in FDA's Center for Drug Evaluation and Research, HOMA is considered to be a reasonable method for estimating insulin resistance where clamp procedures are not feasible.

control group (P<0.049).[45] Notably, the powdered, double-fermented whole grain product used in this study is significantly different from the whole grain products generally available for purchase in the U.S. marketplace (Kranz et al., 2013).

Saltzman et al. (2001) conducted an eight-week parallel intervention study of moderate methodological quality to investigate the effect of a hypocaloric diet containing oat products on body weight, blood pressure and insulin sensitivity. The study participants consisted of 43 healthy U.S. adults, both men and women, with a BMI 26.4 $\pm$ 3.3 kg/m^2. The eight-week protocol was divided into a two-week weight maintenance phase (Phase 1), with habitual diets, followed by a six-week weight-loss phase (Phase 2). During Phase 2, the subjects consumed one of two reduced-calorie diets (weight-maintenance calories minus 1,000 kcal/day). The intervention group (n =22) received a diet that included 45 g of rolled whole-grain oats (roughly equivalent to 1.5 servings of oatmeal) per 1,000 kcal. The control group (n =21) received a diet equivalent in calories, but without oats. All foods and calorie-containing beverages were provided to the subjects. They were required to eat at least four meals per week in the metabolic research unit, and the other meals were provided as take-out. The subjects' compliance with both diets was good. The two diets were matched for insoluble fiber, fat, protein, and carbohydrate content. There was no significant difference in fasting blood glucose or insulin resistance (calculated by HOMA) between the intervention and control groups.

Tighe et al. (2010) conducted a 12-week randomized parallel controlled hypocaloric study of high methodological quality in men (n = 102) and women (n =104) with a BMI (kg/m^2) between 18.5 and 35 in the United Kingdom. After a four-week run-in period on a refined grain diet, subjects (stratified by age, sex and BMI)[46] were randomly assigned to one of three groups. The first group (the control group) (n = 63) consumed a diet that included refined cereals and white bread. The second group (n = 73) replaced three servings of refined grains with whole wheat foods (70-80 g of whole-grain bread plus 30-40 g of whole-grain cereal), and the third group (n = 70) replaced three servings of refined grains with one serving of whole-wheat food plus two servings of whole-grain oats. All refined and whole grain products were provided to the subjects. Compliance was determined by dietary assessment on three occasions during the intervention period. The subjects' compliance with the diets was good. Fasting blood glucose and insulin levels were measured in order to calculate insulin resistance based on the HOMA method. There was no significant difference in fasting blood glucose levels or insulin resistance among the whole grain groups and control group.

[45] P is a measure of the statistical significance of the linear relationship between the substance and risk of the disease. For the outcome of a study to demonstrate a statistically significant difference between groups, p must be < 0.05. See *supra*, note 3 [Section III. F].

[46] A stratified sample is a sampling technique in which an investigator divides the study population into different subgroups of interest (e.g., age, sex) and then randomly selects the subjects from the different subgroups. This type of sampling is used when the investigator wants to examine specific subgroups within the population. For example, male and female subjects may respond differently to an intervention, so a study may stratify subjects by their gender. Such a study would usually ensure that similar proportion of male and female subjects are in each intervention group.

C. Assessment of the Relevant Observational Studies

FDA reviewed 40 articles[47] reporting on 41 observational studies. The articles contained a total of 44 analyses[48] evaluating the relationship between whole grain intake and risk of type 2 diabetes. Two of these articles examined more than one observational study and contained more than one analysis. Specifically, the publication by de Munter et al. (2007) evaluated the relationship between whole grain consumption and incidence of type 2 diabetes based on data from two prospective cohort studies,[49] the Nurses' Health Study I and II (NHS I, NHS II). The authors analyzed data for whole grain consumption and its association with type 2 diabetes separately for each of these studies. Sun et al. (2010) analyzed data from three prospective cohort studies, including the two reported on by de Munter et al. (NHS I and NHS II) and the Health Professionals Follow-Up Study (HPFS), to evaluate the relationship between brown rice intake and type 2 diabetes risk. In addition, Sun et al. (2010) analyzed the relationship between whole grain intake and risk of type 2 diabetes based on data from the HPFS.[50] In total, FDA evaluated 44 individual analyses from the 40 articles on 41 observational studies.

Scientific conclusions could not be drawn from 38 of the articles on observational studies[51] because the whole grain definition in these studies was not consistent with the definition of "whole grain" as set forth in your petition and discussed in Section I.A, or the study report failed to specify what foods were considered to be whole grain, or the studies evaluated dietary patterns and not only whole grains. In the majority of these studies, bran, germ, and/or dietary fiber added separately to food were considered to be part of the whole grain food group. A substance containing only parts (e.g. bran, germ or dietary fiber) of the caryopsis of a cereal grain is not whole grain because it does not consist of the intact, ground, cracked or flaked caryopsis and does not have anatomical components present in the same relative proportions as they exist in the

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[47] Anderson et al., 2012; Azadbakht et al., 2006; de Munter et al., 2007; Deshmukh-Taskar et al., 2009; Esmaillzadeh et al., 2005; Fisher et al., 2009 ; Fung et al., 2001, 2002; Ghattas et al., 2008; Hsu et al., 2008; Hur et al., 2012; Jacobs et al., 1998; Jensen et al., 2006; Kochar et al., 2007; Liese et al., 2003; Liu et al., 2000, 2009; Lutsey et al., 2007; Masters et al., 2010; McGeoch et al., 2011; McIntosh et al., 2003; McKeown et al., 2002, 2004; Meyer et al., 2000; Montonen et al., 2003; Nettleton et al., 2008a, 2008b; Newby et al., 2007; Sahyoun et al., 2006; Salmeron et al., 1997a, 1997b; Schulze et al., 2004; Steemburgo et al., 2009; Steffen et al., 2003; Stevens et al., 2002; Sun et al., 2010; Valachovicova et al., 2006; van Dam et al., 2002, 2006; Wolever et al., 1996.

[48] For purposes of this letter, FDA uses the term "analysis" to refer to a computation regarding the relationship between whole grain intake and type 2 diabetes. Some publications include multiple computations (i.e. analyses) because they use more than one set of data to examine the whole grain-diabetes relationship (e.g., data for different types of whole grains or data from more than one study).

[49] Prospective cohort studies compare the incidence of a disease in subjects who receive a specific exposure to a substance with the incidence of the disease in subjects who do not receive that exposure. See *supra,* note 3 [section III.B].

[50] Thus, FDA evaluated a total of six individual analyses from the total of three prospective cohort studies examined by de Munter et al. (2007) (2 analyses, 2 studies) and Sun et al. (2010) (4 analyses, 3 studies).

[51] Anderson et al., 2012; Azadbakht et al., 2006; Deshmukh-Taskar et al., 2009; Esmaillzadeh et al., 2005; Fisher et al., 2009; Fung et al., 2001, 2002; Ghattas et al., 2008**;** Hsu et al., 2008; Hur et al., 2012; Jacobs et al., 1998; Jensen et al., 2006; Kochar et al., 2007; Liese et al., 2003; Liu et al., 2000, 2009; Lutsey et al., 2007; Masters et al., 2010; McGeoch et al., 2011; McIntosh et al., 2003; McKeown et al., 2002, 2004; Meyer et al., 2000; Montonen et al., 2003; Nettleton et al., 2008a, 2008b; Newby et al., 2007; Sahyoun et al., 2006; Salmeron et al., 1997a, 1997b; Schulze et al., 2004; Steemburgo et al., 2009; Steffen et al., 2003; Stevens et al., 2002; Valachovicova et al., 2006; van Dam et al., 2002, 2006; Wolever et al., 1996.

intact caryopsis. Therefore, FDA could not draw scientific conclusions about the relationship between whole grain intake and risk of type 2 diabetes from these 38 studies.

There were six analyses of three observational studies evaluating the relationship between whole grain intake and risk of type 2 diabetes (de Munter et al., 2007 (examining NHS I and NHS II); and Sun et al., 2010 (examining HPFS, NHS I, and NHS II)) from which scientific conclusions could be drawn. As mentioned above, the HPFS study reported by Sun et al. (2010) included analyses of two diet-disease relationships: (1) the relationship between intake of whole grains, which include brown rice, and risk of type 2 diabetes, and (2) the relationship between brown rice intake and risk of type 2 diabetes.

The article by de Munter et al. (2007) analyzed data from two prospective cohort studies to evaluate whole grain intake and incidence of type 2 diabetes. These studies were of high methodological quality. NHS I followed 73,327 women (37- 65 years old), and NHS II followed 88,410 women (26 – 46 years old). NHS I and II identified 4,747 and 1,739 cases of type 2 diabetes, respectively. In their analysis, de Munter et al. defined whole grains to include both intact and pulverized forms containing the expected proportion of bran, germ and endosperm for the particular type of grain. Whole grain intake from all sources was assessed using a validated food frequency questionnaire. Data for each cohort were analyzed for different quintiles (Q) of whole grain intake, with Q1 representing the lowest quintile of whole grains intake and Q5 the highest.[52] In NHS I, after adjustment for appropriate confounders including BMI, higher whole grain intake was associated with a significant reduction in risk of type 2 diabetes for the three highest quintiles of intake (median intake of 13.2 g/day or higher). Specifically, relative risk (RR)[53] and confidence intervals (CI)[54] were 0.84 (0.77 - 0.92), 0.79 (0.72 - 0.87), and 0.75 (0.68 - 0.83) in Q3 (median whole grain intake 13.2 g/day), Q4 (19.5 g/day) and Q5 (31.2 g/day), respectively, when compared to Q1 (3.7 g/day). The RR and CI for Q2, which did not show a significantly reduced risk of type 2 diabetes compared to Q1, were 0.92 (0.84 -1.00), and median whole grain intake for Q2 was 8.4 g/day.

In NHS II, after adjustment for all relevant confounders including BMI, de Munter et al. observed a significant association between whole grain intake and reduced risk of type 2 diabetes in Q4 (26.1 g/day) compared to Q1 (6.2 g/day) (RR = 0.81 (0.69 -0.95)). However, no significant association between whole grain intake and risk of type 2 diabetes was observed in the highest quintile of intake, Q5 (39.9 g/day), compared to Q1 (RR = 0.86 (0.72 - 1.02)).[55]

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[52] In the NHS I, the numbers of cases of type 2 diabetes in the lowest to the highest quintiles (Q1 to Q5) were 1,036, 1,064, 984, 905 and 758, respectively. In the NHS 2, the numbers of cases from the lowest to the highest quintiles (Q1 to Q5) were 436, 395, 359, 297 and 252, respectively.

[53] Relative risk is expressed as the ratio of the risk (e.g., incidence of the disease) in exposed individuals (e.g., individuals who consume whole grains) to that in unexposed individuals (e.g., individuals who do not consume whole grains) (Epidemiology: Beyond the Basics, page 93, Aspen Publishers, 2000).

[54] Confidence intervals are ranges that provide a statistical analysis of comparative measures of risk (e.g., relative risk, odds ratio and hazard ratio). Confidence intervals are significant when the entire range is less than or greater than "1" (e.g., 0.7-0.9 or 1.1-1.5). If the confidence interval includes "1" within its range, then it cannot be concluded that a relationship exists between the substance and the disease. See *supra*, note 3 [Section III. F].

[55] The article by de Munter et al. focuses on the reduced risk of type 2 diabetes shown for Q5 as compared to Q1 before adjustment for BMI (RR = 0.68 (CI 0.57-0.81)). This reduction in risk was significant (see explanation of confidence intervals and statistical significance in note 54). The article does not acknowledge that the reduction in

Similarly, no significant association between whole grain intake and type 2 diabetes risk was observed in Q2 (12.6 g/day) (RR = 0.94 (0.82-1.08)), or Q3 (18.6 g/day) (RR = 0.90 (0.78-1.08)) compared to Q1.[56] Thus, unlike NHS I, NHS II did not suggest the existence of a consistent dose-response relationship between whole grain intake and reduction in risk of type 2 diabetes.

Sun et al. (2010) analyzed data from the HPFS, NHS I, and NHS II studies to evaluate the relationship between consumption of brown rice (a whole grain) and incidence of type 2 diabetes. These studies were of high methodological quality and followed 39,675 men (32- 87 years old) from the HPFS; 69,120 women (37 - 65 years old) from NHS I; and 88,343 women (26 - 45 years old) from NHS II. The numbers of type 2 diabetes cases in these studies were 2,648 (HPFS), 5,500 (NHS I), and 2,359 (NHS II). In NHS I, after adjustment for appropriate confounders, there was a significant association with reduced risk of type 2 diabetes for those who consumed from 1 serving/month to 1 serving/week of brown rice compared to those at the lowest level of intake (< 1 serving/month) (RR = 0.92 (0.87 – 0.98)), as well as for those who consumed ≥ 2 servings/week compared to those at the lowest level of intake (RR = 0.83 (0.72 – 0.96)). There was no significant association between brown rice consumption and incidence of type 2 diabetes in NHS II or HPFS.[57] Sun et al. also analyzed intake of all whole grains using the

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risk for Q5 becomes non-significant after adjustment for BMI (RR = 0.86 (0.72 - 1.02)), though it does note that adjusting for BMI substantially weakens the association between whole grain intake and reduced risk of type 2 diabetes. FDA considers the non-significant result after adjustment for BMI to be the finding most relevant to our evaluation because BMI is a known confounder for type 2 diabetes, meaning that lower BMI is known to be associated with a lower risk of type 2 diabetes. See National Diabetes Education Program, "Diabetes Risk Factors" [http://ndep.nih.gov/am-i-at-risk/DiabetesRiskFactors.aspx (accessed July 23, 2013)]; NIH, National Diabetes Information Clearinghouse, "Am I at Risk for Type 2 Diabetes? Taking Steps to Lower Your Risk of Getting Diabetes" [http://diabetes.niddk.nih.gov/dm/pubs/riskfortype2/index.aspx#11 (accessed August 27, 2013)]. Therefore, if the data are not adjusted to account for differences in BMI among the subjects, observed effects on risk of type 2 diabetes that may be due to differences in BMI may be incorrectly attributed to differences in intake of whole grains. See *supra* note 3 [section III.E].

[56] In discussing the article by de Munter et al. (2007), the petition states that a two serving/day increment in whole grain consumption was associated with a 21% decrease in the risk of type 2 diabetes (pooled RR = 0.79 (0.72 - 0.87)). This result is not based on the findings of the NHS 1 and NHS 2 studies alone, but on a meta-analysis included in the same article by de Munter et al. The meta-analysis included pooled data from NHS I, NHS 2, and four other studies (Fung et al., 2002; Meyer et al., 2000; Montonen et al., 2003; van Dam et al., 2006). Consistent with FDA's practice of evaluating individual studies used in meta-analyses, the agency reviewed each of the other four studies separately. These four studies did not meet FDA's criteria for studies from which scientific conclusions about risk of type 2 diabetes can be drawn, and thus the results from these studies were not considered in FDA's evaluation. The reasons for exclusion of each of these studies are noted earlier in this section.

[57] In addition to reporting results from the three individual studies (NHS I, NHS 2, and HPFS), the article by Sun et al. (2010) also included results from a meta-analysis of pooled data from all three studies. The meta-analysis applied statistical modeling and used various assumptions to generate percentage estimates of the reduction in risk of type 2 diabetes that would be associated with replacing a specified amount of white rice with either brown rice or whole grains (which include brown rice). In discussing the results reported by Sun et al. (2010), the petition states that high brown rice intake (≥2 servings per week vs. < 1 per month) was associated with a lower risk of type 2 diabetes (pooled RR = 0.89 (0.81 – 0.97)). This result is based on the authors' meta-analysis of pooled data from the three studies. The petition also cites the authors' estimates, based on statistical modeling and assumptions, that replacing 50 g/day intake of white rice with the same amount of brown rice was associated with a 16% lower risk of type 2 diabetes (pooled RR = 0.84 (CI 0.79 - 0.91)), whereas the same replacement with whole grains as a group was associated with a 36% lower risk (pooled RR = 0.64 (CI 0.58 - 0.70)). Because FDA evaluates data reported in individual studies and not meta-analyses of pooled data or data based on statistical modeling and assumptions, the agency did not consider the results from the meta-analysis in its scientific evaluation. See also *supra*, note 9.

same definition as de Munter's. Because the NHS I and NHS II studies had only female subjects and therefore the analysis by de Munter et al. (2007) did not report on the relationship between whole grain intake and incidence of type 2 diabetes in men, Sun et al. evaluated this relationship in the HPFS study, in which the subjects were all male. After adjustment for appropriate confounders, there was a significant association between quintiles of whole grain intake and reduced risk of type 2 diabetes in Q2 (12.6 g/day) (RR = 0.82 (0.73-0.92)), Q3 (20.4 g/day) (RR = 0.86 (0.77 – 0.97)), Q4 (29.9 g/day) (RR = 0.78 (0.69 – 0.88)) and Q5 (47.1 g/day) (RR = 0.72 (0.63 - 0.83)) compared to Q1(5.1 g/day) of whole grain intake.[58]

D. Dietary Guidelines for Americans, 2010

FDA also considered the review on whole grain intake and type 2 diabetes that was conducted by the USDA Nutrition Evidence Library (USDA NEL, 2010) for the 2010 Dietary Guidelines for Americans Advisory Committee (DGAC) and summarized in the DGAC report (DGAC, 2010), as well as in the Dietary Guidelines for Americans, 2010 (DGA, 2010).[59] Because of its earlier cut-off date, the review conducted for the Dietary Guidelines for Americans, 2010 did not include several more recent intervention and observational studies whose results were considered in FDA's review (i.e., Giacco et al., 2010; Sun et al., 2010; Tighe et al., 2010). Based on the USDA Nutrition Evidence Library review, the DGAC concluded that the evidence for whole grain intake and reduced risk of type 2 diabetes was "limited," the lowest rating available (DGAC, 2010).

III. Strength of the Scientific Evidence

Below, the agency rates the strength of the total body of publicly available evidence. The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the number of studies and number of subjects per group, whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated,[60] and the overall consistency[61] of the total body of evidence. Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support a qualified health claim for the substance/disease relationship and, if so, considers what qualifying language should be included to convey the limits on the level of scientific evidence supporting the relationship or to prevent the claim from being misleading in other ways.

As discussed in section II, the evidence for a relationship between whole grain intake and type 2 diabetes risk is based on six intervention studies (Andersson et al., 2007; Brownlee et al., 2010;

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[58] The numbers of cases of type 2 diabetes in the lowest to the highest quintiles (Q1 to Q5) were 667, 574, 559, 475 and 373, respectively.

[59] Details of the Nutrition Evidence Library review are provided at http://nel.gov/conclusion.cfm?conclusion_statement_id=250212.

[60] See *supra*, note 11.

[61] See *supra*, note 12.

Giacco et al., 2010; Rave et al., 2007; Saltzman et al., 2001; Tighe et al., 2010) and two publications that together contain a total of six analyses of three prospective cohort studies (de Munter et al., 2007; Sun et al., 2010).

Of the six intervention studies evaluated, five studies reported no significant association between whole grain intake and incidence of type 2 diabetes (Andersson et al., 2007; Brownlee et al., 2010; Giacco et al., 2010; Saltzman et al., 2001; Tighe et al., 2010). One intervention study reported that consuming a double-fermented whole grain wheat meal replacement significantly reduced insulin resistance compared to a meal replacement containing no whole grains (Rave et al., 2007).

The five intervention studies that did not show a significant relationship between whole grain intake and reduction in risk of type 2 diabetes were of moderate or high methodological quality, and consisted of randomized, controlled trials. Both Brownlee et al. (2010) and Tighe et al. (2010) were randomized, controlled trials of high methodological quality with the longest study duration (16 weeks and 12 weeks, respectively) and the largest number of subjects. Brownlee et al. (2010) had 266 subjects, with about 80 to 100 in each of three groups; Tighe et al. (2010) had 206 subjects, with about 70 per group. Both studies included both men and women. All five of the intervention studies that showed no significant relationship between whole grain intake and type 2 diabetes studied types of whole grain products (e.g., whole wheat bread, oatmeal) that U.S. consumers of whole grain products typically purchase (Kranz et al., 2013).

Rave et al. (2007) was a six-week randomized, controlled cross-over weight loss study of moderate methodological quality. After adjustment for the amount of weight loss, there was no significant reduction in fasting blood glucose in the whole grain group as compared to the control group, but a significant improvement in insulin resistance was observed in the whole grain group as compared to control ($P<0.049$). However, there are serious doubts about this study's applicability to whole grain consumption in the general U.S. population. The whole grain product in this study was a dry powder derived from double-fermented wheat and was consumed in large quantities (total of 200 g/day) as a meal replacement. Study subjects were instructed to dissolve the powder in water, milk, or yogurt and replace at least two of their daily meals with the resulting mix. This product is significantly different from the whole grain products available to consumers for purchase in the U.S. marketplace. Commonly available whole grain products in the U.S. marketplace are neither double fermented, nor in powder form (Kranz et al., 2013). Also, since the study subjects followed a diet designed to cause weight loss, the study does not rule out the possibility that the benefit would only be observed during a period of caloric reduction, such as dieting, and not when whole grains are consumed as part of a weight maintenance or high-calorie diet.

Among the observational studies from which scientific conclusions could be drawn, the results of the six analyses of three prospective cohort studies were mixed. All three prospective studies showed a significant association between whole grain intake and reduced risk of type 2 diabetes (de Munter et al., 2007 (NHS I and NHS II); Sun et al., 2010 (HPFS)). However, when Sun et al. (2010) analyzed the relationship between brown rice consumption and incidence of type 2 diabetes in the same three prospective cohort studies (NHS I, NHS II, and HPFS), the only study that showed a significant association between brown rice intake and reduced risk of type 2

diabetes was the NHS I. No association between brown rice intake and risk of type 2 diabetes was found in the NHS II or the HPFS. Thus, the findings of the brown rice studies were not consistent.

In general, results from large, well-designed, randomized, controlled intervention studies provide the strongest evidence for the claimed effect, regardless of existing observational studies on the same relationship. Intervention studies are designed to avoid selection bias and avoid findings that are due to chance or other confounders of disease (Sempos et al., 1999). Although the evaluation of substance/disease relationships often involves both intervention and observational studies, observational studies generally cannot be used to rule out the findings from more reliable intervention studies (Sempos et al., 1999). One intervention study would not be sufficient to rule out consistent findings of observational studies. However, when several randomized, controlled intervention studies are consistent in showing or not showing a substance/disease relationship, they trump the findings of any number of observational studies (Barton, 2000). This is because intervention studies are designed and controlled to test whether there is evidence of a cause and effect relationship between the substance and the reduced risk of a disease, whereas observational studies are only able to identify possible associations.[62] There are numerous examples -- such as vitamin E and CVD and beta-carotene and lung cancer -- where associations identified in observational studies have been publicized. However, when randomized, controlled intervention studies were later conducted to test these possible associations, the intervention studies found no evidence to support the relationships (Lichtenstein and Russell, 2005).

Consistency of findings among similar and different study designs is important for evaluating the strength of the scientific evidence.[63] The majority of the intervention studies included in FDA's evaluation did not show a significant relationship between whole grain consumption and reduced risk of type 2 diabetes. Only one intervention study (Rave et al., 2007) showed a significant relationship; however, it is doubtful whether the results of that study apply to the general U.S. population because the powdered, double-fermented wheat product tested in that study is markedly different in composition and conditions of use from whole grain products typically used in the U.S. Further, the reported individual findings of Rave et al. (2007) have not been replicated in any other intervention studies, and replication of scientific findings is important in order to substantiate results.[64]

In summary, there are four analyses of three observational studies and one intervention study supporting an association between whole grains and reduced risk of type 2 diabetes, while five intervention studies and two additional analyses of observational studies found no evidence of such a relationship. Among the observational studies, the results of analyses examining intake of whole grains of all types were generally consistent, with three analyses finding a significant association between whole grain consumption and reduced risk of type 2 diabetes at some level of intake. However, of the analyses that were limited to brown rice, only one of three analyses found a significant association between brown rice intake and reduced risk of type 2 diabetes. Based on the above findings of intervention and observational studies, FDA concludes that,

[62] See *supra*, note 3 [Section III.F].
[63] See *supra*, note 3 [Section III.F] and note 12.
[64] See *supra*, note 11.

although a minority of credible studies suggest the existence of a link between whole grain intake and type 2 diabetes risk, the scientific evidence does not consistently show that whole grain intake reduces the risk of type 2 diabetes.

In addition to these individual studies, FDA also considered the evaluation of whole grains and risk of type 2 diabetes that was done as part of the development of the Dietary Guidelines for Americans, 2010. Based on the USDA Nutrition Evidence Library review, the DGAC concluded that there was limited evidence[65] showing an association between whole grain consumption and reduced incidence of type 2 diabetes in large prospective cohort studies (DGAC, 2010).[66] "Limited" is the lowest grade of evidence assigned by the DGAC[67] and reflects either a small number of studies, studies of weak design, and/or inconsistent results (DGA, 2010).

FDA agrees with the DGAC that the limitations of the evidence suggesting a relationship between whole grain intake and reduced risk of type 2 diabetes justify the DGAC's lowest grade for strength of the evidence. In fact, taking into account the DGAC's findings and the additional studies FDA reviewed, the agency concludes that the evidence supporting a risk reduction relationship, while credible, falls near the lower end of the "limited" category and should be described as "very limited" in food labeling to avoid misleading consumers. The sole intervention study suggesting a causal relationship, Rave et al. (2007), is not well suited to assessing whether whole grain foods commonly consumed in the U.S. reduce the risk of type 2 diabetes, as it examined the effects of a whole grain product in an unusual form (powdered mix containing double-fermented whole wheat), at a very high intake level (200 g/day), and under atypical conditions of use (meal replacement to be mixed with a liquid and substituted for two of the day's three meals). Moreover, the results of relevant studies are not consistent within or across study types, and the prospective cohort studies suggesting a link between whole grain intake and reduced risk of type 2 diabetes are undermined by several randomized, controlled intervention studies that measured surrogate endpoints of type 2 diabetes risk and found that whole grain intake had no effect.

Based on the above, FDA concludes that there is very limited credible evidence for a relationship between whole grain consumption and reduced risk of type 2 diabetes.

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[65] The DGAC approved the use of five criteria to grade the strength of the evidence supporting each of its conclusions on topics for which it conducted a systematic review of the evidence. These criteria are as follows: quality of studies; quantity of studies and subjects, consistency of finding across studies, the magnitude of effect, and generalizability of findings. 2010 DGAC Conclusion Chart (http://www.nel.gov/topic.cfm?cat=3210).

[66] See *supra*, note 59.

[67] There are three grades of evidence in *Dietary Guidelines for Americans, 2010*: "strong", "moderate", and "limited." "Limited" is the lowest grade for the strength of the evidence in the USDA Nutrition Evidence Library review system used by the 2010 Dietary Guidelines for Americans Advisory Committee. 2010 DGAC Conclusion Chart (http://www.nel.gov/topic.cfm?cat=3210).

IV. Other Enforcement Discretion Factors

A qualified health claim about reduced risk of type 2 diabetes on the label or in the labeling of whole grain foods is required to meet all applicable statutory and regulatory requirements under the Federal Food, Drug, and Cosmetic Act, with the exception of the requirement that a health claim meet the significant scientific agreement standard, the requirement that the claim be made in accordance with an authorizing regulation, and the qualifying level requirement discussed below in section IV.B.

A. Saturated fat and cholesterol

Your petition proposed model claim language limiting the relationship between whole grain intake and reduced risk of type 2 diabetes to whole grains consumed as part of a diet low in saturated fat and cholesterol. In addition, your petition requested that products that contain other ingredients in addition to whole grains be eligible to bear a qualified health claim about whole grains and reduced risk of type 2 diabetes only if they are "low saturated fat" and "low cholesterol" as defined in 21 CFR 101.62. However, in the studies that form the basis for substantiating the claim, the association between whole grain intake and reduced risk of type 2 diabetes was not limited to diets low in saturated fat and cholesterol or foods low in saturated fat and cholesterol. Thus, the association between whole grain intake and reduced risk of type 2 diabetes observed in these studies was not dependent on the saturated fat or cholesterol content of the diets. Therefore, FDA is not requiring individual foods to meet the regulatory definition of "low" for saturated fat or cholesterol to be eligible to bear the claim. Furthermore, FDA does not intend to exercise enforcement discretion for any statement in the qualified health claim that limits the claim to diets low in saturated fat and cholesterol.

B. Qualifying level of whole grains

The general requirements for health claims provide that, if the claim is about the effects of consuming the substance at other than decreased dietary levels, the level of the substance must be sufficiently high and in an appropriate form to justify the claim. Where no definition for a "high" level of the substance has been established, the claim must specify the daily dietary intake necessary to achieve the claimed effect (see 21 CFR 101.14(d)(2)(vii)).

Although your petition does not propose a qualifying level of whole grains for products that consist entirely of whole grains, it does propose a qualifying level of whole grains for a category you describe as "whole grain-containing products." Specifically, you propose that such products be eligible to bear your requested claim about reducing the risk of type 2 diabetes only if they provide at least 12g whole grains per Reference Amount Customarily Consumed (RACC). In deriving this proposed qualifying level, it appears that you adopted FDA's rule of thumb, used in a number of health claim rulemaking proceedings,[68] that a food bearing a health claim should provide at least one-quarter of the daily intake amount shown to be associated with a reduction in risk, which you estimate to be 48g/day. According to the petition, you determined the 48g daily intake amount by averaging the highest whole grain intake levels associated with reduced risk of

[68] See, e.g., 62 FR 3584 at 3592 (Jan. 23, 1997).

type 2 diabetes in the prospective cohort studies relied on as supporting evidence in your petition. Although the petition is not entirely clear on this point, it appears that you determined that the average of the highest whole grain intake levels in the prospective cohort studies that observed a whole grain effect on type 2 diabetes incidence was approximately 2.22 servings per day, and you then rounded this average to three servings per day. Using a common food industry measure of 16g as the weight of a serving of whole grains,[69] you further calculated that three servings per day would amount to a total daily whole grain intake of 48g (3 servings/day × 16g).

FDA finds that the regulation requiring that the level of the substance be sufficiently high should not be applied to the qualified health claim for whole grains and reduced risk of type 2 diabetes because the very limited scientific evidence for this relationship does not support the establishment of a recommended daily dietary intake level or even a possible level of effect for the general U.S. population. The findings of the sole intervention study that showed a risk reduction effect may not be generalizable to the U.S. population because that study involved an unusual form of whole grains (a powder made from double-fermented wheat), a very high level of intake (200 g/day), and atypical conditions of use (replacing two meals every day with a mix of the fermented whole-wheat powder and milk or water). Moreover, the prospective cohort studies that supply the bulk of the credible evidence to support a qualified health claim did not show a consistent dose-response relationship or threshold level of effect. In the case of the prospective cohort studies that looked at brown rice intake, the studies did not show a consistent association between brown rice at any level of intake and reduced risk of type 2 diabetes. In light of these limitations in the evidence, FDA does not have a sufficient basis to quantify an amount of whole grains that a food must contain to bear a claim about reduced risk of type 2 diabetes. Further, specifying a recommended daily intake level of whole grains to be included in the claim language based on so few studies would imply more consistency in the studies and more certainty about the level of effect than exists. Accordingly, the agency is not specifying any minimum level of whole grain content to be considered as a factor in the exercise of its enforcement discretion for a qualified health claim about whole grain intake and reduced risk of type 2 diabetes, nor is the agency including the petitioner's proposed language tying the risk reduction effect to three servings (48 g) of whole grains in the qualified health claim.

The petition requested that FDA allow the claim to be made on whole grains and on foods that contain whole grains in combination with significant amounts of other ingredients ("whole grain-containing foods"). You describe this category as food products that contain whole grains in varying amounts, with significant amounts of other ingredients. FDA's 2006 draft guidance recommends that foods made with flour (e.g., pizza or bagels) be labeled as whole grain only if the flour used is entirely whole grain.[70] The draft guidance explains that "whole grain" label statements on foods may be understood to mean that the food is 100% whole grain, and therefore may mislead consumers about whole grain content when they appear in the labeling of foods that contain ingredients made from refined grains as well as whole-grain ingredients. The agency continues to be concerned about the misleading use of "whole grains" claims in food labeling. Accordingly, FDA intends to consider the exercise of its enforcement discretion for a qualified

[69] See e.g., Whole Grains Council, "What Counts as a Serving?" [http://wholegrainscouncil.org/whole-grains-101/what-counts-as-a-serving (accessed July 23, 2013)].
[70] See *supra*, note 14.

health claim for whole grains and type 2 diabetes in the labeling of a food that bears a "whole grain" statement only when all of the food's grain ingredients are whole grain as defined in Section I.A of this letter. The agency also intends to consider the exercise of its enforcement discretion for use of the qualified health claim on foods that contain a mixture of whole grain and refined grain ingredients and are not labeled as "whole grain," but in that situation, the agency would look at the whole grain content of the food and monitor for any misleading use of the claim. FDA would similarly monitor, and evaluate for possible enforcement action, situations where foods that bear the qualified health claim contain grain ingredients that are entirely whole grain but are present in trivial amounts. Misleading labeling statements cause a food to be misbranded under section 403(a)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 343(a)(1)).

V. Conclusions

Based on FDA's consideration of the scientific evidence submitted with the petition and other pertinent scientific evidence, FDA concludes that there is very limited credible scientific evidence for a qualified health claim for whole grains and type 2 diabetes, provided that the qualified claim is appropriately worded so as not to mislead consumers.

Thus, FDA intends to consider exercising its enforcement discretion for the following qualified health claims:

> "Whole grains may reduce the risk of type 2 diabetes, although the FDA has concluded that there is very limited scientific evidence for this claim."
>
> "Whole grains may reduce the risk of type 2 diabetes. FDA has concluded that there is very limited scientific evidence for this claim."

When all factors for enforcement discretion identified in Section IV of this letter are met, FDA intends to consider exercising its enforcement discretion for the above qualified health claims in the labeling of foods whose grain ingredients consist solely of whole grains as defined in Section I.A.

Please note that scientific information is subject to change, as are consumer consumption patterns. FDA intends to evaluate new information that becomes available to determine whether it necessitates a change in this decision. For example, scientific evidence may become available that will support significant scientific agreement, that will support a qualified health claim for claims that were denied, that will no longer support the use of the above qualified health claims, or that may raise safety concerns about the substances that are the subject of the claims.

Sincerely,

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Center for Food Safety
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