

December 12, 2016

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RE: Petition for a Health Claim for High-Amylose Maize Starch (Containing Type-2 Resistant Starch) and Reduced Risk Type 2 Diabetes Mellitus (Docket Number FDA-2015-Q-2352)

Dear Dr. Hoadley:

This letter responds to the health claim petition received on March 30, 2015 by the Food and Drug Administration (FDA or the agency), submitted on behalf of Ingredion Incorporated pursuant to § 403(r)(4) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 343(r)(4)). The petitioner requested that the agency authorize a health claim for the relationship between the consumption of high-amylose maize starch and reduced risk of type 2 diabetes mellitus (type 2 diabetes). The petition proposed the following language for an authorized health claim for conventional foods: “Consumption of high-amylose maize resistant starch may reduce the risk of type 2 diabetes” and “Consumption of high-amylose maize resistant starch, a type of dietary fiber, may reduce the risk of type 2 diabetes.”

FDA evaluated the scientific evidence provided with the petition and other evidence related to your claim. Based on this review, FDA determined that the scientific evidence supporting the proposed health claim did not meet the “significant scientific agreement” standard necessary to bear a health claim. FDA received a letter from EAS Consulting Group, LLC (EAS) on July 1, 2015 stating “At this time the petitioner is requesting that FDA consider using their enforcement discretion authority to allow a qualified health claim for the relationship between consumption of high-amylose maize starch and reduced risk of type 2 diabetes.” FDA considers this request to be a substantive amendment to the March 2015 health claim petition that revises the initial request to review the claim under the significant scientific agreement standard in section 403(r)(3)(B) of the Act, and instead review the claim as a qualified health claim. Thus, FDA filed the petition on July 8, 2015 as a qualified health claim petition and posted it on the Regulations.gov website for a 60-day comment period, consistent with the agency’s guidance for procedures on qualified health claims.¹ The agency received two comments that supported the claim.

¹ See FDA “Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements” (July 10, 2003)

This letter sets forth the basis of FDA’s determination that the current scientific evidence regarding the relationship between high-amylose maize starch and reduced risk of type 2 diabetes is appropriate for consideration of a qualified health claim on conventional foods. In addition, this letter sets forth (in the “Conclusions” section) qualified health claim language for which FDA intends to exercise enforcement discretion. This letter also sets forth the factors that FDA intends to consider in the exercise of its enforcement discretion for a qualified health claim with respect to the consumption of high-amylose maize starch and a reduced 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 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*

[<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm053832.htm>].

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).

³ See FDA, “Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims - Final,” January 2009.

[<http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm073332.htm> (accessed April 15, 2016)]

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.

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 publications⁸ 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 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.

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

⁹ Certain meta-analyses may be used as part of the health claim review process. See *supra*, note 3 [Section III.B, “Research Synthesis Studies”].

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 supporting the proposed claim have been replicated,¹¹ and the overall consistency¹² 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 a dietary supplement (21 CFR 101.14(a)(2)).

The substance that is the subject of the petition is high-amylose maize (HAM) starch, containing 50 percent or more type 2 resistant starch that is unmodified and has only been subject to conventional milling practices (hereafter referred to as “HAM starch”). HAM starch is a component of corn and is a complex carbohydrate composed of linear glucose chains known as

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

¹¹ Replication of scientific findings is important for evaluating the strength of scientific evidence (Wilson, 1990).

¹² Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill, 1965); 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].

amylose and branched glucose chains known as amylopectin. A typical amylose:amylopectin ratio is 1:4, and HAM starch is a hybrid of corn that has a higher percentage of amylose starch than traditional corn. The petitioner noted that they used the term maize instead of corn starch to emphasize that the high amylose starch content of this corn makes this corn starch nutritionally distinct from typical corn starch. FDA has established Daily Values (DV) for carbohydrates for the purpose of nutrition labeling and concludes that HAM starch containing 50 percent or more type 2 resistant starch that is unmodified and has only been subject to conventional milling practices, as identified in the petition, is a component of food. Therefore, the agency concludes HAM starch as identified in the petition meets 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.¹⁴ 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 8 hours; or 3) an oral glucose tolerance test (OGTT) 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 (sugar) levels (fasting blood glucose of > 100 mg/dL and < 126 mg/dL)¹⁵ or a OGTT test plasma glucose value of > 140 mg/dL and < 199 mg/dL, and/or insulin resistance¹⁶ are considered risk factors for type 2 diabetes.¹⁷ 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.

¹⁴ National Institutes of Health (NIH), "Diabetes" [<http://www.niddk.nih.gov/health-information/health-topics/Diabetes/Pages/default.aspx> (accessed December 1, 2016)].

¹⁵ National Diabetes Education Program, "Risk Factors for Type 2 Diabetes" [<http://ndep.nih.gov/am-i-at-risk/DiabetesRiskFactors.aspx> (accessed December 1, 2016)]. Also see NIH, "Insulin Resistance and Prediabetes."

¹⁶ 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 December 1, 2016)].

¹⁷ NIH, National Diabetes Information Clearinghouse, "Insulin Resistance and Prediabetes." [<http://diabetes.niddk.nih.gov/dm/pubs/insulinresistance/index.aspx> (accessed December 1, 2016)]

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 or a food ingredient or a component of a food ingredient 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 substance, which is either a food or an 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)).

The petitioner noted that unmodified food starches, including HAM starch containing 50 percent or more type 2 resistant starch that is unmodified and has only been subject to conventional milling practices, are foods of natural biological origin (e.g. a component of corn) that have been commercially available and widely consumed for their nutrient properties prior to January 1, 1958, without known detrimental effects, and for which no known safety hazards exist. The petition also pointed out that corn starch that has been subject to conventional wet grain milling processing, as practiced prior to January 1, 1958, is consistent with FDA's definition of food ingredients ordinarily regarded as GRAS (21 CFR 170.30(d)). Therefore, FDA concludes, that the proponent of the claim has demonstrated to FDA's satisfaction that the preliminary requirements of 21 CFR 101.14(b)(3)(ii), have been met.

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 (FBG), OGTT, and insulin resistance. Therefore, to evaluate the potential effects of high amylose maize (HAM) starch (HAM starch), containing type 2 resistant starch (RS2) consumption on type 2 diabetes risk, FDA considered these four endpoints as indicators or predictors of type 2 diabetes. Insulin resistance is assessed by various measurements of insulin sensitivity,¹⁸ including the euglycemic hyperinsulinemic clamp method; insulin modified frequently sample intravenous glucose tolerance test (FSIVGTT); and homeostasis model assessment (HOMA).

The petition provided 58 publications as evidence to substantiate the relationship for the proposed claims (See Docket Number FDA-2015-Q-2352). Out of these 58 publications, 26 human intervention studies were included in evaluating the relationship between intake of HAM

¹⁸ Insulin sensitivity is the degree to which how effective the body is in using insulin to reduce elevated blood glucose levels. The greater efficacy means more sensitivity, while poorer efficacy indicates being more resistant. Reduced insulin sensitivity means increased resistance to insulin.

starch and risk reduction of type 2 diabetes. In addition to 26 individual intervention studies, the petition cited eight review articles on various topics, such as nutrition implications of resistance starch, the digestibility resistant starch in the human intestine, review of β -cell function, insulin sensitivity, and new paradigms on the treatment of type 2 diabetes (Asp et al., 1996; Bergman et al., 1985; 2002, Brown et al., 1995; DeFronzo, 2009; Englyst and Cummings, 1985, 1992; Huckling et al., 2008), one letter to the editor of a journal (Reaven., 2013), one book chapter (Farris, 1965), two animal studies (Ader et al., 2014; Nyman and Asp, 1982), six studies on various methodologies used for assessment of insulin resistance, insulin sensitivity, fibers in food, or AOAC methods for measuring dietary fiber (AOAC international, 2012; Bergman et al., 1987; Bergman, 2007; DeFronzo et al., 1979; McCleary and Monaghan, 2002; Pacini and Bergman, 1986), three government documents or monograph (FDA, 1985; Food Starch-Unmodified Monograph, 2014; Select Committee on GRAS Substance, 1979), three studies on diabetes trends or resistant starch intake (CDC 2014; Murphy et al., 2008; NDIC, 2014), five studies using incorrect surrogate endpoints or that evaluated diseases or substances that are not subject of the health claim (Brighenti et al., 2006; de Roos et al., 1995; Hylla et al., 1998; Lobleby et al., 2013; Muir et al., 2004), and three studies that were conducted on diseased populations (Bodinham et al., 2014; MacNeil et al., 2013; Zhang et al., 2007).

In addition to the publications cited in the petition, we received two comments from consumers supporting the petition.

We did not identify additional relevant studies through a literature search evaluating the relationship between intake of HAM starch containing RS2 and risk of type 2 diabetes.

A. Assessment of Review Articles and Similar Publications

Although useful for background information, review articles and other similar publications¹⁹ (some of which were submitted with this petition) 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 (e.g., the composition of “HAM starch”) from the review articles and other similar publications submitted with the petition. Similarly, the lack of detailed information on studies summarized in the review articles 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 other similar publications did not provide information from which scientific conclusions can be drawn regarding the substance-disease relationship claimed by the petitioner.

B. Assessment of Animal Studies

¹⁹ See, *supra*, note 8.

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, and they can also be used to generate hypotheses or to explore a mechanism of action, but they cannot adequately support a relationship between the substance and the disease in humans. FDA did not consider the animal or in vitro studies cited with the petition as providing any supportive information about the substance-disease relationship because such studies cannot mimic the normal human physiology that may be involved in the risk reduction of type 2 diabetes, nor can the studies mimic the human body's response to the consumption of HAM starch. Therefore, FDA could not draw any scientific conclusions regarding HAM starch intake and the reduction of risk of type 2 diabetes from the animal studies cited in the petition.

B. Assessment of Intervention Studies

FDA evaluated 26 reports of intervention studies that were designed to evaluate the relationship between HAM starch intake and risk reduction of type 2 diabetes. One of the studies was a correction for another published study (Johnston, 2015). Of the 25 intervention studies reviewed, scientific conclusions could not be drawn from 17 studies. For 14 of the studies, either a meal tolerance test (MTT) was performed or the study duration was too short (approximately 30 minutes to one day intake) to provide any information about the longer-term effect of HAM starch intake on risk of type 2 diabetes.²⁰ Such MTT and short-term studies are designed to assess the glycemic index²¹ 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 HAM starch 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. One study did not conduct statistical analysis between the control and resistance starch group at the end of the study period (Park et al., 2004). Statistical analysis between the two groups is a critical factor because it provides the comparison between subjects consuming HAM starch and those not consuming the resistance starch to determine whether there is a reduction in risk of type 2 diabetes. When statistics are not performed on the specific substance/disease relationship, it cannot be determined whether there is a difference between the two groups (Spilker, 1991). In one study the exact amount of HAM starch and the amount of RS2 it contributed were not provided (Behall et al., 1989). In another study, HAM starch contained only about 33% of RS2 (Noakes et al., 1996). As discussed above, the substance that is the subject of the petition is HAM starch containing 50 percent or more RS2. We could not determine the amount of HAM starch or RS2 in Behall et al. (1986), and the amount of RS2 in HAM starch in Noakes et al. (1996) was not at a level of at least 50 percent. For these reasons,

²⁰ Anderson et al., 2010; Behall and Hallfrisch 2002; Behall and Howe (1995); Behall et al., 2006; Ekstrom et al., 2013; Granfeldt et al., 1995; Heijnen et al., 1995; Howe et al., 1996; MacNeil et al., 2013; Nilsson et al., 2008; Quilez et al., 2007; Reiser et al., 1989; Robertson et al., 2003; Weickert et al., 2005).

²¹ 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).

we could not consider these two studies. In general, these 17 studies provided no information about how HAM starch may reduce the risk of type 2 diabetes; hence, no scientific conclusions could be drawn from these studies.

Based on the above discussion, there were 8 intervention studies available from which scientific conclusions could be drawn about the relationship between the intake of HAM starch containing RS2 and the reduced risk of type 2 diabetes (Bodenham et al., 2012; Dainty et al., 2016; Gower et al., 2016; Johnston et al., 2010; Maki et al., 2012; Penn-Marshall et al., 2010; Robertson et al., 2005, 2012). Each of these studies is discussed in turn below.

Bodenham et al. (2012) was a single-blind, placebo-controlled, randomized crossover study of moderate methodological quality in which 12 insulin resistant, overweight (body mass index (BMI) $28.2 \pm 0.4 \text{ kg/m}^2$) men ($n=8$)²² and women ($n=4$) received either 67 g/day Hi-Maize 260 (HAM starch) (providing 40 g RS2, and 40% rapidly digestible starch (RDS)) or 27 g/day Amioca²³ (also known as RDS or amylopectin, control). The study consisted of two 4-week intervention periods, separated by a 4-week washout period. The HAM starch and control product were provided to participants in ready to use sachets and they were instructed to dissolve in cold liquid and added to their habitual diet. Compliance with the dietary intervention was monitored by 7-day dietary intake at the end of each period. The authors reported that the subjects adhered to the use of the HAM starch and control product and that both HAM starch and the control product were well-tolerated. No changes in body weight were reported. Fasting blood glucose levels were significantly lower following 4 weeks of HAM starch use compared to the control group ($P<0.049$). Insulin sensitivity was not significantly affected by HAM starch diet using an insulin modified frequently sample intravenous glucose tolerance test (FSIVGTT) method. The investigators concluded that although this study showed an improvement in first phase insulin response (insulin secretion) following HAM starch, it did not demonstrate an improvement in insulin sensitivity.

Dainty et al. (2016) conducted a double-blind, placebo-controlled, randomized crossover intervention study. This moderate methodological quality study was conducted in 24 Canadian men ($n=16$) and women ($n=8$) (age 55.3 ± 7.8 years), with a BMI of $30.2 \pm 2.8 \text{ kg/m}^2$. The subjects were categorized at high risk of getting type 2 diabetes. The subjects randomly consumed a bagel containing HAM starch that provided 25.4 g/day of RS2 or a control wheat bagel for a period of 8 weeks each, separated by a 4-week washout period. Bagels were provided to participants, and participants were instructed to substitute one bagel for other bread-based foods per day. A daily study diary on the time of daily bagel consumption, and any discomfort or sickness related to bagel consumption was reported. In addition, subjects completed 3-day food records over the course of the study to determine their average energy and macronutrient intake. On average, the subjects adhered to their assigned bagels. The majority of participants reported no side effects during both treatment periods. No significant differences were observed in energy

²² The abbreviation “n” refers to the number of subjects.

²³ Amioca is a food grade starch consisting primarily of amylopectin - a naturally occurring branched glucose polymer. It is typically used as a natural thickener and texturizing agent.

or macronutrient intake of the groups. Fasting blood glucose or OGTT was not significantly different between the two treatment groups. However, a significant decrease in insulin resistance (HOMA) was observed following consumption of the bagel containing HAM starch compared to control bagels ($P=0.04$).

Gower et al. (2016) conducted a randomized, placebo-controlled, double-blind, crossover study in 40 (18 pre- or peri-menopausal and 22 postmenopausal), overweight/obese ($BMI= 29.8 \pm 6.7$ kg/m^2) women. In this moderate methodological study, participants (mean age 48.3 ± 12.6 years) were randomized to either receive cookies containing 25 or 50 g/day of HAM starch (containing 15 or 30 g/day of RS2, respectively), or about 11.6 g/day of RDS (control) for 4 weeks, separated with a 4-week washout period. The test cookies were provided to all participants and they were instructed to consume two servings per day. They met weekly with dieticians, were weighed, and picked up their test products. Habitual diet was monitored using 4-day food reported at baseline and during each of the three periods. Insulin sensitivity was assessed using insulin-modified frequently sampled intravenous glucose tolerance test (FSIVGTT). Fifty one women entered the study, 43 completed the first phase of the study, but only 40 had a usable insulin sensitivity result. Twenty-five women completed all three phases of the study, one woman did not have usable insulin sensitivity results and one woman's FSIVGTT test indicated an undiagnosed diabetes; therefore, only 23 women completed all three phases of the study. Authors reported that reasons for discontinuing the study included difficulty with the time commitment, transportation problems, and unwillingness to consume the snacks as directed. Fourteen (4 pre- and 10 post-menopausal) insulin resistant (IR), and 9 (3 pre- and 6 post-menopausal) insulin sensitive (IS) women were identified. The authors reported that all IR women were African-Americans and all IS women were white. Results from the diet records showed that habitual diet did not change across the three phases. Fiber intake (not including the treatment fiber product) was similar across all groups. When considering the entire group of 40 women (both IR and IS women) who finished only the first phase of the study (at least one arm), mixed model analysis in the IR group ($n = 28$) showed that insulin sensitivity (FSIVGTT) was significantly higher in those who received HAM starch providing 30 g/day of RS2 compared to control group. However, there was no significant difference in insulin sensitivity between those receiving HAM starch providing 15 g/day RS2 and control group in the IR group. Furthermore, no significant differences were observed in the IS women ($n = 12$) across the three treatment groups. When investigators analyzed data for the women finishing all the three phases of the study, no significant improvement (HOMA and FSIVGTT) in insulin sensitivity was observed for those receiving HAM starch providing either 15 or 30 g/day of RS2 compared to control group in either the IR ($n=14$) or IS ($n=9$) women. The FBG was also not significantly different across the three groups in either IR or IS women.

Johnston et al. (2010) conducted a 12-week randomized parallel, single-blind, placebo-controlled study of moderate methodological quality in 20 insulin resistance, obese (BMI about 31.3 ± 1.70) men ($n=12$) and women ($n=8$) in the United Kingdom. The participants were divided into two groups (10 per group) either receiving 67 g of HAM starch (containing 40 g/day RS2, and 27 g/day RDS) or 27 g/day RDS (control) for 12 weeks. The starches were provided in ready to use sachets and the participants were instructed to incorporate two servings in their habitual daily

diets. The compliance for both intervention products was good and well-tolerated. FBG was measured and insulin sensitivity was also measured by calculating HOMA and using hyperinsulinemic-euglycemic clamp before and after each treatment. Changes in insulin sensitivity using euglycemic clamp (from baseline levels to end of each treatment) were compared between the groups and were reported to be improved significantly in HAM starch group compared to control group ($P = 0.023$). Following HAM starch intake, there was a 19% increase in insulin sensitivity (baseline = $5.8 \times 10^{-2} \pm 7.2 \times 10^{-3}$ post treatment = $6.7 \times 10^{-2} \pm 8.1 \times 10^{-3}$) and a 14% reduction in insulin sensitivity following control intake (baseline = $7.7 \times 10^{-2} \pm 1.6 \times 10^{-3}$, post treatment = $6.6 \times 10^{-2} \pm 1.5 \times 10^{-3}$). It appears that the insulin sensitivity baseline in the placebo group was markedly and significantly²⁴ higher than the baseline value in the HAM starch group. The investigators did not report whether the baseline data for treatment and control groups were significantly different from each other or not. It is not clear why there was a 14% decrease in insulin sensitivity in the placebo group from baseline to post treatment (end of 12 weeks). There was no report of participants' habitual diets in any of the groups. Thus, it is not clear, whether the diet in the control group was changed (e.g., going from a high fiber diet to a low fiber diet) or the drop was due to the RDS supplement. Considering these issues, it cannot be concluded with certainty that the significant difference ($P=0.023$) was due to HAM starch consumption. Also, the insulin resistance data at the end of 12 weeks for both control ($6.6 \times 10^{-2} \pm 1.5 \times 10^{-3}$) and HAM starch ($6.7 \times 10^{-2} \pm 8.1 \times 10^{-3}$) groups do not appear to be significantly different from each other. For the reasons stated above, we cannot conclude that the significant difference in improvement of insulin sensitivity, using euglycemic clamp was only due to the HAM starch diet; therefore, we will not accept this part of the study. Furthermore, insulin sensitivity calculated by HOMA and FBG were not significantly different between groups.

Maki et al. (2012) was a randomized, double-blind, placebo-controlled, crossover study in 41 overweight and obese ($BMI = 30.6 \pm 0.5 \text{ kg/m}^2$) men and women, with waist circumference ≥ 89 cm (women) and ≥ 102 cm (men), receiving either HAM starch or a control starch. Subjects in this moderate methodological quality study were randomized to receive either 25 or 50 g/day of the HAM starch, providing either 15 or 30 g/day RS2, respectively, or 11.6 g/day of RDS (control) for 4 weeks each, separated by a 3-week washout period. Only 33 subjects (11 men, 22 women) with an average age 49.5 ± 1.6 years completed the study. One withdrew due to constipation during the period of the HAM starch diet providing 30 g/day RS2, and about seven participants withdrew without completing at least the control group and one other test condition. All intervention products were provided in ready to use sachets and participants were instructed to mix them into beverages or food and consume two servings at two separate eating occasions daily. At the end of each period, compliance was assessed by counting unopened sachets and query about whether any of the servings were missed. Compliance for each treatment was

²⁴ We calculated a confidence interval, based on the t distribution. The 95% confidence interval for the difference in mean baseline insulin sensitivity for the placebo and resistant starch group is (0.002, 0.036). This suggests that there might be a statistically significant difference between the means. Of course, we do not have the raw data, and thus cannot check the assumptions that must be made. (See Memorandum- Statistical consult- group comparisons of insulin sensitivity - (See references Johnston et al., 2010 and Johnston 2015 Corrigendum).

reported to be good. There were no significant differences between gastrointestinal symptoms with exception of flatulence which was significantly higher in the treatment group with the HAM starch diet providing 30 g/day RS2 compared to control. Data for men and women were analyzed separately. In both men and women, FBG and insulin resistance (HOMA) was not significantly different between the treatment groups receiving HAM starch with either 15 or 30 g/day RS2 and the control group. Furthermore, no significant difference in insulin sensitivity (FSIVGTT) was observed in women across the three treatments, while insulin sensitivity was significantly higher in men who consumed HAM starch, regardless of dose.

Penn-Marshall et al. (2010) was a double-blind, placebo controlled, randomized crossover study of moderate methodological quality in overweight/obese (BMI of $37.7 \pm 2 \text{ kg/m}^2$) African American men (n=8) and women (n=7). The participants were classified as being high risk for type 2 diabetes. They were randomly assigned to receive either bread containing HAM starch or a control bread for a period of 6 weeks each, separated by a 2-week washout period. Each subject was asked to substitute three slices of HAM starch or control bread with the bread they would normally eat. The three slices of HAM starch bread contained about 12.4 g of HAM starch (providing about 7.4 g of RS2)²⁵. Control bread was similar to treatment group bread but without any added HAM starch. There were no significant differences in FBG and insulin resistance (HOMA) between those who consumed HAM starch and the control breads. The authors concluded that the findings from their study and other research studies are inconclusive with regard to how much HAM starch should be eaten to help prevent chronic disease in humans and more research is needed.

Robertson et al. (2005) was a single-blind, placebo-controlled, randomized crossover study of moderate methodological quality consisting of two 4-week study periods with a 4-week washout period conducted in United Kingdom. This study was conducted on 10 healthy (average age 48.5 ± 3.4 years) men (n=4) and women (n=6) with an average BMI of $23.4 \pm 1.4 \text{ kg/m}^2$. The subjects randomly assigned to receive either 50 g/day of HAM starch (providing 30 g of RS2, and 20 g of RDS), or 20 g/day of RDS (control). The starch was provided in the ready to use sachets, which was incorporated into their habitual diet. The diet was monitored using a 7-day food record during each period. The subjects' compliance with both treatment and control products was reported to be good and no significant differences were observed between the habitual diets of each treatment group. The subjects tolerated the products well. Insulin sensitivity was measured by euglycemic clamp at the end of the third week of dietary intervention, while FBG and insulin sensitivity calculated by HOMA were measured at the end of 4 weeks of supplementation. There were no significant differences in FBG and insulin sensitivity (HOMA) between the groups. However, there was a significant increase in insulin sensitivity measured by the euglycemic clamp method after 3 weeks of HAM starch intake compared to control group ($P=0.027$).

²⁵ The authors mentioned that the subjects were given 12 g/day of HAM starch. Each slice contains about 2.5 g of RS2. Thus, three slices of bread appears to contain about 7.4 g/day of RS2. Petition letter also assumes about 7 g/day of RS2 was provided in this study.

Robertson et al. (2012) investigated 15 insulin resistant adults (8 men and 7 women) with an average age of 48.9 ± 3.9 years and a BMI of 33.8 ± 1.9 kg/m² in a randomized, single-blind, placebo-controlled, crossover study. Subjects in this moderate methodological quality study were randomly divided to either receive either 67 g/day HAM starch (providing 40 g RS2 and 27 g RDS) or 27 g/day of RDS (control) for 8 weeks. The treatments were separated by an 8-week washout period. The starch was provided in the ready to use sachets and subjects were instructed to mix in with food/drink daily. A 7-day diet record was completed to evaluate any changes in habitual intake and assess energy and macronutrient intake among groups. Participants did not have any significant side effect (e.g., abdominal pain, flatulence, or bloating) from consumption of HAM starch intake. Mean daily macronutrient intake did not differ between treatment groups and there were no changes in body weight. There was a significant decrease in FBG and insulin resistance (HOMA) after consumption of HAM starch compared to control group. Using the euglycemic clamp method, no significant difference was observed in insulin sensitivity of endogenous glucose production, which is a measure of hepatic glucose production between the two groups. However, consumption of HAM starch resulted in a significant improvement in peripheral tissue glucose uptake (insulin resistance) compared to the control group.

C. Assessment of the Relevant Observational Studies

There were no observational studies available to the agency that evaluated the association between HAM starch intake and risk of type 2 diabetes.

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), the methodological quality rating previously assigned, the quantity of the evidence (number of the various types of studies and sample sizes), 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,²⁶ and the overall consistency²⁷ 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 HAM starch intake and risk reduction of type 2 diabetes is based on eight intervention studies (Bodenham et al., 2012; Dainty et al., 2016; Gower et al., 2016; Johnston et al., 2010; Maki et al., 2012; Penn-Marshall et al., 2010; Robertson et al., 2005, 2012). One study included two groups, investigating the consumption of two levels of HAM starch containing 15 or 30 g of RS2/day) and type 2 diabetes

²⁶ See *supra*, note 11.

²⁷ See *supra*, note 12.

in women (Gower et al., 2016). Maki et al. (2012) included four groups which analyzed the consumption of two levels of HAM starch containing 15 or 30 g of RS2/day on risk reduction of type 2 diabetes in men and women separately. Thus, the total evidence comes from 12 analyses of eight studies.

The results of these eight studies (or 12 analyses) demonstrate marked inconsistency among each other or even within the same study. The studies used various validated surrogate endpoints of type 2 diabetes, such as FBG, OGTT, or determining insulin resistance/sensitivity by calculating HOMA, or using various techniques, such as the euglycemic clamp method or FSIVGTT. Also, these results were not consistent with regard to the amount of HAM starch or RS2 dose provided (about 7.4 g to 40 g/day), study duration (3 to 12 weeks), sample size (9 to 24 per group), gender, and whether the subjects were healthy (not being high risk), insulin resistant and/or having high risk factors²⁸ for developing type 2 diabetes.

The results of six analyses of four moderate methodological quality, randomized control studies reported no relationship between HAM starch and risk of type 2 diabetes when measuring various validated surrogate endpoints (i.e. FBG, HOMA, euglycemic clamp or FSIVGTT) (Gower et al., 2016 (two levels of RS2 intake); Johnston et al., 2010; Maki et al., 2012 (women only at two levels of RS2 intake); Penn-Marshall et al., 2010).

Gower et al. (2016) started with 51 women, but more than half did not complete the study. Analyses of data, from those that completed all the three phases, using either FBG or insulin resistance (HOMA or FSIVGTT) showed no significant benefit in HAM starch providing either RS2 dose (15 or 30 g/day) in IR (n=14) or IS (n=9) groups compared to the control. Throughout this study, a high dropout rate was observed (completion rate about 45%), the sample size was especially small when the data were analyzed for subgroups (i.e., IR or IS groups). The authors indicated that the main limitation of their study was the high dropout rate and that many of the women did not complete all three arms of this study, hence, the small sample size made interpretation of the subgroup analyses difficult.

Johnston et al. (2010) reported no significant difference in FBG or insulin resistance²⁹ (HOMA) in those receiving HAM starch (40 g RS2/day) compared to control group.

²⁸ High risk factors for developing type 2 diabetes include obesity, abdominal obesity, family history of diabetes, elevated or abnormally high fasting blood glucose levels (> 100 mg/dL and < 126 mg/dl), insulin resistance, and metabolic syndrome (consisting of a group of risk factors such as high blood pressure and high fasting blood glucose, high levels of LDL cholesterol and triglycerides) (“Risk Factors for Type 2 Diabetes”

<https://www.niddk.nih.gov/health-information/health-communication-programs/ndep/am-i-at-risk/diabetes-risk-factors/Pages/diabetesriskfactors.aspx> (accessed on December 1, 2016); (“What is Metabolic Syndrome?”

<http://www.nhlbi.nih.gov/health/health-topics/topics/ms/>) (accessed on December 1, 2016)

²⁹ As mentioned in section II above, the investigators reported a significant difference between the control and RS2 group on insulin resistance measured by the euglycemic clamp method. However, they measured significant differences between changes from baseline to the end of the 12 weeks in control and HAM starch group. It appears that baselines are markedly different from each other. In the control group the insulin resistance dropped by 14% (baseline = $7.7 \times 10^{-2} \pm 1.6 \times 10^{-3}$; post treatment ($6.6 \times 10^{-2} \pm 1.5 \times 10^{-3}$)). In the HAM starch group, authors reported an increase of 19% from baseline ($5.8 \times 10^{-2} \pm 7.2 \times 10^{-3}$) compared to the end of 12 weeks ($6.7 \times 10^{-2} \pm 8.1$

Maki et al. (2012) reported no significant differences in FBG, and insulin resistance (HOMA, FSIVGTT) in women receiving HAM starch providing either 15 or 30 g RS2/day compared to control group. However, the findings in men were not consistent (summarized below).

Penn-Marshall et al. (2010) showed no significant differences in FBG and HOMA among those receiving HAM starch compared to control group.

Using various surrogate endpoints of type 2 diabetes risk (i.e., FBG, HOMA, euglycemic clamp or FSIVGTT), the results of six analyses of five moderate methodological quality, randomized studies were mixed (Bodenham et al., 2012; Dainty et al., 2016; Maki et al., 2012 (only men at two levels of RS2 intake), Robertson et al., 2005, 2012).

Bodenham et al. (2012) reported a significant improvement in FBG but not on insulin resistance (FSIVGTT) in Ham starch group (40 g RS2/day) compared to control group.

Dainty et al. (2016) reported a significant decrease in insulin resistance (HOMA), but no significant differences in FBG and OGTT in those receiving HAM starch providing about 25 g RS2/day compared to control group.

Maki et al. (2012) showed that in 11 men receiving HAM starch providing either 15 or 30 g RS2/day or a control, FBG and insulin resistance (HOMA) were not significantly different at either levels of treatment groups (15 or 30 g RS2) compared to control group. However, a significant improvement in insulin resistance (FSIVGTT) was observed at both levels of RS2 compared to control.

Robertson et al. (2005) showed no significant difference on FBG and insulin resistance (HOMA) in those receiving HAM starch compared to control group. A significant increase in insulin sensitivity (euglycemic clamp) was observed in HAM starch group compared to control group.

Robertson et al. (2012), reported significant differences in FBG, and HOMA between those receiving HAM starch and control group. Additionally, using euglycemic clamp, a significant increase in peripheral (muscle and tissue) glucose uptake was observed, while insulin sensitivity of hepatic glucose production was not significantly affected in those receiving HAM starch compared to control group. These investigators suggested that larger randomized controlled feeding studies would be required to add to the evidence for HAM starch in the risk reduction of diabetes.

$\times 10^{-3}$). The level of insulin resistance in both groups at post treatments is similar and does not appear to be significantly different from each other. It is unclear as to why insulin resistance declined during the consumption of the control supplement. The study did not provide statistical analysis on baseline insulin resistance between the HAM starch and control group. Therefore, we cannot accept the significant differences reported between the two groups as credible evidence. (See Memorandum- Statistical consult- group comparisons of insulin sensitivity)

In general, ten analyses of six studies that measured FBG reported no significant difference between HAM starch containing 50% or more RS2 and the control group (Dainty et al., 2016; Gower et al., 2016 (at two RS2 levels); Johnston et al., 2010; Maki et al., 2012 (both men and women at two RS2 levels); Penn-Marshall et al., 2010; Robertson et al., 2005). Two additional studies reported a significant reduction in FBG in those that consumed HAM starch (40 g RS2/day) compared to control group (Bodenham et al., 2012; Robertson et al., 2012). One study measured OGTT and reported no significant difference between those receiving HAM starch and control group (Dainty et al., 2016). Six studies measured HOMA as an indicator of insulin resistance/sensitivity (Dainty et al., 2016; Johnston et al., 2010; Maki et al., 2012; Penn-Marshall et al., 2010; Robertson et al., 2005, 2012). The seven analyses of four studies (out of the six) (Johnston et al., 2010; Maki et al., 2012 (men or women at two levels of RS2); Penn-Marshall et al., 2010; Robertson et al., 2005) reported no significant differences between HAM starch (RS2 levels ranging from 7.4 g to 40 g/day) and the control group. More direct measurements of insulin resistance/sensitivity using either the euglycemic clamp method or FSIVGTT was conducted in ten analyses of six studies (Bodenham et al., 2012; Gower et al., 2016 (at two levels of RS2); Johnston et al., 2010; Maki et al., 2012 (for men and women at two levels of RS2); Robertson et al., 2005, 2012). Four analyses out of three of these studies showed a significant reduction in insulin resistance (Maki et al., 2012 (only in men at two levels of RS2), Robertson et al., 2005, 2012 (significance shown only in peripheral glucose uptake). While six analyses of four studies (Bodenheim et al., 2012; Gower et al., 2016 (two levels of RS2); Maki et al., 2012 (women only at two levels of RS2); Robertson et al., 2012 (no significance shown in hepatic tissues) did not show any significant reduction in insulin resistance among groups.

In summary, six analyses of four intervention studies reported that there was no relationship between HAM starch containing RS2 and the reduced risk of type 2 diabetes, by measuring various surrogate endpoints (Gower et al., 2016 (at two levels of RS2); Johnston et al., 2010; Maki et al., 2012 (women only at two levels of RS2); Penn-Marshall et al., 2010). Six analyses of five studies observed mixed results in the relationship between HAM starch containing RS2 and the reduced risk of type 2 diabetes, depending on the type of surrogate endpoint measured (e.g., FBG, insulin resistance (HOMA, euglycemic clamp, or FSIVGTT) (Bodenham et al., 2012; Dainty et al., 2016; Maki et al., 2012 (men only at two levels of RS2); Robertson et al., 2005, 2012). A consistency of results in HAM starch containing RS2 and risk reduction of type 2 diabetes was not observed in either high risk, or normal/healthy groups. These studies were of various duration (anywhere from 3 to 12 weeks), and had various amount of RS2 (7.4 to 40 g/day).

Consistency of findings among similar and different study designs is important for evaluating the strength of the scientific evidence.³⁰ The majority of the studies (analyses) included in this review did not show a significant relationship between HAM starch consumption and risk of type 2 diabetes. Moreover, the results of the studies evaluated are not consistent within or across studies that measured the surrogate endpoints of type 2 diabetes risk.

³⁰ See *supra*, note 3 [Section III.F] and note 12.

Based on the above findings of intervention studies, FDA concludes that, although a few studies with the mixed results of surrogate endpoints within each (Bodenham et al., 2012; Dainty et al., 2016; Maki et al., 2012 (men only); Robertson et al., 2005, 2012) suggest that HAM starch consumption may reduce the risk of type 2 diabetes, the scientific evidence does not consistently show that HAM starch intake reduces the risk of type 2 diabetes.

Based on the above, FDA concludes that there is limited credible evidence for a relationship between the consumption of HAM starch containing at least 50 percent type 2 resistant starch and a reduced risk of type 2 diabetes.

IV. Other Enforcement Discretion Factors

A qualified health claim on the label or in the labeling of a product containing HAM starch is required to meet all applicable statutory and regulatory requirements under 21 CFR 101.14, with the exception of the requirement that a health claim meet the significant scientific agreement standard and the requirement that the claim be made in accordance with an authorizing regulation.

The substance that is the subject of the petition is high-amylose maize (HAM) starch, containing 50 percent or more type 2 resistant starch that is unmodified and has only been subject to conventional milling processes. Other factors that FDA intends to consider in the exercise of its enforcement discretion for qualified health claims about HAM starch that contains 50 percent or more type 2 resistant starch that is unmodified and has only been subject to conventional milling processes and reduced risk of type 2 diabetes are discussed below.

A. 10 Percent Minimum Nutrient Content Requirement

Under the general requirements for health claims, a conventional food may not bear a health claim unless it contains, prior to any nutrient addition, at least 10 percent of the DV of certain nutrients per reference amount customarily consumed (RACC) (21 CFR 101.14(e)(6)). The purpose of this requirement is to prevent the use of health claims on foods with minimal nutritional value. The specific nutrients listed in 21 CFR 101.14(e)(6) are vitamin A, vitamin C, iron, calcium, protein, and fiber.³¹ For the purposes of this health claim, the agency intends to exercise its enforcement discretion with respect to 21 CFR 101.14(e)(6) for the qualified health claim to be used on food labels when the food contains 10 percent or more of the DV for vitamin D or potassium, in addition to nutrients currently listed (i.e., vitamin A, vitamin C, iron, protein, fiber) per reference amount customarily consumed prior to any nutrient addition.

³¹We note that the final rule entitled “Food Labeling: Revision of the Nutrition and Supplement Facts Labels” (81 Fed. Reg. 33742; May 27, 2016) changed the mandatory declaration of vitamins and minerals as a percent of the RDI in 21 CFR 101.9(c)(8) from vitamin A, vitamin C, calcium, and iron to vitamin D, calcium, iron, and potassium. Therefore, vitamin D and potassium are now nutrients of public health significance. We plan to address, as appropriate and as time and resources permit, the impact of the changes in nutrient declarations in the final rule to other regulations, such as 21 CFR 101.14(e)(6), in separate rulemaking actions (see 81 Fed. Reg. 33742 at 33751).

Ham starch is used as an ingredient in conventional foods. The food applications for HAM starch developed by the petitioner for the North American market include breads, muffins, cakes/cupcakes, breakfast cookies, pasta, pretzels, ready-to-eat cereals, nutrition bars, waffles, pancakes, and smoothies.³² Many of these products will not meet the 10 percent minimum nutrient content requirement, such as cakes and cupcakes. However, many types of bakery products including bread, muffins, breakfast cookies, pretzels, nutrition bars, waffles, pancakes, cereal and grain products including ready-to-eat cereals and pasta³³, that are formulated with grains that contain significant amounts of dietary fiber³⁴ and/or protein may meet the 10 percent minimum nutrient content requirement for fiber and/or protein. Also, not all smoothies will meet the 10 percent minimum nutrient content requirement, but like “Bakery” products or “Cereals and Other Grain” products, smoothies may be formulated with significant amounts of protein, fruits, and vegetables so that the 10 percent minimum nutrient content requirement per RACC can be met.

Therefore, we intend to exercise enforcement discretion for the use of a qualified health claim about HAM starch and a reduced risk of type 2 diabetes for food applications for HAM starch identified by the petitioner for the North American market, listed in Table 8 of the health claim petition (pg. 43) when the food contains 10 percent or more of the DV for vitamin A, vitamin C, iron, protein, fiber, vitamin D or potassium per reference amount customarily consumed prior to any nutrient addition.

B. Qualifying Level of HAM starch

³² See health claim petition submitted by EAS Consulting Group, Inc. (March 26, 2015), Table 8, page 43.

³³ FDA includes, in the food category “Bakery” products, breads, muffins, cakes, cupcakes, breakfast cookies, pretzels, nutrition bars, waffles, and pancakes. FDA includes, in the food category “Cereal and Other Grain” products, pasta, and ready-to-eat cereals (See Table 2 for individuals 4 and older in 21 CFR 101.12(b)(2)). FDA has not categorized smoothies products and many types of these products can be dairy-based, fruit-based, vegetable-based or contain any combination of dairy, fruits and vegetables.

³⁴ We note that the final rule entitled “Food Labeling of the Nutrition and Supplement Facts Labels” (NFL final rule) ((81 Fed. Reg. 33742; May 27, 2016) includes a definition of “dietary fiber.” The NFL final rule, among other things, defines dietary fiber as non-digestible soluble and insoluble carbohydrates (with 3 or more monomeric units), and lignin that are intrinsic and intact in plants; isolated or synthetic non-digestible carbohydrates (with 3 or more monomeric units) determined by FDA to have physiological effects that are beneficial to human health (21 CFR 101.9(c)(6)(i)). The NFL final rule also identifies seven isolated or synthetic non-digestible carbohydrates that we determined to have beneficial effects for human health when added to foods (21 CFR 101.9(c)(6)(i)). The seven isolated or synthetic non-digestible carbohydrates are: [beta]-glucan soluble fiber (as described in 21 CFR 101.81(c)(2)(ii)); psyllium husk (as described in 21 CFR 101.81(c)(2)(ii)); cellulose, guar gum, pectin, locust bean gum; and hydroxypropylmethylcellulose. However, the regulation in 21 CFR 101.14(e)(6) states “fiber” as a nutrient and does not limit the fiber to “dietary fiber” as defined in the NFL final rule. Therefore, the current regulation in section 101.14(e)(6) would permit a 10% minimum nutrient contribution from dietary fibers in the NFL final rule in addition to other non-digestible carbohydrates not included in the definition of dietary fiber. As stated in footnote 31, we plan to address, as appropriate and as time and resources permit, the impact of the changes in nutrient declarations in the final rule to other regulations, such as 21 CFR 101.14(e)(6), in separate rulemaking actions (see 81 Fed. Reg. 33742 at 33751).

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 “high” has been established, the claim must specify the daily dietary intake necessary to achieve the claimed effect (21 CFR 101.14(d)(2)(vii)).

However, the agency finds that this provision should not be applied to the qualified health claim for HAM starch and reduced risk of type 2 diabetes because there is limited scientific evidence for this relationship and the available evidence does not support the establishment of a recommended daily dietary intake level or even a possible level of effect for the general United States population. Therefore, the agency considers any label or labeling suggesting a level of HAM starch to be useful in achieving a reduction in the risk of type 2 diabetes for the general healthy population to be false and misleading under section 403(a) of the Act. Further, FDA would monitor and evaluate for possible enforcement action situations where foods that bear the qualified health claim for HAM starch and type 2 diabetes that contain HAM starch in trivial amounts.

V. Conclusions

Based on FDA’s consideration of the scientific evidence submitted with the petition, FDA concludes that there is limited credible scientific evidence for a qualified health claim for high-amylose maize resistant starch and reduced risk of 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:

“High-amylose maize resistant starch may reduce the risk of type 2 diabetes, although the FDA has concluded that there is limited scientific evidence for this claim.”

“High-amylose maize resistant starch may reduce the risk of type 2 diabetes. FDA has concluded that there is limited scientific evidence for this claim.”

“High-amylose maize resistant starch, a type of fiber, may reduce the risk of type 2 diabetes, although the FDA has concluded that there is limited scientific evidence for this claim.”

“High-amylose maize resistant starch, a type of fiber, may reduce the risk of type 2 diabetes. FDA has concluded that there is limited scientific evidence for this claim.”

FDA intends to consider exercising its enforcement discretion for the above qualified health claims when all factors for enforcement discretion identified in Section IV of this letter are met.

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 no longer support the use of the above qualified health claims, or that may raise safety concerns about the substance that is the subject of the claims.

Sincerely,

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Center for Food Safety
and Applied Nutrition

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