Review of the Scientific Evidence on the Physiological Effects of Certain Non-Digestible Carbohydrates

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June 2018

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I. Introduction

The Food and Drug Administration (FDA or we) is providing a summary of the scientific evidence that we identified for isolated or synthetic non-digestible carbohydrates that meet the definition of dietary fiber. We intend to propose this list of isolated or synthetic non-digestible carbohydrates be added to the dietary fiber definition, based on a review of the scientific evidence related to at least one physiological endpoint that is beneficial to human health.

We previously identified two dietary fibers for which health claims may be made (beta-glucan soluble fiber and psyllium husk) (21 CFR 101.81). In the *Federal Register* of May 27, 2016 (81 FR 33742), we published a final rule amending our Nutrition Facts and Supplements Facts labels regulations (hereafter "the final rule"). The final rule, among other things, identifies these two dietary fibers and five additional isolated or synthetic non-digestible carbohydrates (cellulose, guar gum, locust bean gum, pectin, and hydroxypropylmethylcellulose) (81 FR 33742, Reference #137) that we have determined meet our definition of dietary fiber (81 FR 33742 at 33979; 21 CFR 101.9(c)(6)(i)). We made the determinations for the five additional non-digestible carbohydrates in a manner consistent with the approach we have set forth in our final guidance for industry entitled "Scientific Evaluation of the Evidence on the Beneficial Physiological Effects of Isolated or Synthetic Non-Digestible carbohydrates Submitted as a Citizen Petition (21 CFR 10.30)."[1] Our scientific evaluation of these five additional isolated or synthetic non-digestible carbohydrates from the final rule is referenced for each fiber in Section II of this Science Review.

In a related guidance, entitled "The Declaration of Certain Isolated or Synthetic Non-Digestible Carbohydrates as Dietary Fiber on Nutrition and Supplement Facts Labels: Guidance for Industry,"[2] we announced our decision to consider the exercise of our enforcement discretion relative to the declaration of eight more isolated or synthetic non-digestible carbohydrates as dietary fibers when included in the amount of dietary fiber declared in Nutrition and Supplements Facts labels until we complete a rulemaking that would propose to amend our regulations at 21 CFR 101.9(c)(6)(i) to include them in the list of non-digestible carbohydrates that meet our definition of dietary fiber. These eight additional non-digestible carbohydrates are: (1) mixed plant cell wall fibers[3]; (2) arabinoxylan; (3) alginate; (4) inulin and inulin-type fructans; (5) high amylose starch (resistant starch 2); (6) galactooligosaccharide; (7) polydextrose; and (8) and resistant maltodextrin/dextrin.

We based our scientific evaluation for isolated or synthetic non-digestible carbohydrates on: the publicly available scientific literature, data and information provided in citizen petitions requesting additional non-digestible carbohydrates be identified as a "dietary fiber";[4] comments that we received in response to

[1] Available at: https://www.fda.gov/downloads/Food/GuidanceRegulations/GuidanceDocumentsRegulatoryInformation/UCM528533.pdf.
[2] Available at: https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm610111.htm.
[3] "Mixed plant cell wall fibers" refers to ingredients that contain two or more of the following plant cell wall fibers in varying proportions: cellulose; pectin; lignin; beta-glucan; and arabinoxylan. Plant cell wall fibers may include variable amounts of vitamins, minerals, and macronutrients depending on the methods that may be used for isolating and extracting the fiber.
[4] Docket No. FDA-2016-P-1674, "Citizen Petition Regarding the Listing of PROMITOR® Soluble Corn Fiber as a Source of Dietary Fiber," submitted by Tate & Lyle Ingredients Americas LLC; Docket No. FDA-2016-P-2377, "Citizen Petition Regarding Nutrition Labeling of Fibersol® Resistant Maltodextrin as a Dietary Fiber," submitted by Archer Daniels Midland

our notice requesting scientific data, information, including comments related to potential physiological effects of isolated or synthetic non-digestible carbohydrates on human health;[5] and comments[6] that we received regarding a scientific literature review,[7] which summarizes clinical studies associated with 26 specific non-digestible carbohydrates. Many of these 26 non-digestible carbohydrates (e.g., sugar cane fiber and oat hull fiber) are considered to be mixed plant cell wall fibers. We intend to consider the exercise of our enforcement discretion with respect to declaring mixed plant cell wall fibers as dietary fiber.

Section II of this document provides a short overview of the non-digestible carbohydrates that were determined to meet the dietary fiber definition in the final rule. The remainder of the document summarizes the clinical studies on which we relied and presents our evaluation of the strength of the publicly available scientific evidence that support our decision to consider enforcement discretion for including the earlier identified eight additional isolated (Section III) or synthetic (Section IV) non-digestible carbohydrates in the declared amount of dietary fiber on Nutrition Facts and Supplement Facts labels, when any one of these non-digestible carbohydrates is present in food.

II. Previously Identified Non-Digestible Carbohydrates that Meet the Dietary Fiber Definition

Cellulose

Cellulose is a linear homopolymer of β-(1-4) linked glucose units. Cellulose is the main structural component of the cell wall of most plants and therefore is present in vegetables, fruits, and cereals. Cellulose is not digested by human enzymes nor fermented by the colonic microflora. Cellulose meets the dietary fiber definition based on improved laxation[8] (21 CFR 101.9(c)(6)(i)).

Company; Docket No. FDA-2016-P-2736, "A Citizen Petition Requesting that FDA Amend 21 CFR §101.9(c)(6)(i) to Recognize that Inulin-Type Fructans Derived from Chicory Root Qualify as Dietary Fiber for Purposes of Nutrition Labeling," submitted by Hyman, Phelps & McNamara, P.C. on behalf of Beneo, Cosucra Groupe Warcoing, S.A., and Sensus B.V.; Docket No. FDA-2016-P-2860, "A Citizen Petition Regarding the Inclusion of Inulin-Type Fructans Extracted from Chicory Root in the Definition of Dietary Fiber," submitted by General Mills; Docket No. FDA-2016-P-3070, "A Citizen Petition to Request the Commissioner of Food and Drugs to Add Soy Fiber to the List of Isolated or Synthetic Non-digestible Carbohydrates that Have Been Determined by FDA to Have Physiological Effects that Are Beneficial to Human Health at 21 CFR 101.9(c)(6)(i)," submitted by DuPont Nutrition & Health; Docket No. FDA-2016-P-3311, "Citizen Petition Regarding the Listing of Polydextrose as a Source of Dietary Fiber and the Caloric Value of Polydextrose for Use in Nutrition Labeling and Claims," submitted by Tate & Lyle Ingredients Americas LLC and DuPont Nutrition & Health; Docket No. FDA-P-2017-0970, "A Citizen Petition Requesting that FDA Amend 21 C.F.R. § 101.9(c)(6)(i) to Recognize Rice Bran Derived Products that Contain Rice Bran Fiber and Other Components of Rice Bran as Containing Dietary Fiber for Purposes of Nutrition Labeling, submitted by RiceBran Technologies; and Docket No. FDA-2016-P-4233, "A citizen petition requesting that Phytocel™ and Kfibre™ sugarcane flour made from whole sugarcane be classified as a dietary fiber for label declaration purposes," submitted by KFSU Ltd.

[5] FDA. "Evaluation of the Beneficial Physiological Effects of Isolated or Synthetic Non-Digestible Carbohydrates; Request for Scientific Data, Information, and Comments" (81 FR 84595; November 23, 2016), and see Docket No. FDA-2016-N-3389.

[6] See Docket No. FDA-2016-N-3389.

[7] FDA. "Evaluation of the Beneficial Physiological Effects of Isolated or Synthetic Non-Digestible Carbohydrates," November 2016. Available at: https://www.fda.gov/Food/LabelingNutrition/ucm525656.htm.

[8] U.S. Food and Drug Administration. "Memorandum to the File: Scientific Review of the Beneficial Physiological Effects of Non-Digestible Carbohydrates for Meeting the FDA Definition of Dietary Fiber," 2016 (FDA, 2016).

Some forms of cellulose are chemically equivalent to isolated cellulose, including powdered cellulose and microcrystalline cellulose. Microcrystalline cellulose is purified, partially depolymerized cellulose prepared by using mineral acid to hydrolyze cellulose pulp. Microcrystalline cellulose is also called cellulose gel. Powdered cellulose is generally obtained by mechanically micropulverizing cellulose.

Common names used to identify cellulose as an ingredient include microcrystalline cellulose, cellulose gel, and cellulose powder.

Guar Gum

Guar gum is a linear chain of β 1,4-linked mannose residues to which galactose residues are 1,6-linked at every second mannose, forming short side-branches. Guar gum is hydrophilic and with gel-forming properties (IOM, 2002). As a food ingredient, guar gum is obtained from the maceration of the seed of the guar plant *Cyamopsis tetragonoloba* or *Cyamopsis psoraloides.* Guar gum is added to foods as an emulsifier, formulation aid, thickener, and firming agent (21 CFR 184.1339). Guar gum meets the dietary fiber definition based on its effect of attenuating blood cholesterol levels (FDA, 2016; 21 CFR 101.9(c)(6)(i)).

Locust Bean Gum

Locust bean gum is primarily the macerated endosperm of the seed of the locust bean tree. Locust bean gum is a galactomannan that meets the definition of dietary fiber based on its effect of attenuating blood cholesterol levels (FDA, 2016; 21 CFR 101.9(c)(6)(i)).

Common names used to identify locust bean gum as an ingredient include carob bean gum and carob seed gum.

Pectin

Pectic polysaccharides have a backbone chain of α- (1→ 4)-linked D-galacturonic acid units interrupted by the insertion of (1→ 2)-linked L-rhamnopyranosyl residues in adjacent or alternate positions. Pectins are present in cell walls and intracellular tissues of fruits and vegetables. While pectin is most abundant in fruits, it is also present in vegetables, legumes, and nuts. Pectin meets the definition of dietary fiber based on its effect of attenuating blood cholesterol levels (FDA, 2016; 21 CFR 101.9(c)(6)(i)).

Common names used to identify pectin as an ingredient include hydrolyzed pectin, fruit pectin, citrus pectin, and modified pectin.

Hydroxypropylmethylcellulose

Hydroxypropylmethylcellulose (HPMC) is a propylene glycol ether of methylcellulose containing methoxyl groups and hydroxypropyl group. HPMC is a gum that has multiple technical effects, including use as a film former, stabilizer, and thickener. HPMC meets the definition of dietary fiber based on its effect of attenuating blood cholesterol levels (FDA, 2016; 21 CFR 101.9(c)(6)(i)).

A common name used to identify HPMC as an ingredient is hypromellose.

Beta-Glucan

Mixed-link (1-3, 1-4) beta-glucans are a major component in the cell walls of oats, barley and rye, and smaller quantities in wheat. Beta-glucans in these plants are considered to be a form of hemicellulose. Beta-glucans are isolated and added to foods (e.g., barley betafiber). Beta-glucan soluble fiber meets the definition of dietary fiber based on its effect of reducing the risk of coronary heart disease (21 CFR 101.81).

Common names used to identify beta-glucan-containing ingredients are barley beta fiber, and barley beta-glucan.

Psyllium Husk

Psyllium seed husks, also known as ispaghula, isabgol, or psyllium, are portions of the seeds of the plant *Plantago ovata*, (genus *Plantago*). Psyllium husk is the seed coat that has been removed from the psyllium seed and milled. The psyllium seed includes nutrients that are not components of psyllium husk (63 FR 8103 at 8105, February 18, 1998). Psyllium husk is a concentrated source of the soluble fiber, arbinoxylan (a form of hemicellulose), and is used as a food or food component in a number of foods in the United States (62 FR 28234 at 28235, May 22, 1997). Psyllium husk, as a source of soluble fiber, meets the definition of dietary fiber based on its effect of reducing the risk of coronary heart disease (21 CFR 101.81).

Common names used to identify psyllium husk as an ingredient include psyllium, psyllium seed husk, and ispaghlua husk.

References

U.S. Food and Drug Administration (FDA, 2016). "Memorandum to the File: Scientific Review of the Beneficial Physiological Effects of Non-Digestible Carbohydrates for Meeting the FDA Definition of Dietary Fiber," 2016.

III. Additional Isolated Non-Digestible Carbohydrates that Meet the Dietary Fiber Definition

Mixed Plant Cell Wall Fibers

Many plants contain a variety of fibers, with common ones primarily being present in plant cell walls (i.e., cellulose, hemicelluloses, and pectin), as well as lignin (Marlett et al., 1992; Kumar et al., 2012). Fiber ingredients obtained from plant cell walls, in whole or in part, often contain a mixture of cellulose, hemicellulose, and pectin. The content and profile of these mixed plant cell wall fibers can vary depending on the processing methods that are used to isolated the fibers from a particular type of plant, which, in turn, often makes it difficult to determine whether or not a particular fiber is intact and intrinsic, particularly when the processing methods used to extract the fiber or the composition of the ingredient are unknown. The distinction is relevant for purposes of determining whether a plant cell wall fiber is included in the definition of "dietary fiber." An "intrinsic and intact" fiber is defined as a "dietary fiber" and therefore must be included in the declaration of dietary fiber on the Nutrition and Supplement Facts labels (21 CFR 101.9(c)(6)(i)). For a plant cell wall fiber that is not intrinsic and intact, FDA must determine whether the carbohydrate provides a physiological effect that is beneficial to human health and, if so, complete rulemaking to include the carbohydrate as a "dietary fiber" in § 101.9(c)(6)(i).

Cellulose, pectin, β-glucan are found in plant cell walls and meet the definition of dietary fiber based on their physiological effects that are beneficial to human health (21 CFR 101.9(c)(6)(i); 21 CFR 101.81). Plant cell wall fibers also contain a category of non-digestible carbohydrates referred to as "hemicelluloses." There are various types of hemicelluloses found in different plant-based foods and at different levels. β-Glucan is present in the plant cell walls of barley, oats, and rye and is considered to be a form of hemicellulose (Kumar et al., 2012). The hemicellulose fibers may be considered "intrinsic and intact" in plants[9], or may be isolated after undergoing different types of processing. For example, the dietary fiber β-glucan may be intrinsic and intact (e.g., whole oat flour), or may be an isolated fiber added to food as an ingredient (e.g., barley betafiber). Similarly, the soluble fiber in psyllium husk, arabinoxylan, is another form of hemicellulose that is abundant in the walls of cereal grains and is an example of an isolated non-digestible carbohydrate.

We intend to propose mixed plant cell wall fibers as a category of isolated fibers because they are generally processed using methods that result in the plant cell being disrupted and/or various nutrients being removed from the plant, such that they are no longer intrinsic and intact, as indicated in a number of notifications submitted to FDA about a manufacturers' determination that certain plant cell wall fibers added to food provide a technical effect and are generally recognized as safe (GRAS).[10] Examples of processing methods that have been provided to FDA by manufacturers in GRAS notifications that have been used for isolating various plant cell wall fiber ingredients include enzymatic digestion, aqueous

[9] We note that, although lignin is not a carbohydrate, it is covalently bound to hemicellulose within the plant cell matrix, and as such, is indicative of being intrinsic and intact in plants (IOM, 2001). Accordingly, we consider lignin to be a dietary fiber when present in food.

[10] See FDA's GRAS Notices Inventory website, available at: https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&sort=GRN_No&order=DESC&showAll=true&type=basic&search=; e.g., GRAS Notices Nos. 366 (oat hull fiber), 368 (corn hull fiber), 373 (rice bran fiber), 430 (sugar beet fiber), 478 (rice hull fiber), 525 (pea fiber), and 599 (citrus fiber).

extractions, and hydrolyses, extractions and precipitations using various chemicals (e.g., sodium hydroxide, alkaline peroxide, sulfuric acid, and alcohol).

Plant cell wall fibers are generally composed of fibers that include cellulose, pectin, β-glucan, and/or arabinoxylan, and, based on our review of the science, we consider that each of these fibers provides a beneficial physiological effect. The non-digestible carbohydrates from the plant cell wall fiber ingredients extracted from food are generally mixed and can contain variable amounts of vitamins, minerals, and macronutrients based on the methods that may be used for isolating and extracting the fiber. Examples of mixed plant cell wall fibers that we intend to consider enforcement discretion for as a dietary fiber are those obtained from whole or parts of fruits, vegetables, grains, legumes, pulses, nuts, and other plants that undergo processing methods.[11] The interrelatedness of cellulose, pectin, β-glucan, and/or arabinoxylan within the plant cell wall and the scientific evidence for each supports our decision to consider enforcement discretion for declaring these mixed plant cell wall fibers, as well as lignin, as dietary fiber if any of these plant cell wall fibers is present in a food. We can extrapolate the physiological effects of these individual fibers to these same fibers when found in combination as part of a mixed plant cell wall. These mixed plant cell wall fiber ingredients contain two or more plant cell wall fibers and the proportions can vary.

References

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[11] While not an exhaustive list, examples of mixed plant cell wall fibers that we have identified are apple fibers, bamboo fibers, barley fibers, carrot fibers, citrus fibers, cocoa fibers, corn fibers (e.g., corn hull fiber), cotton seed fibers, oat fibers (e.g., oat hull fiber), pea fibers (e.g., pea hull fiber, pea seed coat fiber, inner cotyledon pea fiber), rice bran fibers, soy fibers (e.g., soy hull fiber, soy polysaccharide, soy cotyledon fiber), sugar beet fibers, sugar cane fibers, and wheat fibers.

Arabinoxylan

Background

Arabinoxylan (AX) is a diversely composed (1→4)-β-D-xylan polymer that contains arabinose and varying uronic acid residues. AX is a hemicellulose and is a major component of the cell walls of cereal grains. The non-starch polysaccharide content in wheat bran is approximately 65% AX and 15% to 31% cellulose, whereas the non-starch polysaccharide content in wheat endosperm is approximately 85% AX. AX is a predominant non-digestible carbohydrate found in the alkali soluble fraction of psyllium husk (Bernstein et al., 2013).

Blood Glucose and Insulin Levels

We identified six studies that evaluated the effect of AX intake on blood glucose/insulin levels.

Garcia et al. (2006) (2007)

In a randomized, single-blind, controlled, cross-over intervention study, 11 overweight men and women with impaired glucose tolerance consumed white bread rolls that alternately contained no AX (control) or that were supplemented with AX for six weeks, with a six-week washout period in between. Study subjects consumed 15 grams (g) AX supplement per day supplied as two bread rolls (each containing 5 g AX concentrate) plus 5 g AX in concentrate powder form during the treatment phase of the study. The study subjects mixed the AX concentrate powder in any food of their choice. After six weeks of consuming the rolls and immediately following a 12 hour fast, fasting blood glucose levels were measured. In addition, a control or liquid meal containing AX was consumed for measuring post-prandial blood glucose levels. Blood samples were collected at various time points up to 240 minutes. Fasting serum glucose was significantly lower after AX consumption compared to the placebo control phase of the study ($P = 0.029$). No effect was observed on fasting serum insulin. Post-prandial serum glucose ($P < 0.005$) and insulin levels ($P < 0.003$) were significantly lower after AX consumption compared to the control phase of the study.

Hartvigesen et al. (2014)a

Fifteen Danish men and women with metabolic syndrome participated in a randomized, cross-over intervention study. After an overnight fast, the study subjects consumed bread that provided 50 g of digestible carbohydrate as wheat bread (control) and with bread that contained 6 g of added AX. Blood samples were drawn at various time points for up to 270 minutes. Peak blood glucose levels were significantly lower during the AX consumption phase of the study ($P < 0.001$) compared to the control phase of the study. Peak blood insulin levels were measured but not compared between the two groups.

Hartvigesen et al. (2014)b

Fifteen Danish men and women with metabolic syndrome participated in an acute, randomized, cross-over intervention study. After an overnight fast, the study subjects consumed a meal that alternately provided 50 g of digestible carbohydrate (control) or 2.6 g of added AX. Blood samples were drawn at various time points up to 360 minutes. Immediately after the 240 minute blood sample, the study subjects consumed a standard lunch. The peak glucose level was not significantly different between the AX

treatment and control phases of the study. However, the glucose area under the curve (AUC) (0 to 120 minutes) was significantly lower (80%) in the AX treatment phase of the study compared to the control phase ($P = 0.005$).

Lu et al. (2000)

In a randomized, cross-over design study, 14 healthy Australian men and women consumed three isoenergetic breakfasts of bread, margarine, and jam. The breakfasts provided 75 g of available carbohydrates containing either 0 g (control), 6 g, or 12 g of AX. After an overnight fast, blood samples were collected for up to 120 minutes. The AUC value for glucose was 20% ($P < 0.01$) and 41% ($P < 0.001$) lower in the study subjects after they had consumed the breakfasts containing 6 g and 12 g of AX, respectively, compared to the AUC value for glucose after they had consumed the control breakfast. The difference in the AUC values for glucose between the breakfasts containing 6 g and 12 g of AX was also significant ($P < 0.05$). The corresponding reduction in the AUC values for insulin was 17% ($P < 0.05$) and 32.7% ($P < 0.001$), respectively, compared with the insulin AUC values for the control breakfast phase of the study. The difference in the AUCs for insulin between the breakfasts containing 6 g and 12 g of AX was not statistically significant. An inverse relationship was observed between the amount of AX present in the breakfasts and the mean AUC for glucose ($r^2 = 0.989$, $P = 0.033$) and insulin ($r^2 = 0.999$, $P = 0.008$).

Lu et al. (2004)

In a randomized, cross-over intervention study, 15 Australian men and women with type II diabetes consumed their usual diet that was supplemented with a control bread and muffins (50% whole wheat and 50% white flour) (control) or with bread and muffins (50% whole wheat, 36% white flour) that contained 15 g of AX for five weeks each. The control and treatment bread and muffins contained the same amount of available carbohydrate. Fasting plasma glucose levels in the study subjects were significantly lower ($P < 0.05$) after they consumed the AX diet compared to the control diet. Furthermore, the two-hour oral glucose tolerance test (OGTT) was significantly lower during the AX consumption phase of the study ($P < 0.01$). There was no difference in fasting serum insulin levels between the two diet groups. After the AX diet, however, the two-hour OGTT serum insulin level was significantly lower ($P < 0.015$).

Mohlig et al. (2004)

In a cross-over design study, 15 German men and women consumed a breakfast with 0 g (control) and 6 g of AX. Post-prandial blood glucose levels were measured up to 120 minutes. There was no significant difference in post-prandial glucose values between the two groups ($P = 0.13$). Post-prandial insulin levels, however, were significantly lower in the study subjects after they had consumed the breakfast enriched with AX compared to the control phase of the study ($P = 0.035$).

Strength of the Scientific Evidence

We evaluated the strength of the scientific evidence by considering the factors provided in Section III.C of our guidance for industry entitled, "Scientific Evaluation of the Evidence on the Beneficial Physiological Effects of Isolated or Synthetic Non-Digestible Carbohydrates Submitted as a Citizen Petition (21 CFR 10.30)." Based on this evidence, we evaluated whether the findings presented in the

relevant clinical studies demonstrated that there is a beneficial physiological effect of AX to human health.

Six studies evaluated the effect of AX on blood glucose and insulin levels. The two studies that measured fasting blood glucose levels showed a statistically significant reduction in individuals with impaired glucose tolerance or with type 2 diabetes at an intake level of 15 g of AX (Garcia et al., 2006/2207; Lu et al., 2004). A significant reduction in the AUC for post-prandial glucose was demonstrated in three of four studies that provided 2.6 g, 6 g, and 12 g of AX to healthy individuals or individuals with impaired glucose tolerance (Garcia et al., 2006/2007; Hartvigesen et al. (2014)b; Lu et al., 2000). One study demonstrated a dose-response effect (6 g and 12 g) of AX on post-prandial glucose levels in healthy subjects (Lu et al., 2000). One study demonstrated that AX consumption reduced blood glucose in an oral glucose tolerance test when type 2 diabetics were given 15 g of AX (Lu et al., 2014). Three studies showed that AX consumption (6 g, 12 g, and 15 g) lowered post-prandial insulin levels (Garcia et al., 2006/2007; Lu et al., 2000; Mohlig et al., 2004). Attenuation of post-prandial glycemic response is associated with a reduced risk of diabetes and cardiovascular disease (Augustin et al., 2015). Therefore, the strength of the evidence supports that AX has a beneficial physiological effect on blood glucose and insulin levels. The evidence from which scientific conclusions could be drawn supports our decision to propose to include AX in the definition of dietary fiber and, until completion of such a rulemaking, to consider enforcement discretion for declaring the amount of AX as dietary fiber.

References

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Alginate

Background

Alginate is a soluble fiber composed of β-1,4-D-mannuronic acid and α-1,4-L-guluronic acid organized in homopolymeric compounds of either mannuronate or guluronate, or as heteropolymeric compounds, expressed as mannuronic acid to guluronic acid ratio. Alginate is extracted from brown seaweeds as the calcium, magnesium, and sodium salts of alginic acid of various species, (e.g., *Ascophyllum*, *Durvillaea*, *Ecklonia*, *Laminaria*, *Lessonia*, *Macrocystis* and *Sargassum*) (McHugh et al., 2003). Alginate is widely used in the food industry to improve texture of salad dressings, yogurts, and jellies because of its gelling, viscosifying, and stabilizing properties (Jensen et al., 2013). Common names used to identify alginate as an ingredient include sodium alginate and algin.

Blood Glucose and Insulin Levels

We identified ten studies that evaluated the effect of alginate intake on blood glucose/insulin levels. Scientific conclusions could not be drawn from four of the studies because: (1) the intervention arm included alginate, in addition to other non-digestible carbohydrates that were not controlled for, and therefore the role of alginate could not be independently evaluated (Williams et al., 2004); or (2) the study did not provide an appropriate control (Arshad et al., 2016; Hall et al., 2012; Wolf et al., 2002).

<u>Post-Prandial Blood Glucose</u>

El Khoury et al. (2014)

Twenty-four healthy Canadian males were randomly provided with the following treatments: (1) chocolate milk (CM-control), (2) alginate CM (1.25%, weight/weight), and (3) alginate CM (2.5 %, weight/weight), in a cross-over design study. Sodium alginate was composed of 56% guluronic and 44% mannuronic residues. An *ad libitum* pizza meal was served after 120 minutes of each treatment. Blood glucose was measured at pre- (0 to 120 minutes) and post- (120 to 260 minutes) meal intervals. In the pre-meal period, the addition of 2.5% alginate to CM resulted in a lower peak glucose level compared with the CM control ($P < 0.05$). In the post-meal period, the two alginate-enriched pre-loads reduced post-prandial and total glucose responses compared with CM alone ($P < 0.0001$). The AUCs were not provided. Insulin peaks, at 30 minutes, were lower by 46% following 2.5% alginate CM consumption compared with CM alone ($P < 0.01$).

Harden et al. (2012)

Forty healthy English men participated in a randomized, single-blinded, controlled, parallel trial to determine the glycemic response to a controlled test-lunch following an ionic-gelling alginate (1.5 g of sodium alginate) pre-load drink compared to an acidic-gelling control. There was a 14% lower mean peak post-prandial blood glucose at 90 minutes following the ionic-gelling alginate compared to the acidic-gelling control ($P < 0.05$). The AUC was also significantly lower with alginate consumption ($P < 0.01$). Insulin was not measured.

Jensen et al. (2012a)

In a randomized double-blind, placebo-controlled, Latin square cross-over design study, twenty Danish men and women consumed pre-load beverages at two different volumes, 330 mL-low volume (LV) and 500 mL-high volume (HV) containing alginate (3% alginate concentration equivalent to 9.9 g and 15 g, respectively), and without alginate (LV-control and HV-control). The subjects consumed the pre-load beverages 30 minutes before consuming a standard breakfast. The HV-alginate pre-load group resulted in a 40% smaller post-prandial glucose AUC compared to the HV-control group ($P = 0.046$). No difference between LV-alginate and LV-control was observed in post-prandial AUC for glucose concentration ($P = 0.93$). There was no effect on post-prandial insulin levels ($P = 0.31$).

Paxman et al. (2008)

Fourteen healthy English men participated in a randomized, single-blinded, controlled cross-over study consuming a 100 mL pre-load drink (1.5 g of sodium alginate or control), followed by a lunch. There were no significant differences after alginate consumption compared to the control for post-prandial glucose AUC ($P = 0.874$) or peak blood glucose ($P = 0.687$). Insulin was not measured.

Torsdottir et al. (1991)

Seven Swedish men with well-controlled, type 2 diabetes participated in a randomized, cross-over study consuming on two different mornings, meals with or without a 5 g sodium alginate supplement. The meals contained similar amounts of digestible carbohydrates, fats, and proteins. Sodium alginate consumption significantly reduced the post-prandial peak rise in blood glucose and serum insulin by 31% and 42%, respectively ($P < 0.02$). The AUC value was not reported.

Fasting Blood Glucose

Jensen et al. (2012b)

In a randomized, double-blinded, parallel-intervention study, 96 obese Danish men and women were assigned into two groups who consumed either an energy-restricted diet plus an alginate-based pre-load supplement (15 g) or an energy-restricted diet plus a control pre-load supplement before each of the three main meals of the day over a 12-week period. No differences were observed in fasting blood glucose between the two groups in the intention-to-treat analysis ($P > 0.1$).

Strength of the Scientific Evidence

We evaluated the strength of the scientific evidence by considering the factors provided in Section III.C of our guidance for industry entitled, "Scientific Evaluation of the Evidence on the Beneficial Physiological Effects of Isolated or Synthetic Non-Digestible Carbohydrates Submitted as a Citizen Petition (21 CFR 10.30)." Based on this evidence, we evaluated whether the findings presented in the relevant clinical studies demonstrated that there is a beneficial physiological effect of alginate to human health.

Five alginate studies measured post-prandial blood glucose levels, three studies measured post-prandial insulin levels, and one study measured fasting blood glucose levels. The findings for post-prandial insulin

levels were mixed. One study (Jensen et al., 2012a) showed no effect, and two studies (Khoury et al., 2014; Torsdottir et al., 1991) showed a significant reduction in post-prandial insulin levels. Alginate did not have a statistically significant effect on fasting blood glucose levels (Jensen et al., 2012b). Four of the five studies (Harden et al., 2012; Jensen et al., 2012a; Khoury et al., 2014; and Torsdottir et al., 1991) showed that alginate added to a beverage significantly reduced post-prandial glucose levels in healthy men and women and in men with type 2 diabetes by measuring either peak rise or the AUC after consumption. Attenuation of post-prandial glycemic response is associated with a reduced risk of diabetes and cardiovascular disease (Augustin et al., 2015). A statistically significant effect was observed with a dose of as low as 1.5 g. Therefore, the strength of the evidence supports that alginate has a beneficial physiological effect on post-prandial glucose levels. The evidence from which scientific conclusions could be drawn supports our decision to propose to include alginate in the definition of dietary fiber and, until completion of such a rulemaking, to consider enforcement discretion for declaring the amount of alginate as dietary fiber.

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Inulin and Inulin-Type Fructans[12]

Background

Inulin is a naturally occurring polysaccharide that belongs to a class of carbohydrates known as fructans. Individual fructan products may be distinguished by their source, method of production, chemical structure, and degree of polymerization (DP) (the number of fructose or glucose residues in the chain). Inulin is a mixture of fructose polymers that varies from 3 to 60 DP, with longer chain products being predominant (approximately 70%) (Food Chemicals Codex, 10th Edition). Inulin may or may not have a terminal glucose residue. The characteristic aspect of inulin structure is its linear β (2,1) linkages. Inulin is not digested by human enzymes in the gastrointestinal tract because of these linkages, but rather is fermented by microorganisms in the colon. While inulin is a soluble fiber, it does not possess some of the typical properties of other soluble dietary fibers, such as viscosity (Schneeman, 1999). Inulin is extracted from numerous plant products, many of which typically are not consumed as part of the U.S. diet (e.g., chicory root, agave, and Jerusalem artichoke). Inulin is used as a bulking agent in foods (FDA GRAS Notification No. 118).

Oligofructose (OF) is a shorter chain inulin that is extracted from plants. OF refers to fructans that have a DP < 10 and accounts for approximately 30% of total inulin present in chicory root extract. OF also can be produced from extracted inulin that is enzymatically hydrolyzed (Niness, 1999). OF is not digested by human enzymes in the gastrointestinal tract because of its β (2,1) linkages, but rather is fermented by microorganisms in the colon.

Short chain fructooligosaccharides (short chain FOS) can be manufactured from sucrose and fructose by an enzymatic process (FDA GRAS notification No.44). Short chain FOS also contain β (2,1) linkages and are fermented in the colon. The number of fructose units varies from two to four.

Common names used to identify inulin and inulin-type fructans as an ingredient include inulin, chicory root extract, chicory root, chicory root fiber, inulin from chicory, chicory vegetable fiber, fructooligosaccharide, and oligofructose.

Calcium Absorption & Markers of Bone Health

We identified twenty-three studies that evaluated the effect of inulin-type fructans on calcium absorption and/or markers of bone health. Scientific conclusions could not be drawn from 11 of these studies because: (1) no control group or an inappropriate control group was used (Abrams et al., 2007); (2) it was unclear whether the control and treatment periods were comparable and whether appropriate statistical analyses were used (Yap et al., 2005); (3) a mixture of inulin-type fructans and other nutrients or components were provided to the study subjects and were not controlled for, therefore the role of inulin and/or inulin-type fructans could not be independently evaluated (Adolphi et al., 2009); (4) unhealthy individuals with conditions that would affect mineral absorption or bone metabolism were included in the studies (e.g., ulcerative colitis, non-ambulatory individuals) (Dahl et al., 2005; Ellegard et al., 1997); or

[12] FDA received two citizen petitions requesting that inulin-type fructans derived from chicory root and extracted inulin-type fructans be listed as dietary fiber (Docket # FDA-2016-P-2736 and FDA-2016-P-2860). We have included in this review inulin and inulin-type fructans (OF, scFOS), regardless of source because of their common β (2,1) linkages.

(5) the dietary intervention was of an insufficient length of time or urine/fecal samples were collected for an insufficient length of time (e.g., one day fecal collection for balance studies or ≤ 24-hour urine collection for isotope studies, which does not capture the colonic component[13]) (Fukushima et al., 2002; van den Heuvel et al., 1998; Kim et al., 2004; Lopez-Huertas et al., 2006; Ohta et al., 1999; Uenishi et al., 2002). The remaining studies are summarized below.

Calcium Absorption

Stable Isotope Studies

Abrams et al. (2005)

In a double-blind, randomized parallel study, adolescent girls and boys (aged 9-13 years) received 8 g/day of inulin + OF from chicory root (n = 48) or a maltodextrin placebo (n = 50). The treatment or placebo was mixed in calcium fortified orange juice and consumed daily for one year. The inulin + OF was a 1:1 mixture of OF (average DP of 4) and long-chain inulin (average DP of 25). Endpoints were measured at eight weeks and at one year. Mean calcium intake, assessed by weighed food records and 24-hour dietary recall, was 907 ± 33 mg/day at baseline, 959 ± 33 mg/day at eight weeks and 906 ± 29 mg/day at one year. There were no significant differences in calcium intake between groups. Fractional calcium absorption was measured over 48 hours using dual-tracer stable isotopically labeled calcium. The oral tracer was mixed with calcium-fortified orange juice and provided with a breakfast meal. The amount of calcium in the meal varied based on usual intake of calcium (e.g., addition of dairy products for individuals with higher usual calcium intakes), but was the same for each subject at all time points. After adjusting for multiple covariates (sex, ethnicity, Tanner stage of puberty, calcium intake, *Fok1* genotype for vitamin D receptor, and calcium absorption at baseline), the consumption of inulin + OF significantly increased the percentage rate of calcium absorption compared with the control group, after eight weeks (38.5 ± 1.2 *versus* 30.0 ± 1.3, respectively; $P < 0.001$) and one year (37.7 ± 2.1 *versus* 31.7 ± 2.3, respectively; $P = 0.04$).

Griffin et al. (2002, 2003)

In the Griffin et al. (2002) study, 59 girls (aged 11-13.9 years) participated in a double-blind, randomized cross-over study in which they were provided 8 g/day of the following for three weeks each: sucrose (control), OF from chicory root, and inulin + OF from chicory root. The OF had a DP of 2-8. The inulin + OF was a mixture of 50% long chain chicory inulin (average DP = 25) and 50% OF (average DP = 4). There was a two-week washout period in between the diet periods. During the eight-week study, participants were instructed to maintain a calcium intake of approximately 1,200-1,300 mg/day by consuming a glass of calcium-fortified orange juice at breakfast and dinner, and a glass of calcium-fortified orange juice or yogurt with lunch. Treatments and placebo were mixed with orange juice during the two three-week intervention periods. Calcium intake, assessed by weighed food records, was not significantly different between OF, inulin + OF, and placebo phases (mean intake ranged from ~1500-1600 mg/day). Calcium absorption was measured using dual-tracer stable isotopically labeled calcium over 48 hours. The oral tracer was mixed with calcium-fortified orange juice and was provided with a low-calcium breakfast and 4 g of either placebo, OF, or inulin + OF. The mid-day meal contained 400

[13] Urine collection of 24 hours or less is considered to be insufficient for measurement of calcium absorption if the treatment is acting in the lower gut, as is assumed with inulin-type fructans (Weaver et al., 2006).

mg of calcium, while the evening meal contained another serving of calcium-fortified orange juice with the tracer and 4 g of either placebo, OF, or inulin + OF. There was no significant difference in fractional calcium absorption (%) between the control phase of the study (31.8 ± 9.3) and the OF phase of the study (31.8 ± 10.0) ($P > 0.05$). However, there was a significant increase in calcium absorption with inulin + OF (38.2± 9.8) compared to the control (32.3 ± 9.8) ($P < 0.01$). Absolute calcium absorption (mg/day) also was significantly increased with inulin + OF compared with placebo (575 ± 148 *versus* 485 ± 154; $P < 0.01$).

In the Griffin et al. (2003) study, data from 29 girls in the Griffin et al. 2002 study were combined with 25 additionally recruited girls (aged 10-15 years) to evaluate the effect of 8 g/day inulin + OF from chicory root (the same product as used in Griffin et al. 2002 study), compared to a placebo (sucrose), on calcium absorption measured by dual-tracer stable isotopes. The treatment and placebo were consumed by the 25 new participants in a double-blind, randomized cross-over design study, for three weeks each (separated by a two-week washout period). The study subjects were instructed to increase their calcium intake to 1,200 mg/day by consuming calcium-fortified orange juice (two glasses per day) during the entire eight-week study period. Mean calcium intake, assessed by weighed food records, was 1390 ± 453 mg/day. The oral tracer was provided in 240 mL of calcium-fortified orange juice with a low-calcium breakfast and 4 g of inulin + OF or the placebo. An additional 240 mg of calcium-fortified orange juice with tracer was provided with a low-calcium evening meal. The overall calcium absorption percentage measured over 48 hours was significantly higher with inulin + OF (36.1 ± 9.8) compared to placebo (33.1 ± 9.2) ($P < 0.05$).

van den Heuvel et al. (1999)

In a double-blind, randomized cross-over design study, 12 male adolescents (aged 14-16 years) consumed orange juice containing 5 g of either OF derived from chicory root or sucrose (control), three times daily (with breakfast, lunch and dinner) for nine days each (15 g/day). The study subjects were asked to consume their usual diets, but to restrict consumption of fiber-rich and oligosaccharide-containing products. On the last two days of each treatment period, participants stayed in a metabolic unit and consumed a controlled diet which contained 1267 mg of calcium. On the eighth day of each treatment period, absorption was measured using dual-tracer stable isotopically-labeled calcium over 36 hours. The oral tracer was provided in orange juice containing OF or the control and was consumed with a standard breakfast (~200 mg calcium). The mean increase in true fractional calcium absorption was significantly higher after the OF compared with the control phase (% mean difference = 10.8 ±5.6; $P < 0.05$, one-sided).

van den Heuvel et al. (2009)

The effect of short-term and long-term consumption of short chain FOS on mineral absorption was evaluated in 14 adolescent girls with calcium intake below the Dutch recommended amount of 1,100 mg/day. In a double-blind, randomized cross-over design study, the study subjects consumed 10 g of short chain FOS or maltodextrin (control) for 37 days each, separated by a 12 day washout period. In the case of the short chain FOS treatment, the short chain FOS was consumed daily for the first eight days of the treatment period, followed by intermittent consumption of short chain FOS or of the placebo for the remainder of the study phase; the study subjects consumed short chain FOS on 16 of the remaining 28 days. The subjects were instructed to dissolve the short chain FOS or the placebo in hot or cold dairy

beverages and to not consume prebiotics and probiotics during the study. The mean calcium intake, assessed by dietary diaries, was 644 ± 194 mg/day. True calcium absorption was measured using dual-tracer stable isotopes in urine on day 8 and day 36 of each study period. The oral tracer was dissolved in orange juice and consumed as part of a standard breakfast meal (261 mg of calcium). There were no significant differences in calcium absorption between the short chain FOS (short- or long-term consumption) and control phases ($P > 0.05$).

Holloway et al. (2007)

In a double-blind, randomized cross-over design study, 15 post-menopausal women (mean age = 72 years) consumed 10 g/day of inulin + OF from chicory root or maltodextrin (control) for six weeks. The study subjects with calcium intake of less than 800 mg/day were provided a calcium carbonate supplement (500 mg/day) throughout the study. The subjects were asked to consume the products with heated coffee or tea. There was a six-week washout period between the diet periods. The inulin + OF treatment was a 1:1 mixture of chicory OF (DP of 3 to 8, with an average DP of 4) and long-chain inulin (DP of 10 to 65, with an average DP of 25). The mean calcium intake was not significantly different between the inulin + OF (1086 ± 232 mg/day) and control phases of the study (1018 ± 251 mg/day) ($P > 0.05$). Calcium absorption was measured before and after each treatment period using dual-tracer stable isotope methods over 72 hours. The oral tracer was provided in 118 mL of calcium fortified orange juice as part of a standardized test meal (English muffin, margarine, jelly, 118 mL of additional calcium fortified orange juice, and 237 mL of decaffeinated coffee/tea), providing a total of 396 mg of calcium. The mean change in calcium absorption (%) was significantly higher between the inulin + OF phase of the study compared to the control phase (5.1 ± 2.1 *versus* -3.3 ± 2.2; $P < 0.05$).

Martin et al. (2010)

Fourteen healthy adolescent girls (aged 11-13 years) with calcium intake of 567 ± 213 mg/day participated in a double-blind, randomized cross-over design study in which they consumed a controlled diet that included calcium fortified cereal (1059 mg of calcium) that contained 0 g/day (control) or 9 g/day of inulin + OF from chicory root for three weeks each. There was a two-week washout period between the diet periods. The controlled diet provided a total of ~1500 mg of calcium. The treatment was a 1:1 mixture of OF (DP of 2 to 8, with an average DP of 4) and inulin (DP of 10 to 65, with an average DP of 25). Calcium retention and net calcium absorption were measured by metabolic balance. Fractional calcium absorption was measured using a single oral stable isotope. Blood samples were collected at 0 and 72 hours, urine was collected for four days, and fecal samples were collected for five days. The tracer was provided as calcium carbonate in capsules and consumed during the test meal (cereal and milk), which provided 500 mg of calcium and 0 or 3 g of inulin + OF. Calcium absorption (net or fractional) and retention were not significantly different between the inulin + OF and the control phases of the study ($P > 0.05$).

Tahiri et al. (2003)

Post-menopausal French women ($n = 12$) received 10 g/day of short chain FOS or placebo (sucrose) for five weeks each in a randomized, cross-over, double-blind study. A washout period of at least three weeks separated the diet periods. Baseline calcium intake was 1171 mg/day. The study subjects were instructed to decrease their calcium intake and to not take supplements (vitamins, minerals, polyols,

fiber, or FOS) during the study and for the three months before the start of the study. During the first four days of each of the treatment periods, 5 g/day of short chain FOS was provided to the subjects to allow for adaptation. Participants consumed their usual diet for the first 23 days of each study period. A low-fiber controlled diet (12 g dietary fiber/day, 900 mg/day of calcium) was provided to the participants for the remainder of each diet period (10-12 days), and a single oral stable isotope was provided during the midday meal on day 29. Calcium intake, assessed by a food intake questionnaire, was 900 mg/day. Blood, urine, and fecal samples were collected on day 28 to serve as baseline values before isotope intake. Following the stable isotope dose, blood was collected at 24 hours, urine was collected for two days (two 24-hour collections), and fecal samples were collected for five to seven days. There was no significant difference in isotopically labeled calcium absorption or apparent calcium absorption between short chain FOS consumption and the control ($P > 0.05$).

Metabolic Balance Studies

Abrams et al. (2005)

Adolescent girls and boys (aged 9-13 years) were randomly assigned to receive either 8 g/day of inulin + OF from chicory root (n = 48) or maltodextrin (control) (n = 50), which were mixed in calcium fortified orange juice and consumed daily for one year. The inulin/OF was a 1:1 mixture of OF (average DP of 4) and long-chain inulin (average DP of 25). Bone mineralization measurements were performed after one year by dual-energy X-ray absorptiometry (DXA). After adjusting for multiple covariates (sex, ethnicity, Tanner stage of puberty, and *Fok1* genotype for vitamin D receptor), change in whole-body bone mineral content (g) and change in bone mineral density (g/cm^2) were significantly greater in the inulin + OF group (245 ± 11 and 0.047 ± 0.004, respectively) compared to the control group (210 ± 10 and 0.032 ± 0.004, respectively) ($P < 0.05$).

Coudray et al. (1997)

Nine healthy young men (mean age = 22 years) were given a controlled diet (859 ± 196 mg/day of calcium) with or without (control) 40 g/day of inulin extracted from chicory root in a 28-day randomized cross-over design study. The inulin diet consisted of two days of the control diet, followed by 14 days of progressive increase in inulin consumption, and then 12 days of constant inulin consumption. The inulin was a polymer of 15 fructose units and one glucose unit, and was added to bread (24 g/day) and liquid foods (16 g/day). Urine and fecal samples were collected between day 20 and day 28 and blood was collected at day 25. The consumption of inulin significantly increased the apparent absorption of calcium (%) compared to the control group (33.7 ± 12.1 *versus* 21.3 ± 12.5, respectively; $P < 0.01$). The consumption of inulin resulted in a significant positive calcium balance compared to the control ($+91.8 \pm 115$ *versus* -10.1 ± 136 mg/day; $P < 0.05$).

Holloway et al. (2007)

In a double-blind, randomized cross-over design study, 15 post-menopausal women (mean age = 72 years) consumed 10 g/day of inulin + OF from chicory root or a placebo (maltodextrin) for six weeks. The study subjects with calcium intake of less than 800 mg/day were provided a calcium carbonate supplement (500 mg/day) throughout the study. The subjects were asked to consume the products with heated coffee or tea. There was a six-week washout period between the diet periods. The inulin + OF

treatment was a 1:1 mixture of chicory OF (DP of 3 to 8, with an average DP of 4) and long-chain inulin (DP of 10 to 65, with an average DP of 25). The mean calcium intake was not significantly different between the inulin + OF (1086 ± 232 mg/day) and control phases of the study (1018 ± 251 mg/d) ($P > 0.05$). Deoxypyridinoline cross-links, a marker of bone resorption activity, and osteocalcin, a measure of bone formation activity, were measured. There was no significant difference in either marker of bone activity after six weeks when comparing the inulin + OF and control phases of the study ($P > 0.05$).

van den Heuvel et al. (2009)

The effect of short chain FOS on markers of bone resorption, pyridinoline and deoxypyridinoline, was evaluated in adolescent girls with calcium intake below the Dutch recommended amount of 1,100 mg/day (n = 14). In a double-blind, randomized cross-over design study, the study subjects consumed 10 g of short chain FOS or maltodextrin (control) for 37 days each, separated by a 12 day washout period. The study subjects consumed short chain FOS daily for the first eight days of the treatment period, followed by intermittent consumption of short chain FOS or maltodextrin for the remainder of the treatment period (short chain FOS was consumed on 16 of the remaining 28 days). Participants were instructed to dissolve short chain FOS or the maltodextrin in hot or cold dairy beverages, and to not consume prebiotics and probiotics during the study. Mean calcium intake, assessed by dietary diaries, was 644 ± 194 mg/day. There were no significant differences in markers of bone resorption between the short chain FOS and control groups ($P > 0.05$).

Mathey et al. (2008)

In this randomized, parallel, placebo-controlled, double-blind study, post-menopausal French women (n = 39) were given soy products (100 mg/day of isoflavones aglycon equivalents) for 30 days and then randomized into one of the following groups for 30 days: (1) soy (n = 12; control); (2) soy and short chain FOS (7 g/day; n = 13); or (3) soy and lactic bacteria (n = 14). Markers of osteoblastic activity and bone formation (serum bone-specific alkaline phosphatase) and bone resorption (urinary deoxypyridinoline) were measured and reported as percent changes from baseline. There was no significant difference in bone-specific alkaline phosphatase when comparing the short chain FOS and control groups ($P > 0.05$). Deoxypyridinoline was lower in the short chain FOS group compared to the control group. However, statistical values were not reported, and therefore, it is not clear if this finding was statistically significant. Subgroup analysis of women in early stage menopause demonstrated a significant decrease in deoxypyridinoline in the short chain FOS group compared with the control group ($P < 0.02$), but not in women in late stage menopause (P-value not reported).

Slevin et al. (2014)

Non-osteoporotic post-menopausal women participated in a double-blind, parallel design, randomized controlled study where they received 800 mg/day of calcium or calcium (800 mg/day) + short chain FOS (3 g/day) (n = 100/group), for 24 months. Bone mineral density and bone turnover markers were measured at baseline and 24 months. Bone turnover markers also were measured at 12 months. There was a significantly smaller decline over time in total-body bone mineral density in the calcium + short chain FOS group (-0.4 ± 1.7%) compared to calcium alone (-0.7 ± 1.8%) ($P = 0.03$). There were no significant differences in markers of bone turnover between the calcium and calcium + short chain FOS groups at 12 or 24 months ($P > 0.05$).

de Souza et al. (2010)

In a double-blind, randomized, cross-over design study, 60 pre-pubescent girls (aged 9-12 years) with low habitual calcium intake (mean intake = 500 mg/day) consumed calcium-enriched formulations, supplemented with or without (control) inulin + OF (8 g/day) from chicory root, for 11 weeks each with a three-week washout period between the study periods. Blood was collected at 4, 8, and 11 weeks during each study period. There was no significant difference in serum bone alkaline phosphatase activity between the inulin + OF and control groups at any time point ($P > 0.05$).

Tahiri et al. (2003)

Post-menopausal French women (n = 12; menopause duration of 2-22 years) received 10 g/day of short chain FOS or placebo (sucrose) for five weeks each in a randomized, cross-over, double-blind study. A washout period of at least three weeks separated the diet periods. Baseline calcium intake was 1171 mg/day. The study subjects were instructed to decrease their calcium intake and to not take supplements (vitamins, minerals, polyols, fiber, or FOS) during the study and for the three months before the start of the study. During the first four days of each of the treatment periods, 5 g/day of short chain FOS was provided to the subjects to allow for adaptation. Participants consumed their usual diet for the first 23 days of each study period. A low-fiber controlled diet was provided to the subjects for the remainder of each study period (10-12 days). Markers of bone formation (plasma osteocalcin) and resorption (urinary deoxypyridinoline) were measured. There was no significant effect of short chain FOS consumption on markers of bone formation and bone resorption ($P > 0.05$).

Strength of the Scientific Evidence

We evaluated the strength of the scientific evidence by considering the factors provided in Section III.C of our guidance for industry entitled "Scientific Evaluation of the Evidence on the Beneficial Physiological Effects of Isolated or Synthetic Non-Digestible Carbohydrates Submitted as a Citizen Petition (21 CFR 10.30)." Based on this evidence, we evaluated whether the findings presented in the relevant clinical studies demonstrated that there is a beneficial physiological effect of inulin and inulin-type fructans to human health. Fermentation of carbohydrates has been shown to increase the production of short chain fatty acids, resulting in increased solubility and active and passive diffusion of ionized calcium in the cecum of rats (Lutz and Scharrer, 1991). Studies that use stable-isotopically labeled calcium are considered to be the most reliable and direct measures of calcium absorption.

In our review of the scientific data, information, and comments, we identified 23 studies that evaluated the effect of inulin and inulin-type fructans on calcium absorption or markers of bone health. Scientific conclusions could not be drawn from 11 of these studies. The studies demonstrating a beneficial effect of inulin and/or inulin-type fructans on calcium absorption or markers of bone health were conducted with a range of doses and sample sizes (3 to 40 g/day; n = 9 to 100). The duration of the studies ranged from nine days to two years.

The studies that evaluated bone health measured bone mineral density and/or markers of bone turnover. Two large (n = 48-100), long-term (1-2 years) studies measured the effect of inulin and/or inulin-type fructans on bone mineral density. Both studies reported a beneficial effect of inulin and/or inulin-type fructans (i.e., inulin + OF and short chain FOS) on bone mineral density (Abrams et al., 2005; Slevin et

al., 2014). There was no effect of inulin and/or inulin-type fructans on markers of bone turnover (e.g., osteocalcin, bone-specific alkaline phosphatase, urinary deoxypyridinoline) in the studies that measured these markers (Holloway et al., 2007; van den Heuvel et al., 2009; Mathey et al., 2008; Slevin et al., 2014; de Souza et al., 2010; Tahiri et al., 2003).

There were nine studies measuring the effect of inulin and/or inulin-type fructans on calcium absorption, eight of which used stable-isotopically labeled calcium and one of which was a metabolic balance study. Of the nine studies, six reported a statistically significant beneficial effect of inulin and/or inulin-type fructans on calcium absorption (Abrams et al., 2005; Coudray et al., 1997; Griffin et al., 2002; Griffin et al., 2003; Holloway et al., 2007; van den Heuvel et al., 1999). Griffin et al., 2002 reported a beneficial effect of inulin + OF on calcium absorption and no effect of OF alone.

Bone mineral density is a recognized surrogate endpoint for osteoporosis and fracture risk. Calcium has been determined to be a nutrient of public health significance and is required on the Nutrition Facts label (21 CFR 101.9(c)(8) (ii)) because of its beneficial role in bone health and reducing the risk of osteoporosis (21 CFR 101.72). The strength of the evidence supports that inulin-type fructans extracted from chicory root or extracted inulin-type fructans from all sources, as well as synthetic inulin-type fructans, have a beneficial physiological effect on bone mineral density and absorption of calcium. The evidence from which scientific conclusions could be drawn supports our decision to propose to include inulin and inulin-type fructans in the definition of dietary fiber and, until completion of such a rulemaking, to consider enforcement discretion for declaring the amount of inulin and inulin-type fructans as dietary fiber.

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High Amylose Starch (Resistant Starch 2)

Background

Resistant starch 2 (RS2) is uncooked native starch that is comprised primarily of α-1,4 glycosidic links that are inaccessible to enzymes; it is found in products such as raw green bananas, raw potatoes, and uncooked high amylose maize/corn and potato starch.

Common names used to identify RS2 as an ingredient include high-amylose maize starch and high-amylose corn starch. "High-amylose" can also be used to describe other sources of RS2 (i.e., high-amylose [source] starch).

Blood Glucose and Insulin Levels

We identified 40 studies that evaluated the effect of RS2 consumption on blood glucose and insulin levels. For evaluating post-prandial blood glucose and insulin levels, scientific conclusions could not be drawn from 25 of these studies because: (1) an inappropriate control was used (Anderson et al., 2010; Behall et al., 1988; Behall et al., 1989; Behall and Howe, 1995; Behall and Hallfrisch, 2002; Behall et al., 2006a; Bodinham et al., 2012; Brighenti et al., 2006; Dainty et al., 2016; Ekström et al., 2013; Granfeldt et al. 1995; Goddard et al., 1984; Heijnen et al., 1995a; Heijnen et al., 1995b; Higgins et al., 2004; Hoebler et al., 1999; Juliano and Goddard et al., 1986; Luhovvy et al., 2014; Noakes et al., 1996; Quilez et al., 2007; Wolever et al., 2016); (2) the intervention provided study subjects with RS2, in addition to other non-digestible carbohydrates that were not controlled for, and therefore the role of RS2 could not be independently evaluated (Ekström et al., 2016); or (3) glucose response was measured solely in response to the direct consumption of RS2 instead of the consumption of RS2 that had been added to a food and/or a beverage (i.e., glycemic index) (Haub et al., 2010; Jenkins et al., 1998; Ranganathan et al., 1994).

<u>Fasting Blood Glucose and Insulin Levels</u>

Behall et al. (1989)

Twelve men consumed a diet containing 35% of calories as 70% amylose or 70% amylopectin starch for five weeks each in a cross-over design study. The study did not provide the amount of RS2 contained in the 70% amylose diet. The study evaluated the effect of substituting amylopectin with high amylose corn starch. Mean fasting blood glucose and insulin levels were not significantly different between the two starch diets ($P > 0.05$).

Bodinham et al. (2012)

In a randomized, single-blinded, cross-over study, 12 men and women with insulin resistance consumed either 40 g/day of RS2 from high amylose corn starch or a placebo containing a highly digestible starch in a ready-to-use sachet for four weeks each, separated by a four-week washout period. The consumption of 40 g/day of RS2 resulted in significantly lower fasting blood

glucose levels compared to the placebo (4.8 *versus* 5.0 mmol/L) ($P = 0.049$), but no significant difference was observed for fasting insulin ($P > 0.05$).

Dainty et al. (2016)

In a randomized, double-blinded, cross-over study, 24 Canadians at risk of type 2 diabetes were instructed to consume one bagel per day containing either 6.8 g (control) or 25 g of RS2 from high-amylose corn starch for eight weeks (56 days) each, separated by a four-week washout period. Fasting blood samples were collected on days 1 and 57. On study day 57, no significant difference in fasting blood glucose was observed between the control and RS2 bagel groups ($P > 0.05$). Fasting insulin levels however were significantly lower for the RS2 treatment group compared to the control bagel ($P = 0.04$).

Gower et al. (2016)

In a randomized, placebo-controlled, double-blinded, cross-over study, 23 American women (14 insulin resistant and 9 insulin sensitive) consumed two cookies per day containing 0 g (control), 15 g, or 30 g of RS2 from high-amylose corn starch for four weeks each, separated by a four-week washout period. No significant differences in fasting blood glucose and fasting insulin levels were observed after four weeks of daily consumption of either 15 g or 30 g of RS2 compared to the control group ($P > 0.05$).

Maki et al. (2012)

In a randomized, double-blinded, placebo controlled, cross-over study, 33 men and women consumed 0 g, 15 g, or 30 g/day of RS2 as a supplement for four weeks each, separated by a three-week washout period. Highly digestible corn starch served as the control for the study. No significant difference in fasting blood glucose and fasting insulin levels between the three diets was observed for either the men or women ($P > 0.05$).

Noakes et al. (1996)

In a randomized, cross-over study, 23 hypertriglyceridemic Australians consumed diets that contained 25% of carbohydrate as high amylose corn starch (approximately 17 g of RS2 for the women subjects and 25 g of RS2 for the men) or a low-amylose control diet (1.3 g of RS2) for four weeks each with no washout period between the intervention period. The study substituted amylopectin with high amylose corn starch on four test foods. After four weeks of consuming the two diets, there was no significant difference in fasting plasma glucose levels or fasting insulin between the low amylose (control) and high amylose diets ($P > 0.05$).

Penn-Marshall et al. (2010)

In a double blind, cross-over study, 15 men and women at risk of type 2 diabetes consumed bread containing 12 g of added RS2 isolated from high amylose corn starch or a control bread for six weeks each, separated by a two-week washout period. There was no significant difference in

fasting blood glucose levels or fasting insulin levels between the RS2 and control diets ($P > 0.05$).

Robertson et al. (2005)

Ten healthy men and women were provided a placebo supplement (control) or a supplement containing 30 g of RS2 for four weeks each, separated by a four-week washout period. No significant difference in fasting plasma glucose (5.04 *versus* 5.06 mmol/L; $P > 0.05$) and fasting insulin (79.8 *versus* 84 mmol/L; $P > 0.05$) was observed between the control and the RS2 diets.

Robertson et al. (2012)

In a randomized, single-blinded, cross-over study, 15 English men and women who had insulin resistance were provided ready-to-use sachets containing either a placebo (27 g of rapidly digestible starch (RDS)) (control) or 27 g of RDS plus 40 g of RS2 from high amylose to be consumed with food and/or drink for eight weeks each, separated by an eight-week washout period. There was a significant decrease in fasting blood glucose levels (5.2 *versus* 5.0 mmol/L; $P = 0.017$) and fasting insulin (129 *versus* 108 picomoles per liter (pmol/L); $P = 0.041$) during the RS2 consumption phase of the study compared to the control phase.

Post-Prandial Blood Glucose and Insulin Levels

Behall and Scholfield (2005)

In a randomized, Latin square cross-over study, 24 U.S. men and women consumed corn chips or corn muffins made with low amylose (30%) or high amylose (70%) corn starch. The study evaluated the effect of substituting amylopectin with high amylose corn starch while matching for available carbohydrate. The low amylose corn chips and corn muffins did not contain RS2 and served as a control. The RS2 content was 8.7 g or 11.9 g for the high amylose corn chips and 16 g or 24.7 g for the high amylose corn muffins. The study also evaluated the effect of particle size by using either corn starch or cornmeal plus starch. The study subjects' post-prandial blood glucose levels were measured immediately after they consumed the corn chips or muffins for up to three hours. The post-prandial glucose and insulin AUCs were significantly lower for the high amylose compared to the low amylose corn chips, regardless of particle size ($P < 0.0001$). No significant differences were observed on the post-prandial glucose AUC after consumption of high amylose compared to low amylose muffin, regardless of particle size ($P > 0.05$). The post-prandial insulin AUCs were significantly lower for the high amylose compared to the low amylose muffin made with corn meal plus starch ($P < 0.023$), but not for muffin made with corn starch ($P > 0.05$).

Behall et al. (2006b)

In a Latin square cross-over study, 20 U.S. normal-weight and overweight men consumed 9 different muffins containing: (1) 75 g of available carbohydrate; (2) either 0.1 g, 3.1 g, or 5.8 g of β-glucan; and added (3) either 0.1 g (RS2 control), 6.1 g, or 11.6 g of RS2 from high amylose cornstarch. The plasma glucose levels were significantly lower between the high RS2 muffin

group compared to the low RS2 muffin group at 30 minutes (with low and high levels of β-glucan) and at 60 minutes (with medium level of β-glucan) ($P < 0.05$). There was no significant difference in the plasma glucose and insulin AUCs between the control and two levels of RS2 when low, medium, or high levels of β-glucan were present ($P > 0.05$).

Bodinham et al. (2010)

In a randomized, single-blinded, cross-over study, 20 young men consumed either 32 g of a rapidly digestible starch (RDS) (control) or 32 g of RDS plus 48 g of RS2 that was added as a supplement to test breakfasts and lunch meals. There was no significant difference in post-prandial blood glucose levels between the RS2 supplement group and the control supplement group ($P > 0.05$). The post-prandial insulin levels were significantly lower following the RS2 supplement compared to the placebo supplement ($P = 0.029$).

Bodinham et al. (2013)

In a randomized, single-blinded, cross-over study, 30 healthy English men were provided with 32 g of RDS (control group) or 32 g of RDS plus 48 g of RS2 from high amylose maize that were consumed in a mousse consumed at breakfast and lunch. Blood samples were collected for three hours after breakfast and four hours after lunch. There was no significant difference in post-prandial blood glucose levels when the study subjects consumed the RS2 supplement compared to the control ($P > 0.05$) for both breakfast and lunch. After lunch, the incremental AUC for insulin was significantly lower when subjects consumed the RS2 supplement compared to the control ($P < 0.05$).

Kwak et al. (2012)

In a randomized, double-blinded, parallel study, 85 Korean men and women with pre-diabetes or type 2 diabetes were assigned either to a group consuming rice containing 6.51 g RS2 or 0 g RS2 (control) for four weeks. After the intervention, subjects received a meal tolerance test after an overnight fast which contained the respective rice consumed during the intervention. Post-prandial blood glucose levels were significantly lower at 30 and 120 minutes when the rice containing RS2 was consumed compared to the control rice ($P < 0.05$). Post-prandial glucose AUC was significantly lower when rice containing RS2 was consumed compared to the control rice ($P < 0.05$), but not the post-prandial insulin AUC ($P > 0.05$). Scientific conclusions on the data from post-prandial insulin levels could not be drawn because insulin response in individuals with diabetes cannot be extrapolated to the healthy population.

MacNeil et al. 2013

In a randomized, cross-over study, 12 Canadian men and postmenopausal women with type 2 diabetes consumed four different bagel meals which provided: 1.18 g of RS2 (treatment A-control); 21 g of RS2 (treatment B); 33 g of RS2 (treatment C); and 21 g of RS2 (treatment D). Different amounts of total and digestible carbohydrate were provided to the study subjects. Treatment B, for example, had the lowest amount of digestible carbohydrate compared to the other treatments arms. Three hours after the study subjects consumed the test bagel (first meal),

they consumed a standard sandwich (second meal). After the first meal, post-prandial glucose was significantly lower at 60, 90, and 120 minutes after treatment B compared to the other treatment groups and the study subjects' AUCs also were significantly lower for treatment B compared to treatments C and D ($P < 0.05$). After the second meal, the peak glucose levels were not significantly different among all four treatment groups ($P > 0.05$). Scientific conclusions on the data from post-prandial insulin levels could not be drawn because insulin response in individuals with diabetes cannot be extrapolated to the healthy population.

Nilsson et al. (2008)

In a randomized, cross-over study, 15 men and women were provided cereal-based test breads that were consumed in the evening and were made of either white wheat flour containing approximately 8 g of RS2 from high amylose corn starch or 1.3 g RS2 (control). Post-prandial blood glucose levels were measured for three hours after the study subjects had consumed two meals (the test evening meal and a standardized breakfast on the next day). Although consumption of the bread containing RS2 significantly lowered the study subject's blood glucose peak increments compared to the consumption of the control bread ($P < 0.05$) after the standardized breakfast, there was no significant difference in the post-prandial blood glucose and insulin AUCs between the two test breads ($P > 0.05$).

Rahat-Rozenbloom et al. (2017)

In a randomized, cross-over study, 25 men and women (12 normal weight and 13 overweight or obese study subjects) consumed test drinks containing either 75 g of glucose (control) or 75 g of glucose with 28 g of RS2. Four hours after the study subjects started consuming the test drinks, a standard lunch (second meal) was provided to them. Blood was drawn from the subjects at several time intervals up to six hours after they consumed the test drinks. The overweight and obese subjects had higher fasting insulin levels, but similar fasting glucose levels, compared with normal weight subjects. There was no significant difference between post-prandial blood glucose and insulin levels after the test drinks. However, after the standard lunch, the post-prandial glucose and insulin AUCs (measured over four to six hours) were significantly lower when subjects had consumed the RS2 test drink prior to lunch compared to the control phase of the study ($P < 0.05$).

Robertson et al. (2003)

In a randomized, single-blinded, cross-over study, 10 healthy men and women consumed, within one day, two low fiber diets, one of which was supplemented with 60 g of RS2 from high amylose corn starch. On the following morning, a RS2-free meal tolerance test was carried out for five hours to measure the effect of the prior meals on post-prandial glucose and post-prandial insulin levels. The study subject's glycemic and insulin responses were significantly lower after consuming the RS2 diet compared to the control ($P = 0.037$ and $P = 0.038$, respectively).

Robertson et al. (2005)

In a randomized, single-blinded, cross-over study, 10 healthy men and women were provided a placebo supplement (control) or a supplement containing 30 g of RS2 for four weeks each, separated by a four-week washout period. The study subject's post-prandial insulin AUCs were significantly lower for the RS2 supplement group ($P = 0.024$) compared to the control group, but their post-prandial glucose AUCs were not ($P > 0.05$).

Weickert et al. (2005)

In a randomized, single-blinded, cross-over study, nine healthy German women consumed white bread (control) or bread containing 10.4 g of RS2 per portion to measure the effects of RS2 consumption on post-prandial glucose and insulin levels. The effects were measured immediately after the consumption of either a white or RS2 bread (day 1) and as a delayed effect, when post-prandial glucose and insulin levels were measured after consumption of only white bread on day 2. Blood samples were taken from study subjects at baseline until five hours after consumption of one portion of bread. No significant difference in post-prandial glucose and insulin AUCs was observed between the control group and the RS2 treatment group ($P > 0.15$). There also was no significant difference in the post-prandial glucose and insulin AUCs after consumption of white bread (control) on day 2 (delayed effect).

Strength of the Scientific Evidence

We evaluated the strength of the scientific evidence by considering the factors provided in Section III.C of our guidance for industry entitled "Scientific Evaluation of the Evidence on the Beneficial Physiological Effects of Isolated or Synthetic Non-Digestible Carbohydrates Submitted as a Citizen Petition (21 CFR 10.30)." Based on this evidence, we evaluated whether the findings presented in the relevant clinical studies demonstrated that there is a beneficial physiological effect of RS2 to human health.

Nine studies reported on post-prandial insulin response in healthy subjects (Behall and Scholfield 2005; Behall et al., 2006b; Bodinham et al., 2010; Bodinham et al., 2013; Nilsson et al., 2008; Rahat-Rozenbloom et al., 2017; Robertson et al., 2003; Robertson et al. 2005; Weickert et al., 2005). Six studies, including the largest studies, reported reductions in post-prandial insulin response when RS2 was added to a food or given as a supplement, including two studies that showed a reduction in the post-prandial insulin AUC after the second meal (Bodinham et al., 2013; Rahat-Rozenbloom et al., 2017).

The six studies demonstrated that RS2 reduced post-prandial insulin response in the absence of a rise on post-prandial glucose. A lower insulin response after a meal, without a higher glycemic response among healthy subjects, is a beneficial physiological effect of RS2 because less insulin is required to achieve a similar glycemic effect. Attenuation of post-prandial insulin response is associated with a reduced risk of coronary heart disease (Bhat et al., 2013). Therefore, the strength of the evidence supports that RS2 has a beneficial physiological effect on post-prandial insulin levels. The evidence from which scientific conclusions could be drawn supports our decision to propose to include RS2 in the definition of dietary fiber and, until

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IV. Additional Synthetic Non-Digestible Carbohydrates Subject to FDA's Consideration of Enforcement Discretion if Declared as Dietary Fiber

Galactooligosaccharides (GOS)

Background

GOS is produced by the enzymatic treatment of lactose to produce oligosaccharides of varying lengths (typically between 2 and 8 saccharide units) including various linkages of galactose (e.g., β-(1-4), β-(1-6) galactose) and a terminal glucose (Macfarlane et al., 2008). GOS is a prebiotic and is used to improve the texture of foods and as a bulking agent.

Calcium Absorption

We identified three studies that evaluated the effect of GOS consumption on calcium absorption. Scientific conclusions could not be drawn from one study (van den Heuvel et al., 1998) because urine samples were collected for an insufficient length of time. Urine collection of 24 hours or less is considered to be insufficient for measurement of calcium absorption if the treatment is acting in the lower gut, as is assumed with GOS (Weaver et al., 2006).

van den Heuvel et al. (2000)

In a double-blind, randomized, dual-tracer stable isotope, cross-over design study to assess the effect of GOS intake on calcium (Ca) absorption, 12 healthy Dutch postmenopausal women drank a yogurt beverage twice a day that provided either 20 g/day GOS or sucrose (control) for nine days each. On day eight of each treatment period, ^{44}Ca and ^{48}Ca were administered orally and intravenously, respectively, to all study subjects. Calcium absorption was evaluated by measuring the excretion of calcium isotopes in urine collected over 36 hours after oral and intravenous isotope administration. Compared to the control, GOS consumption increased calcium absorption by 16%, from an average of 20.6 to 23.9% ($P = 0.04$, one-sided). The increased calcium absorption was not accompanied by a significant difference in urinary calcium excretion ($P = 0.45$, one-sided). No correlation was found between the GOS-enhanced effect of calcium absorption and excretion in urine at the 36-hour mark, implying that GOS also may increase the uptake of calcium by the bones and/or inhibit bone resorption.

Whisner et al. (2013)

In a randomized, double-blind, dual-tracer stable isotope, cross-over study, 31 healthy U.S. adolescent girls (10-13 years) consumed smoothie drinks twice daily that provided either 0 g (control), 5 g/day, or 10 g/day of GOS for three 3-week periods in a random order. Calcium chloride ($^{44}CaCl_2$) was added to the smoothies for each treatment and allowed to equilibrate overnight before consumption. A second stable isotope, ^{43}Ca (3.5 mg) as $^{43}CaCl_2$, was given intravenously one hour after the oral isotope. All urine samples were collected for four 12-hour time points up to 48 hours following administration of the isotope. Fractional calcium absorption was determined from urinary calcium excretion over 48 hours at the end of each three-week period using a dual stable isotope method. Over all four time points, 5 g/day and 10

g/day of GOS had significantly greater effects on fractional calcium absorption than the control ($P = 0.0132$). Significant improvements in calcium absorption were observed for both 5 g and 10 g GOS ($P < 0.02$). This paper noted that an approximate 10% increase in calcium absorption is estimated to equate to an additional 130 mg/day or 49 g/year of calcium being available for deposition into bone. In addition to increasing calcium absorption, GOS consumption did not affect calcium excretion ($P > 0.05$), which would be expected to lead to improved calcium retention.

Strength of the Scientific Evidence

We evaluated the strength of the scientific evidence by considering the factors provided in Section III.C of our guidance for industry entitled "Scientific Evaluation of the Evidence on the Beneficial Physiological Effects of Isolated or Synthetic Non-Digestible Carbohydrates Submitted as a Citizen Petition (21 CFR 10.30)." Based on this evidence, we evaluated whether the findings presented in the relevant clinical studies demonstrated that there is a beneficial physiological effect of GOS to human health.

Fermentation of carbohydrates has been shown to increase the production of short chain fatty acids, resulting in increased solubility and active and passive diffusion of ionized calcium in the cecum of rats (Lutz and Scharrer, 1991). GOS has specifically been shown to increase calcium absorption in rats through fermentation (Weaver et al., 2011). Two dual-tracer stable isotope studies demonstrated that GOS consumption at three levels of intake (5 g/day, 10 g/day, and 20 g/day) increased calcium absorption for up to 48 hours after consumption in healthy females (van den Heuvel et al., 2000; Whisner et al., 2013). For all three doses, it was demonstrated that the increased calcium absorption was not accompanied with an increase in urinary calcium excretion, indicating that increased calcium absorption leads to improved calcium retention. Dual stable-isotopically labeled calcium studies are the most reliable and direct measure for evaluating the effect of GOS on calcium absorption and retention. Calcium has been determined to be a nutrient of public health significance and is required on the Nutrition Facts label (21 CFR 101.9(c)(8)(ii)) because of its beneficial role in bone health and reducing the risk of osteoporosis (21 CFR 101.72). Therefore, the strength of the evidence supports that GOS has a beneficial physiological effect on calcium absorption. The evidence from which scientific conclusions could be drawn supports our decision to propose to include GOS in the definition of dietary fiber and, until completion of such a rulemaking, to consider enforcement discretion for the declaration of the amount of GOS as dietary fiber.

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Polydextrose[14]

Background

Polydextrose is a synthetic and partially metabolizable water-soluble polymer which primarily consists of D-glucose. Polydextrose is highly branched and contains α- and β- 1-2, 1-3, 1-4 and 1-6 linkages, with the 1-6 linkage predominating in the polymer. Polydextrose is added to foods for multiple technical effects including as a bulking agent, a formulation aid, a humectant, and a texturizer (21 CFR 172.841). Polydextrose is a soluble non-digestible carbohydrate that is partially fermented in the colon (Roytio and Ouwehand, 2014).

Energy Intake

We identified 16 studies that evaluated the effect of polydextrose consumption on energy intake. Scientific conclusions could not be drawn from 10 studies because: (1) an inappropriate control was used such that the satiating effect of polydextrose *per se* could not be evaluated (Astbury et al., 2014); (2) there were large differences in the volume of food provided to the study subjects between the study groups and volume has been shown to affect satiety (Lummela et al., 2009; Rolls et al., 1998); (3) energy/food intake was not measured (Costabile et al., 2012; Konings et al. 2014; Olli et al., 2015; Willis et al., 2009); (4) a statistical analysis was not conducted for energy intake (Schwab et al., 2006); (5) only an abstract was available (Astbury et al., 2008); or (6) only a meta-analysis was conducted, which does not provide sufficient information for the purposes of evaluating the individual studies (Ibarra et al., 2015).

Astbury et al. (2013)

In a randomized, single-blinded, cross-over study, 21 English men and women consumed isocaloric chocolate-flavored liquid preloads as a mid-morning snack containing 0 g/day (the control), 6.3 g/day, 12.5 g/day, or 25 g/day of polydextrose. The study subjects were provided with a standardized breakfast (equivalent to 10% of subject's total energy expenditure) to eat at home and upon arrival at the study facility. The study subjects recorded their motivational ratings for satiety before ingesting the liquid preload. Additional ratings were collected 30, 60, and 90 minutes after the preload test was ingested. After 90 minutes, the study subjects were provided a test meal and instructed to consume as much as they wished until they felt comfortably full (*ad libitum* lunch) and the energy intake was determined by the weight of food consumed. Before the subjects left the study facility, they were provided with a food diary and instructed to record all their food and drink intake during the remainder of the day. Using the visual analogue scales (VAS), there was no significant difference in "fullness," "hunger," and "desire- to-eat" ratings between the four preload test groups. The mean energy intake during the *ad libitum* lunch following the three polydextrose preloads of 6.3, 12.5, and 25 g/day were 1,207 ± 92, 1,129 ± 92, and 1,043 ± 76 kcal, respectively, accounting for a 12.3 %, 17.9 %, and 24.2 % significant reduction in the mean energy intake compared to the control group (1,376 ± 101 kcal) ($P < 0.01$). Furthermore, the mean energy intake following the 25 g polydextrose preload was significantly reduced by 13.6 % when compared to the 6.3 g of the polydextrose preload ($P <$

[14] FDA received a citizen petition requesting that polydextrose be listed as a dietary fiber (Docket # FDA-2016-P-3311). The citizen petition also requested a caloric value of 1 kcal/g for polydextrose.

0.01). The self-reported energy intake for the rest of the day was not significantly different between the polydextrose preload groups and the control group ($P > 0.05$). The daily energy intake (breakfast + preload + *ad libitum* lunch + food diary) was significantly lower for those who consumed the preload tests containing either 12.5 g/day or 25 g/day ($P < 0.05$) of polydextrose, but not 6.3 g/day ($P > 0.05$), compared to the control group.

Hull et al. (2012)

Thirty-four English men and women participated in a randomized, single-blinded, placebo controlled, double Latin square cross-over study. The study subjects consumed yogurt-based drinks containing 0 g (the control), 6.25 g, or 12.5 g of polydextrose and that were similar in calories and volume 90 minutes before an *ad libitum* lunch, followed by an *ad libitum* dinner. Analysis of data collected from the VAS showed that the "desire to eat" scores were significantly lower during the *ad libitum* lunch ($P < 0.001$) and the *ad libitum* dinner ($P = 0.002$) when 6.25 g of polydextrose was consumed compared to the control group. "Fullness" scores were significantly lower with 6.25 g ($P < 0.04$) and 12.5 g ($P < 0.007$) polydextrose consumption compared to the control. The mean energy intake during the *ad libitum* lunch after consumption of polydextrose at 6.25 and 12.5 g/day were 731 ± 39 and 712 ± 45 kcal, respectively, accounting for a 6.8% significant reduction with consumption of polydextrose at 12.5 g/day ($P = 0.022$), but not with the consumption of 6.25 g/day ($P > 0.05$), when compared to the control group (764 ± 40 kcal). There was no significant difference in the subjects' energy intake during the *ad libitum* dinner and total daily intake (breakfast + test product + *ad libitum* lunch + *ad libitum* dinner) when the polydextrose groups were compared to the control group ($P > 0.05$).

King et al. (2005)

Fifteen English men and women were provided a control yogurt containing 25 g/day of sucrose (control) or yogurt containing 25 g/day of polydextrose for up to ten days to evaluate the effect of polydextrose on hunger and energy intake. The weight of food can influence feelings of hunger, and therefore the weight and volume of the yogurts were held constant. The control yogurt had a higher calorie count (204 kcal) compared to the polydextrose yogurt (130 kcal) because sucrose provides more calories than polydextrose. On days one and ten, the subjects visited the study facility to consume a breakfast and a mid-morning yogurt. Immediately before and after consumption of yogurt, subjects were asked to complete an electronic appetite rating system using VAS. One and a half hours after they had consumed the yogurt, the study subjects consumed a test lunch *ad libitum* and were instructed to eat to a comfortable level of fullness. Subjects were provided the yogurt and were instructed to consume it at home during days two through nine of the study. There was no significant difference in either "fullness" or "hunger" scores between the two groups on days one and ten of the study. There was a 10% reduction in energy intake (mean differential of days one and ten = 74 kcal, without the pre-load energy accounted for) in the test lunch with prior polydextrose consumption compared to the control group, which was not significantly different ($P = 0.06$). When the energy differential of the yogurts was accounted for (yogurt + lunch), the energy intake with prior polydextrose consumption was significantly lower compared to the control ($P = 0.002$).

Monsivais et al. (2011)

In a double-blinded, Latin square cross-over study, 36 U.S. men and women each consumed a solid snack and a liquid beverage (as pre-loads) given in two separate occasions, at early (first pre-load) and mid-morning (second pre-load). The preloads provided a total of 23.6 g/day of polydextrose and 186 kcal for the treatment group. The two control groups, the isocaloric low-fiber control group and the low-energy control groups, were provided with 1.9 g of fiber and 179 kcal, and 0.5 g of fiber and 43 kcal, respectively. Subjects used a VAS to rate "hunger," "fullness" and "desire-to-eat" at 20 minute intervals just before and until 220 minutes after ingestion of the first pre-load dose. One and one-half hours after the second pre-load was consumed, an *ad libitum* lunch was served and the study subjects' energy intake was measured. Significant differences were only observed when the polydextrose group was compared to the low-energy control group ($P < 0.05$). Otherwise, there was no significant difference in "hunger," "desire-to-eat," or "fullness" between the isocaloric control group and the polydextrose intervention group ($P > 0.05$). Furthermore, there was no significant difference in energy intake from lunch between the isocaloric control group and the polydextrose group ($P > 0.05$), including no significant difference in the percent energy intakes from macronutrients in the test meal (protein, 16.1% to 16.7%; fat, 32.8% to 33.7%; total carbohydrate, 50.8% to 51.9%) ($P > 0.05$).

Ranawana et al. (2013)

In a randomized, single-blinded, cross-over study, 26 English men consumed a fruit smoothie containing 0 g/day (control) or 12 g/day of polydextrose. Both the treatment and control fruit smoothies were isocaloric and weighed 400 g. The subjects were provided with the smoothie three hours after breakfast was consumed and one hour before an *ad libitum* lunch was served. The motivational ratings for satiety were measured before and after breakfast, before and 15, 30, and 45 minutes after drinking the smoothies, and before and after lunch. There was no significant difference in "hunger," "fullness," "desire-to-eat," and "prospective eating" between the two groups ($P > 0.05$). There was a significant reduction (10%) in energy intake observed at lunch following the consumption of polydextrose (993 ± 75 kcal) compared to the control group (1,095 ± 64 kcal) ($P = 0.007$). The reduction in energy intake resulted from a reduced intake of calories from carbohydrate, fiber, and fat ($P < 0.05$), but not from protein ($P = 0.054$).

Soong et al. (2016)

In a randomized, cross-over study, 27 Chinese men consumed soyabean curd containing 12 g/day of polydextrose as low protein polydextrose (LPP) or high protein polydextrose (HPP) with their respective controls, low protein (LP) and high protein (HP) preloads, containing 0 g/day of polydextrose. All four preloads were isocaloric and weighed between 451 g and 473 g. The subjects were provided with a standardized dinner to be consumed the day before the intervention, and a standardized breakfast meal that was consumed at the study facility. The preloads were served three hours after breakfast and the subjects were served an *ad libitum* lunch (time not specified). The motivational ratings for satiety were measured: (1) before breakfast, and one and two hours after breakfast; (2) before preload, 15, 30, 45, 60, and 75 minutes after preload; and (3) before and after lunch. There was no significant difference in "hunger,"

"fullness," "desire-to-eat," and "prospective eating" among the four groups ($P > 0.05$). There was a statistically significant 11% reduction in energy intake at lunch following the consumption of the LPP preload (791 ± 45 kcal) compared to the LP control group (885 ± 42 kcal) ($P < 0.05$). There was no significant difference between the HPP preload when compared to the HP control group (HP) ($P > 0.05$).

Strength of the Scientific Evidence

We evaluated the strength of the scientific evidence by considering the factors provided in Section III.C of our guidance for industry entitled "Scientific Evaluation of the Evidence on the Beneficial Physiological Effects of Isolated or Synthetic Non-Digestible Carbohydrates Submitted as a Citizen Petition (21 CFR 10.30)." Based on this evidence, we evaluated whether the findings presented in the relevant clinical studies demonstrated that there is a beneficial physiological effect of polydextrose to human health.

Five out of the six studies demonstrated that polydextrose consumption statistically significantly reduced energy intake during subsequent meals. Four of the six studies (Astbury et al., 2013; Hull et al., 2012; Ranawana et al., 2003; Soong et al., 2016) provided approximately 12 g/day of polydextrose and showed a 6.8% to 17.9% significant reduction in energy intake during subsequent meals. Two studies evaluated the effect of 25 g/day of polydextrose on energy intake. Monsivais et al. (2011) showed no statistically significant effect while King et al. (2005), the only chronic intervention study (10 days), showed a statistically significant 9.9% reduction in energy intake at a subsequent meal. Furthermore, two studies (Astbury et al., 2013; Hull et al., 2012) demonstrated a statistically significant reduction in energy intake at a subsequent meal because of polydextrose intake that was not compensated for at other meals throughout the day. The evidence from which scientific conclusions could be drawn supports our decision to propose to include polydextrose in the definition of dietary fiber and, until completion of such a rulemaking, to consider enforcement discretion for the declaration of the amount of polydextrose as dietary fiber.

Caloric Value

We identified three human studies that evaluated the energy value of polydextrose.

Figdor and Bianchine (1983)

The energy value of polydextrose was evaluated in 4 healthy U.S. men in a disposition study using radioisotope labeled carbon-14 (^{14}C)-polydextrose. Subjects received 10 g of non-labeled polydextrose dissolved in chocolate milk consumed immediately after breakfast for 10 days. On day 8, a dose (72 microcuries (µCi)) of ^{14}C-polydextrose was added to the chocolate milk containing the non-labeled polydextrose. Carbon-14 was measured at several intervals in the breath for a total of 48 hours and in urine and stool for 7 days after the subjects had ingested the radiolabeled dose. The energy value was determined by measuring the amount of ^{14}C-labeled carbon dioxide ($^{14}CO_2$) exhaled in the breath between 0 to 24 hours and applying a correction factor to consider that 60% of the available carbon source is exhaled as $^{14}CO_2$ within 24 hours. The $^{14}CO_2$ recovery within 24 hours was 16%, on average. A corrected energy value of

^{14}C-polydextrose was estimated to be 26.6% of the dose or approximately 1 kcal/g. This value may be overestimated because it may contain $^{14}CO_2$ produced by bacterial fermentation.

Achour et al. (1994)

The energy value of polydextrose was evaluated in 7 healthy non-obese French men in a disposition study using labeled radioisotope ^{14}C-polydextrose. The energy value was calculated by using fecal data only or in combination with CO_2 exhaled in breath derived from short-chain fatty acids. The study was separated into control (days 1 through 8), acute (days 9 through 16), and chronic (days 17 through 38) phases. A controlled diet and a fruit juice drink containing 10 g of non-labeled polydextrose were provided to the subjects three times a day (i.e., 30 g of polydextrose per day from days 1 through 16 and days 31through 40). On days 17 through 30, subjects continued with the same polydextrose regimen but were allowed to eat their usual diet at home. The radiolabeled dose (20 µCi) of ^{14}C-polydextrose was added to the morning fruit juice containing 10 g of non-labeled polydextrose and was given to the subjects once during the acute (day 13) and chronic (day 35) phases. Starting on days 5 (control), 13 (acute phase) and 35 (chronic phase), stool and urine samples were collected for three days, and breath was collected at several intervals for 48 hours. A complete 12 hour-collection of flatus was achieved for three subjects only on days 13 and 35. On day 40, subjects received an infusion of ^{14}C-acetate and 5 g of polydextrose in the colon and the $^{14}CO_2$ derived from the oxidation of short-chain fatty acids was measured in the exhaled breath within 24 hours.

The polydextrose dose was a mixture of monomers and polymers. The monomeric component accounted for 5% of the dose and it was assumed to be directly absorbed in the small intestine. Therefore, the percentage of the dose available for fermentation was 95% minus 33% of the intact polydextrose eliminated in stool (36% of total stool radioactivity minus 3% radioactivity derived from the short-chain fatty acids). Of the remaining 62% of the dose, 3% was incorporated into bacterial mass and 59% was available to produce short-chain fatty acids and gas (although, the excretion of $^{14}CO_2$ in flatus was negligible). At this point, the energy value generated from the 59% of the polydextrose dose was calculated by using two different approaches.

1) <u>Theoretical formation of short-chain fatty acids</u>
   Using the Miller and Wolin's stoichiometric equation of colonic fermentation:
   $34.5\ C_6H_{12}O_6 + 37\ H_2O \longrightarrow 48$ acetate + 11 propionate + 5 butyrate + 58 CO_2 + 95 H_2
   59% of the dose (i.e., 59 g) produces 2.7 g of acetate, 0.8 g of propionate, and 0.4 g of butyrate, which multiplied by their respective gross energy values, would generate 65.8 kilojoules (kJ).[15] Considering an 80% efficiency rate for conversion to ATP, 52.6 kJ was available; which added to 8.4 kJ from the monomeric polydextrose absorbed in the small intestine, produces an estimated energy value of 61 kJ from 10 g of polydextrose or 6.1 kJ/g (1.46 kcal/g).

2) <u>Short-chain fatty acids formation based on the measurement of $^{14}CO_2$ derived from the bacterial fermentation (experimental data)</u>

[15] 1 kcal = 4.184 kJ (NIST, 2006).

Fifty-nine percent of the dose was fermented and 31% was recovered as $^{14}CO_2$ exhaled in the breath within 48 hours originating from: bacterial $^{14}CO_2$ produced during fermentation; oxidation of short-chain fatty acids in the colon; and oxidation of polydextrose monomers in the small intestine. Considering that 60% of the radiolabeled dose is recovered in the breath, the $^{14}CO_2$ originated from the short chain fatty acids would be 11.5% derived from: [31% (total recovery) – [monomeric fraction (60% of 5%) + carbon dioxide calculated from the Miller and Wolin equation (60% of 28%)]]. The experimental data using the infusion of labeled ^{14}C-acetate determined that 90% was absorbed and 49% of the label appeared in the breath within 48 hours. Therefore, the estimated 11.5% of short-chain fatty acid in the breath at 48 hours was adjusted accordingly, resulting in 23.5% of the dose to which 80% is converted to adenosine triphosphate (ATP), i.e. 18.8% of the dose yield energy. In addition to the 5% from absorbed monomers, the final energy produced from short-chain fatty acids was 23.8% which applied to the gross energy value of polydextrose is 4.0 kJ/g (0.96 kcal/g).

Oku and Nakamura (2014)

Nine healthy Japanese women participated in a study that used an indirect method to estimate the relative energy of value of polydextrose when compared to FOS used as a reference. On the day of the experiment, subjects were provided with three regular meals and two snacks. Two test meals, either polydextrose (5g) or FOS (5g), were dissolved in 120 mL of boiled soy flavored soup. Subjects consumed the test meal two hours after they had received their first meal, followed by collection of breath at several intervals for 12 hours. The breath collection continued the next day, 30 minutes after waking up and 24 hours after ingestion. The AUC for the breath hydrogen gas excretion was compared, followed ingestion of polydextrose and FOS. Assuming that FOS is completely fermented by the microflora, an energy value of 2 kcal/g was used as a reference. The calculated energy value for polydextrose based on the AUC of 8 hours, 14 hours, and 24 hours post-collection was 0.77 kcal/g.

Summary of the Scientific Evidence

Three human studies (Achour et al., 1994; Figdor and Bianchine 1983; Oku and Nakamura 2014) evaluated the caloric value of polydextrose. The caloric values ranged from 0.77 to 1.46 kcal/g with a mean value of 1.05 kcal/g. The strongest evidence was provided by Achour et al. (1994), which discriminated the formation of the radiolabeled carbon dioxide ($^{14}CO_2$) originated in the colon by the metabolism of short-chain fatty acids from that of bacterial fermentation (caloric value of 0.96 kcal/g). Therefore, based on our evaluation, the strength of the evidence supports a caloric value of 1 kcal/g for polydextrose. The evidence from which scientific conclusions could be drawn supports our decision to propose a caloric value of 1 kcal/g for polydextrose and, until completion of such a rulemaking, to consider enforcement discretion for a caloric value of 1 kcal/g for polydextrose.

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Resistant Maltodextrin[16]/Dextrin

Background

Resistant maltodextrin/dextrin is a glucose oligosaccharide. Resistant maltodextrin and dextrin products are composed of non-digestible oligosaccharides of glucose molecules that are joined by digestible linkages and non-digestible α-1,2 and α-1,3 linkages.

Common names used to identify resistant maltodextrin as an ingredient include soluble corn fiber, resistant dextrin, resistant wheat dextrin, soluble wheat fiber, and wheat dextrin.

Calcium Absorption/Retention

We identified four studies that evaluated the effect of resistant maltodextrin consumption on calcium absorption or retention.

Stable-Isotope Studies

Jakeman et al. (2016)

In a randomized, cross-over study, 12 U.S. postmenopausal women were provided 0 g/day (the control), 10 g/day, and 20 g/day of resistant maltodextrin in a muffin or beverage for 50 days. The control muffin and beverage contained nonresistant maltodextrin in place of resistant maltodextrin. Subjects were intravenously administered ^{41}Ca and the isotope was allowed to equilibrate with whole-body calcium for greater than 100 days. The urinary appearance of isotopically labeled calcium from pre-labeled bone was measured to assess the effect of resistant maltodextrin on retention of calcium in bone. Biomarkers of bone formation (bone-specific alkaline phosphatase) and turnover (osteocalcin and n-terminal telopeptide) were also measured. A significant, positive dose-response relationship was observed with 10 g/day (4.8%; $P < 0.05$) and 20 g/day (7%; $P < 0.04$) resistant maltodextrin and bone calcium retention. This increase in calcium retention was estimated to represent an increase in bone calcium balance by 50 mg/day. While osteocalcin and n-terminal telopeptide were not significantly different ($P > 0.05$), a significant increase in bone-specific alkaline phosphatase was observed with the consumption of 20 g/day resistant maltodextrin when compared to the control ($P = 0.035$).

Whisner et al. (2014)

In two three-week double-blind, cross-over studies, and with a one-week washout period, 24 U.S. adolescent boys and girls consumed 0 g/day of resistant maltodextrin (the control) or 12 g/day (6 g twice a day) of resistant maltodextrin added to fruit snacks. Controlled diets were provided to the subjects during the study. During the last week of both treatments, subjects consumed a breakfast that included milk that contained stable-isotopically labeled calcium (^{44}Ca). Stable isotopically labeled calcium was also administered intravenously (^{43}Ca). Calcium

[16] FDA received two citizen petitions requesting that Fibersol resistant maltodextrin and PROMITOR® Soluble Corn Fiber ("Soluble Corn Fiber") be listed as a dietary fiber (Docket # FDA-2016-P-1674 and FDA-2016-P-2377).

was measured using stable-isotopically labeled calcium (^{44}Ca and ^{43}Ca) and two 24-hour urine collections were conducted to evaluate fractional absorption. Urinary calcium excretion and biomarkers of bone turnover were not significantly different between the resistant maltodextrin and control groups ($P > 0.05$). While there was no significant difference in fractional calcium absorption up to 24 hours after administration, calcium absorption was 12% higher 24 to 48 hours following resistant maltodextrin consumption compared to the control ($P = 0.02$). The lack of a significant difference in calcium absorption during the first 24 hours is supported by evidence demonstrating that microbial involvement and lower intestinal absorption does not occur until 24 hours after isotope administration (Whisner et al., 2013).

Whisner et al. (2016)

For four weeks, 28 U.S. adolescent girls were provided with 0 g/day (maltodextrin control), 10 g/day and 20 g/day of resistant maltodextrin for four weeks each in a double-blind, cross-over design study. Half of the daily dose of resistant maltodextrin was consumed in a muffin and half in a fruit-flavored beverage. Fractional calcium absorption was measured using stable-isotopically labeled calcium (^{44}Ca orally and ^{43}Ca intravenously). The 48-hour fractional absorption of calcium increased significantly for both 10 g/day ($P = 0.042$) and 20 g/day ($P = 0.026$) compared to the control diet. While there was no significant difference in bone-specific alkaline phosphatase between the control and resistant maltodextrin groups, there was a significant positive correlation between change in bone-specific alkaline phosphatase and the change in fractional calcium absorption ($r = 0.31$, $P = 0.03$).

Balance Studies

Vermorel et al. (2004)

In a 31-day cross-over design study, with a four-week washout period, ten healthy young French men consumed study diets that provided dextrose (the control) or resistant dextrin. The experimental diet provided 20 g/day of dextrose or resistant dextrin, and the level for each was increased to 100 g/day over the first 18 days. For the remaining 13 days, 100 g/day of dextrose or resistant dextrin was consumed by the study subjects. Apparent calcium absorption (%) was calculated by measuring calcium intake (mg/day) and fecal excretion (mg/day). Calcium retention was calculated by subtracting urinary excretion (mg/day) from absorbed calcium (mg/day). There was no significant difference in either calcium absorption ($P = 0.191$) or calcium retention ($P = 0.122$).

Strength of the Scientific Evidence

We evaluated the strength of the scientific evidence by considering the factors provided in Section III.C of our guidance for industry entitled "Scientific Evaluation of the Evidence on the Beneficial Physiological Effects of Isolated or Synthetic Non-Digestible Carbohydrates Submitted as a Citizen Petition (21 CFR 10.30)." Based on this evidence, we evaluated whether the findings presented in the relevant clinical studies demonstrated that there is a beneficial physiological effect of a resistant maltodextrin/indigestible dextrin to human health.

Fermentation of carbohydrates has been shown to increase the production of short chain fatty acids, resulting in increased solubility and active and passive diffusion of ionized calcium in the cecum of rats (Lutz and Scharrer, 1991). Stable-isotopically labeled calcium is the most reliable and direct measure for evaluating the effect of resistant maltodextrin/dextrin on calcium absorption and retention. For the three studies that used stable-isotopically labeled calcium, two studies showed that consumption of resistant maltodextrin statistically significantly increased calcium absorption in adolescents and postmenopausal women (Whisner et al., 2014; Whisner et al., 2016). The body retention of stable isotopically labeled calcium was statistically significantly increased with resistant maltodextrin consumption and in a dose-response manner (Jakeman et al., 2016). The consumption of resistant dextrin did not result in a statistically significant increase in calcium absorption or retention when unlabeled calcium intake and excretion was measured in the diet, feces, and urine (Vermorel et al., 2004). In post-menopausal women, bone-specific alkaline phosphatase, a marker of bone formation, was statistically significantly increased with the consumption of resistant maltodextrin (Jakeman et al., 2016), with a significant positive correlation between change in bone-specific alkaline phosphatase and the change in fractional calcium absorption (Whisner et al., 2016). While bone formation was observed to increase with resistant maltodextrin consumption, there was no effect on biomarkers of bone turnover (Jakeman et al., 2016).

Calcium has been determined to be a nutrient of public health significance and is required on the Nutrition Facts label (21 CFR 101.9(c)(8)(ii)) because of its beneficial role in bone health and reducing the risk of osteoporosis (21 CFR 101.72). The strength of the evidence supports a beneficial physiological effect of resistant maltodextrin in increasing calcium absorption and body retention, as well as bone formation. The evidence from which scientific conclusions could be drawn supports our decision to propose to include resistant maltodextrin/ingestible dextrin in the definition of dietary fiber and, until completion of such a rulemaking, to consider enforcement discretion for declaring the amount of resistant maltodextrin/indigestible dextrin as dietary fiber.

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