DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

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To: Administrative File to" Food Labeling: Revision of the Nutrition and Supplement Facts Labels" (Docket No. FDA-2012-N-1210)

Subject: Scientific Review of the Beneficial Physiological Effects of Non-digestible Carbohydrates for Meeting the FDA Definition of Dietary Fiber.

The purpose of this memorandum is to provide a summary of the scientific review of certain isolated or synthetic non-digestible carbohydrates that we determined provide beneficial physiological effects to human health and describe the process we used to review the scientific evidence concerning such effects.

I. General Process for Reviewing the Scientific Evidence

We identified and reviewed all of the publically available studies on numerous specific individual isolated or synthetic non-digestible carbohydrates. For five of these carbohydrates (i.e., cellulose, guar gum, hydroxypropylmethylcellulose, locust bean gum, and pectin), we determined that the scientific evidence supports a beneficial physiological effect to human health. Thus, these five non-digestible carbohydrates meet the dietary fiber definition, and are listed as dietary fibers in 21 CFR 101.9 (c)(6)(i). The listed dietary fibers also include β-glucan soluble fiber and psyllium husk dietary fiber, which are each the subject of an authorized health claim.

The scientific evidence we reviewed for the other isolated or synthetic non-digestible carbohydrates was inconsistent (e.g., some studies showed a benefit, while other studies showed no benefit), or insufficient (e.g., there was no replication of findings). We did not make a determination about whether these isolated or synthetic non-digestible carbohydrates are dietary fibers. We intend to include the scientific evidence for these other non-digestible carbohydrates in a *Federal Register* notice and seek comment on whether there are additional studies available on the beneficial physiological effects to human health from these carbohydrates that we should consider.

For purposes of our reviews, although an isolated or synthetic non-digestible carbohydrate may provide more than one beneficial physiological effect to human health, only one beneficial physiological effect is necessary to meet the dietary fiber definition. Therefore, if a beneficial physiological effect was demonstrated, then we did not need to consider other beneficial physiological effects for that isolated or synthetic non-digestible carbohydrate. Further, information on the Nutrition and Supplement Facts labels is intended for the general healthy population rather than individuals with chronic diseases. The general healthy population includes individuals who are at increased risk (e.g., hypercholesterolemia[1]) of a disease (e.g., cardiovascular disease). Therefore, for each isolated or synthetic non-digestible carbohydrate, we only considered studies that included human subjects that did not have a disease that was relevant to the physiological endpoint being evaluated. For example, studies involving human subjects with diabetes were not considered in the evaluation of an isolated or synthetic non-digestible carbohydrate and its effect on blood glucose levels. Further, we evaluated human studies that were designed to evaluate the physiological effect of an individual isolated or synthetic non-digestible carbohydrate, rather than studies that evaluated a mixture of these non-digestible carbohydrates. It was also important that the studies provided an appropriate control group and statistical analysis so that it was possible to ascertain whether an effect on the physiological endpoint (e.g., change in blood cholesterol level) was due to the isolated or synthetic non-digestible carbohydrate or due to unrelated and uncontrolled extraneous factors of the study.

When evaluating the strength of the scientific evidence for the role of foods/nutrients in health-related outcomes, such as physiological beneficial effects to human health, we considered various scientific issues that are generally accepted in the scientific community for conducting scientific reviews, such as the type, number and size of the studies, whether limited evidence showing an effect has been replicated, and whether the findings are consistent in showing a statistically significant effect ($P < 0.05$) on the health-related endpoint being evaluated. Such an approach is generally recognized and consistent with other approaches used in nutrition scientific reviews (FDA, 2009; AHRQ, 2014).

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[1] Hypercholesterolemia is defined as having total blood cholesterol levels greater than 200 mg/dL and/or LDL cholesterol levels greater than 130 mg/dL.

II. Science Review for Cellulose

Background

Cellulose is a linear homopolymer of β-(1-4) linked glucose units (IOM, 2001). 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.

Bowel Function

Beneficial physiological effects to human health, such as improved laxation/bowel function (elimination of fecal waste), are evaluated by measuring transit time of food in the intestinal tract and rate of defecation (e.g., stools per day) (Topping, 2007). While fiber intake can increase fecal bulk, an increase in fecal weight does not necessarily equate with improved bowel function (i.e., laxation) (IOM, 2002). Therefore, fecal weight was not used to evaluate improved bowel function.

Eleven human studies were identified that evaluated the relationship between cellulose consumption and laxation. Scientific conclusions could not be drawn from three studies (Fleming et al., 1983; Raymond et al., 1977; Stephen et al., 1986) for one or more of the following reasons: 1) a mixture of nondigestible carbohydrates, including cellulose, was provided and therefore the effect of cellulose *per se* on bowel function could not be evaluated and 2) statistical comparisons between the cellulose and the control group were not conducted and therefore the effect of cellulose on laxation could not be compared to the control group.

Behall et al. (1987)

Eleven US men consumed a basal diet with and without (control) 7.5 g cellulose/1,000 calories for 4 weeks each. There was no significant difference in average bowel transit times (26.7 versus 24.2 hours) ($P > 0.05$) between the control and cellulose diet, as well as frequency of defecation (7.4 *versus* 9.0 stools/8 days).

Danjo et al. (2008)

In Japan, 15 women with normal defecation were provided an experimental diet (16.7 g/day of dietary fiber), followed by the experimental diet containing 4 and 8 g/day of cellulose for 1 week each. In this study, no significant difference was observed for defecation rate (bowel movements per day) between the experimental diet and the 4 or 8 g/day of cellulose diets.

Eastwood et al. (1973)

Four healthy Scottish men consumed a control diet and the control diet that provided 16 g/day cellulose for three weeks each. This study showed that there was no significant difference in intestinal transit time (hours) between the two diets.

Hillman et al. (1983)

In a randomized cross-over design, consisting of two periods of 4 weeks, cellulose (15 g/day) was added or not added (control) to the diets (approximately 21 g/day of dietary fiber) of 10 healthy men and women living in New Zealand. This study showed that the consumption of cellulose resulted in a significant decrease in transit time (40.4 *versus* 55.3 hours) ($P < 0.01$).

Park and Jhon (2009)

Eight healthy Korean women received a dietary fiber-free diet (control) and a diet containing 25 g/day of cellulose with each diet segment lasting 6 days. The frequency of bowel movements was significantly higher when cellulose was consumed (5.6 stools/6 days) compared to the control (4.3 stools/6 days) ($P < 0.05$).

Slavin and Marlett (1980)

Seven healthy US women consumed a low-fiber diet (9.6 g/day) (control) and the same diet to which 16 g/day of cellulose was added for approximately 30 days each. The mean transit time was significantly shorter when cellulose was consumed compared to the control (102 *versus* 62.8 hours) ($P < 0.05$). Furthermore, there was a significant increase in the average frequency of defecation with cellulose consumption compared to the control (1.1 *versus* 0.85 per day) ($P < 0.02$).

Spiller et al. (1980)

US healthy men and women were fed low-fiber diets for two weeks, followed by 3 weeks on the same diet plus either 14 g/day cellulose (n=10) or sucrose (n=10) (control). In this study, diets excluded whole grain products, legumes, raw vegetables, and raw fruits that would contain dietary fiber. There was a significant decrease in transit time when cellulose was consumed compared to the control (2.6 *versus* 4.8 days) ($P < 0.05$).

Wrick et al. (1983)

This study provided a diet with and without (control) added cellulose for at least 2 weeks to 24 US men. The mean transit time was significantly shorter when cellulose was added to the diet compared to the control ($P < 0.0005$). Furthermore, the average laxation rate (stools per week) was significantly greater with cellulose (6.9) compared to the control (5.2) ($P < 0.0005$). A positive correlation was observed between an increase in the amount of cellulose consumed and laxation rate. Increasing cellulose intake from approximately 5 to 30 g/week increased the number of stools per week from 4 to 9, as well as increased fecal output (g/week).

Strength of the Scientific Evidence

The strength of the total body of publicly available evidence was evaluated by considering the number of studies and number of subjects per group, whether the body of scientific evidence supports a beneficial physiological effect to human health for the U.S. population, whether study results supporting the beneficial physiological effect have been replicated (Wilson, 1990), and the overall consistency of the findings (Hill, 1965; AHRQ, 2002) of the evidence from which scientific conclusions could be drawn. Based on this evidence, FDA determined whether the findings concluded that there is a beneficial physiological effect of a non-digestible carbohydrate to human health and therefore meets the agency's definition of dietary fiber.

The strength of the evidence supports cellulose in improving laxation/bowel function with three of five studies showing increased frequency of bowel movements and four of six studies showing reduced transit time. The largest study (Wrick et al., 1983) that showed a decrease in transit time and increased frequency of bowel movements with cellulose intake also demonstrated a dose-response relationship between cellulose intake and frequency of defecation. Based on the above studies from which scientific conclusions could be drawn, cellulose meets the definition for dietary fiber.

III. Science Review for Guar Gum

Background

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 consists of mannose and galactose, is hydrophilic and with gel-forming properties (IOM, 2002). Therefore, guar gum is considered a soluble non-digestible carbohydrate.

Blood Cholesterol Levels

Beneficial health effects, such as reduced risk of heart disease, are associated with the reduction of blood total and low-density lipoprotein (LDL) cholesterol levels. Therefore, these biomarkers were used for evaluating the beneficial physiological effects of attenuation of blood cholesterol levels.

Thirty seven studies were identified that evaluated the relationship between guar gum consumption and blood cholesterol levels. Scientific conclusions could not be drawn from 21 of these studies (Botha et al., 1981; Castro et al., 2007; Fuessl et al., 1987; Gatti et al., 1984; Haskell et al., 1992; Hunnighake et al., 1994; Jenkins et al., 1975; Jenkins et al. 1979; Jenkins et al., 1980; Jensen et al., 1993; Jensen et al., 1997; Johansen 1981;

Khan et al., 1981; Knopp et al., 1999; McIvor et al., 1986; Niemi et al., 1988; Penagini et al., 1986; Salenius et al. (1995); Smith and Holm, 1982; Spiller et al., 1991; Tai et al., 1999) for one or more of the following reasons: 1) a mixture of non-digestible carbohydrates, including guar gum, was provided and therefore the physiological effect of guar gum *per se* could not be evaluated, 2) an appropriate control was not provided and therefore it was not possible to ascertain whether changes in blood cholesterol levels were due to guar gum or due to unrelated and uncontrolled extraneous factors, 3) statistical comparisons between the guar gum and the control group were not conducted and therefore the effect of guar gum on lowering blood cholesterol levels could not be compared to the control group, 4) the study was conducted in human subjects that had a disease that was relevant to the physiological endpoint being evaluated, and 5) the study was not conducted long enough to evaluate the effect of guar gum on fasting blood cholesterol levels.[2]

Aro et al. (1981)

Dietary supplementation of a granulated guar gum (21 g/day in 3 divided doses at the main meals) were compared with a placebo response during 3 months in a double-blind, cross over study on 11 type 2 diabetic, hypercholesterolemic Finnish subjects. Serum total and LDL cholesterol levels were significantly lower with guar gum consumption compared to the placebo ($P < 0.02$).

Aro et al. (1984)

Fourteen Finnish men with hypercholesterolemia received supplements containing guar gum (15 g/day) or a placebo for 12 weeks in a double-blind, cross-over trial. After 6 weeks of taking the supplements, there was a significant reduction in total cholesterol ($P < 0.01$) and LDL cholesterol ($P < 0.05$) for those taking guar gum. This reduction was no longer significant after 12 weeks.

Blake et al. (1997)

In a randomized, double-blind crossover of two 3-week feeding periods, wheat bread with and without (control) guar (6% weight) was provided to 11 hypercholesterolemic English men and women. This study showed that guar gum significantly reduced total and LDL cholesterol levels compared to the control ($P < 0.001$).

Bosello et al. (1984)

Twelve Italian hypercholesterolemic men and women were provided a flavored guar gum formulation (16 g/day) that was consumed for 2 months before and after consuming diets without the guar gum formulation (control). Total cholesterol levels were significantly

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[2] Three weeks is considered to be the minimum duration for evaluating the effect of a dietary intervention on fasting blood cholesterol concentration (Kris-Etherton et al. (1997)).

lower when guar gum was consumed compared to the control phases ($P < 0.05$). Guar gum consumption had no effect on LDL cholesterol levels when compared to the control.

Chuang et al. (1992)

In a randomized, double-blind cross-over study conducted in Taiwan, 16 men and women with type 2 diabetes and normal or slightly elevated (borderline) blood cholesterol levels received a placebo and guar gum (15 g/day) for 4 weeks each. After this time period, there was no significant difference in total or LDL cholesterol levels between the placebo and guar gum ($P > 0.05$).

Ebeling et al. (1988)

In a randomized, double-blind, crossover intervention conducted in Finland, nine type 1 diabetic subjects with normal blood cholesterol levels consumed their usual diet that contained either guar gum (5 grams) or a placebo before or with meals four times daily for 4 weeks each. Serum LDL cholesterol levels were reduced significantly after consuming the guar gum diet compared to the placebo ($P < 0.05$).

Kondo et al. (2004)

Eleven Japanese hypercholesterolemic men consumed yogurt with or without 6 g of partially hydrolyzed guar gum in a crossover design study. Shortly after consuming the yogurt, postprandial blood cholesterol was measured. The addition of guar gum to yogurt has no significant effect on postprandial cholesterol levels ($P > 0.05$).

Landin et al. (1992)

A double-blind, placebo-controlled, crossover study was carried out on 25 healthy Swedish men with slightly elevated blood cholesterol levels to test the effect of 30 g/day of guar gum for 3 weeks on fasting blood cholesterol levels. Total cholesterol levels were significantly lower when guar gum was consumed compared to the placebo, and with a significant net reduction of 0.6 mmol/L ($P < 0.001$).

Makkonen et al. (1993)

In a double-blind, placebo-controlled parallel study conducted in Finland, menopausal hypercholesterolemic women (15 per group) consumed 15 g/day of guar gum or a placebo for 6 months. No significant difference between the guar gum and placebo was observed for fasting total blood cholesterol levels after 3 and 6 months ($P \geq 0.05$).

Pasman et al. (1997)

After weight-loss from consuming an energy-restricted diet, obese Belgian women (10-11 per group) with slightly high blood cholesterol levels, on a weight maintenance diet, consumed 0 or 20 g/day guar gum. After 14 months on the weight maintenance diets, blood cholesterol levels were measured. No significant difference in total or LDL cholesterol levels was observed between the control subjects and subjects who had consumed 80% or 50-80% of the supplemental amount of guar gum.

Simons et al. (1982)

In a placebo-controlled, single-blind study, 17 Australian hypercholesterolemic men and women consumed 18 g/day of guar gum or a placebo control with a typically-consumed cholesterol-lowering diet. After 3 months on these diets, there was a significant reduction in plasma total cholesterol concentration with guar gum consumption compared to the control ($P < 0.001$).

Superko et al. (1988)

Fifty US men with moderately elevated blood cholesterol levels were randomized to receive various forms of guar gum (15 g/day) or a placebo, along with their diet. After 5 weeks of consumption, guar gum significantly reduced total cholesterol levels ($P = 0.029$) but not LDL cholesterol levels ($P = 0.073$).

Turner et al. (1990)

In a double-blind placebo-controlled crossover study, 9 Finnish men and women with hypercholesterolemia consumed 0 or 30 g/day of guar gum along with their meals for 6 weeks each. After the 6 week intervention the mean total cholesterol concentrations were 10.1 and 9.1 mmol/L for the placebo and guar gum treatments, respectively, which were significantly different ($P < 0.05$). There was no significant difference, however, for LDL-cholesterol ($P < 0.06$)

Uusitupa et al. (1989)

In Finland, 39 men and women with type 2 diabetes and high blood cholesterol levels were randomly allocated in an intervention where they received 5 g of guar gum or a placebo (wheat flour) three times per day for 3 months, along with their diet. Consumption of guar gum resulted in a significant reduction in serum total cholesterol when compared to the placebo ($P < 0.05$).

Uusitupa et al. (1990)

Nine Finnish patients with type 2 diabetes and high blood cholesterol levels participated in a randomized double-blind controlled crossover study to evaluate the effect the inclusion of 15 g/day on serum cholesterol levels. After 4 weeks on each intervention, serum total cholesterol was significantly lower with guar gum consumption compared to the control ($P < 0.05$).

Vuorinen-Markkola et al. (1992)

The effect of guar gum on blood cholesterol levels in 17 mildly hypercholesterolemic Finnish men and women with type 2 diabetes was examined in a randomized, double-blind study. Either 5 g guar gum or a placebo (wheat flour) four times daily was consumed with their diets for 6 weeks each. The reduction in total and LDL cholesterol levels in the guar gum group was significantly greater ($P < 0.01$) than in the placebo group.

Strength of the Evidence

The strength of the total body of publicly available evidence was evaluated by considering the number of studies and number of subjects per group, whether the body of scientific evidence supports a beneficial physiological effect to human health for the U.S. population, whether study results supporting the beneficial physiological effect have been replicated (Wilson, 1990), and the overall consistency of the findings (Hill, 1965; AHRQ, 2002) of the evidence from which scientific conclusions could be drawn. Based on this evidence, FDA determined whether the findings concluded that there is a beneficial physiological effect of a non-digestible carbohydrate to human health and therefore meets the agency's definition of dietary fiber.

The strength of the evidence supports guar gum in reducing blood cholesterol levels with 12 of 16 studies showing a reduction in total and/or cholesterol levels. Based on the above studies from which scientific conclusions could be drawn, guar gum meets the definition for dietary fiber.

IV. Science Review for Locust Bean Gum

Background

Locust bean gum (LBG) (also called carob bean gum) is primarily the macerated endosperm of the seed of the locust (carob) bean tree *Ceratonia silique* (Linne), a leguminous evergreen tree, with lesser quantities in the seed coat and germ (21 CFR 184.184.1343). The seeds are dehusked, followed by milling and screening of the endosperm (native carob bean gum) (Dakia et al., 2007). LBG is added to a variety of foods either as an emulsifier, stabilizer, or thickener.

Blood Cholesterol Levels

Beneficial health effects, such as reduced risk of heart disease, are associated with the reduction of blood total and low-density lipoprotein (LDL) cholesterol levels. Therefore, these biomarkers were used for evaluating the beneficial physiological effects of attenuation of blood cholesterol levels.

Nine studies were identified that evaluated the relationship between LBG consumption and blood cholesterol levels. Scientific conclusions could not be drawn from four of these studies (Haskell et al., 1992; Jensen et al., 1993; Jensen et al., 1997; Zunft et al., 2001) for one or more of the following reasons: 1) a mixture non-digestible carbohydrates, including LBG, was provided and therefore the physiological effect of LBG *per se* could not be evaluated, 2) the study was not conducted long enough to evaluate the effect of LBG on fasting blood cholesterol levels,[3] and 3) a control group was not included and therefore it was not possible to ascertain whether changes in blood cholesterol levels were due to LBG or due to unrelated and uncontrolled extraneous factors.

Behall et al. (1984)

Twelve US men (mean total cholesterol, 196 mg/dL) were provided a low-fiber basal diet for 20 weeks followed by the diet with added LBG (0.75 g/100 calories, or 19 to 27 g/day) for 4 weeks. Consumption of LBG significantly reduced total cholesterol levels (169 mg/dL) compared to the basal diet (196 mg/dL) ($P < 0.05$).

Behall et al. (1987)

Eleven US men consumed a basal diet with a rotating menu that contained or did not contain (control) 7.5 g LBG/1,000 calories for 4 weeks each. Consuming locust bean gum resulted in a significantly lower total cholesterol level (169 mg/dL) compared to the control (210 mg/dL) ($P < 0.05$).

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[3] Three weeks is considered to be the minimum duration for evaluating the effect of a dietary intervention on fasting blood cholesterol concentration (Kris-Etherton et al. (1997)).

Ruiz-Roso et al. (2010)

In a double-blind randomized, placebo-controlled study, 88 Spanish hypercholesterolemic (total cholesterol, 200 to 299 mg/dL) men and women consumed either 4 g twice a day carob fiber or a placebo for 4 weeks. Compared to the placebo, serum total cholesterol and LDL cholesterol levels were significantly lower ($P < 0.001$) when the carob fiber was consumed.

Zavoral et al. (1983)

This study evaluated US subjects with familial hypercholesterolemia, as well as 10 healthy subjects. Familial hypercholesterolemia is a genetic condition, resulting in very high blood cholesterol levels, and may not necessarily reflect the response by the general population. Therefore, only the evidence for healthy subjects was evaluated. Identical food products, with and without LBG (10 to 25 g/day) were provided in a cross-over design for up to 8 weeks. This study showed that, compared to the control, LBG significantly lowered total (11%) and LDL (6%) cholesterol ($P < 0.001$) in the healthy subjects.

Zunft et al. (2003)

Fifty-eight German men and women with hypercholesterolemia (total cholesterol, 261 mg/dL; LDL cholesterol, 171 mg/dL) participated in a randomized, double-blind, placebo controlled parallel study. Subjects consumed specific foods containing added LBG (carob fiber) for 6 weeks. Compared to the control, total and LDL cholesterol levels were significantly reduced ($P < 0.01$).

Strength of the Evidence

The strength of the total body of publicly available evidence was evaluated by considering the number of studies and number of subjects per group, whether the body of scientific evidence supports a beneficial physiological effect to human health for the U.S. population, whether study results supporting the beneficial physiological effect have been replicated (Wilson, 1990), and the overall consistency of the findings (Hill, 1965; AHRQ, 2002) of the evidence from which scientific conclusions could be drawn. Based on this evidence, FDA determined whether the findings concluded that there is a beneficial physiological effect of a non-digestible carbohydrate to human health and therefore meets the agency's definition of dietary fiber.

The strength of the evidence supports a beneficial physiological effect of LBG (carob gum fiber) on attenuation of blood cholesterol levels with the five available studies showing a reduction in total and/or LDL cholesterol. Based on these studies, from which scientific conclusions could be drawn, LBG (carob gum fiber) meets the definition for dietary fiber.

V. Science Review for Pectin

Background

Pectins are present in the cells walls and intracellular tissues of fruits and vegetables (IOM, 2001). Fruits contain the most pectins representing 15-20% of the dietary fiber in vegetables, legumes and nuts. Pectins are a group of complex, high molecular weight polysaccharides found in plants and composed chiefly of partially methylated polygalacturonic acid units. Portions of the carboxyl group occur as methyl esters, and the remaining carboxyl groups exist in the form of the free acid or its ammonium, potassium, or sodium salts, and in some types as the acid amide. Pectins that are used as food additives are the high-ester pectins, low-ester pectins, amidated pectins, pectinic acids, and pectinates (21 CFR 184.1588).

Blood Cholesterol Levels

Beneficial health effects, such as reduced risk of heart disease, are associated with the reduction of blood total and low-density lipoprotein (LDL) cholesterol levels. Therefore, these biomarkers were used for evaluating the beneficial physiological effects of attenuation of blood cholesterol levels.

Twenty one studies were identified that evaluated the relationship between pectin consumption and blood cholesterol levels. Scientific conclusions could not be drawn from 16 of these studies (Bell et al., 1990; Cerda et al., 1988; Davidson et al., 1998; Durrington et al., 1976; Haskell et al., 1992; Hunninghake et al., 1994; Jenkins et al., 1975; Jensen et al., 1997; Judd and Truswell, 1982; Kay and Truswell, 1977; Knopp et al., 1999; Miettinen and Tarpil, 1977; Palmer and Dixon, 1966; Schwab et al., 2006; Sitori et al., 2012; Veldman et al., 1997) for one or more of the following reasons: 1) a mixture of non-digestible carbohydrates, including pectin, was provided and therefore the physiological effect of pectin *per se* could not be evaluated 2) a control group was not included or an inappropriate control group was used and therefore it was not possible to ascertain whether changes in blood cholesterol levels were due to pectin or due to unrelated and uncontrolled extraneous factors, 3) statistical comparisons to the control group were not conducted and therefore the effect of pectin in lowering blood cholesterol levels could not be compared to the control group, and 4) the study was not conducted long enough to evaluate the effect of pectin on fasting blood cholesterol levels.[4]

Brouns et al. (2012)

In the Netherlands, a cross-over study was conducted in 30 hypercholesterolemic men and women in which experimental diets provided 15 g/day of citrus pectin, apple pectin or cellulose (control) for four weeks. Compared to the control, both sources of pectin

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[4]Three weeks is considered to be the minimum duration for evaluating the effect of a dietary intervention on fasting blood cholesterol concentration (Kris-Etherton et al. (1997)).

resulted in a significant reduction in blood total and LDL cholesterol levels ($P < 0.05$). The significant reduction was observed for those pectins that a high proportion of methyl esters (high-methoxyl pectins).

Challen et al. (1983)

Six healthy English men took part in a randomized cross-over study that included consuming a diet with and without 36 g pectin for 3 weeks each. Total cholesterol levels were significantly lower with pectin consumption (5.18 mmol/L) compared to the control (5.73 mmol/L) ($P < 0.25$).

Hillman et al., 1985

An eight-week randomized cross-over study conducted in New Zealand provided 10 healthy normocholesterolemic men and women highly methoxylated pectin (12 g/day) supplemented to their diets for 4 weeks. There was no significant change in blood total cholesterol levels (5.4 *versus* 5.1 mmol/L) with pectin supplementation compared to the control (without pectin supplementation).

Stasse-Wolthuis et al. (1980)

Under strict dietary control, Dutch normocholesterolemic men and women consumed a low-fiber diet (15 g/day) supplemented with (n=15) or without (control, n=16) citrus pectin (9 g/day) for up to 5 weeks. Citrus pectin was added to desserts. After 5 weeks on the diets, serum total cholesterol levels were significantly reduced (0.34 mmol/L) with the addition of pectin to the diets ($P < 0.01$).

Vargo et al. (1985)

The diets of ten US healthy men and women were supplemented with 15 g/day of citrus pectin. There was a significant reduction ($P < 0.05$) in serum total cholesterol levels after 3 weeks of supplementation with pectin (168 *versus* 206 mg/dL).

Strength of the Evidence

The strength of the total body of publicly available evidence was evaluated by considering the number of studies and number of subjects per group, whether the body of scientific evidence supports a beneficial physiological effect to human health for the U.S. population, whether study results supporting the beneficial physiological effect have been replicated (Wilson, 1990), and the overall consistency of the findings (Hill, 1965; AHRQ, 2002) of the evidence from which scientific conclusions could be drawn. Based on this evidence, FDA determined whether the findings concluded that there is a beneficial physiological effect of a non-digestible carbohydrate to human health and therefore meets the agency's definition of dietary fiber.

The strength of the evidence supports pectin in reducing blood cholesterol levels with four of five studies showing reduced total and/or LDL cholesterol levels. The largest studies showed that pectin isolated from different sources (apple and citrus) lowered total and/or LDL cholesterol levels (Brouns et al., 2012; Stasse-Wolthuis et al., 1980. Based on the above studies from which scientific conclusions could be drawn, pectin meets the definition for dietary fiber.

VI. Science Review for Hydroxypropylmethylcellulose

Background

HPMC is a propylene glycol ether of methylcellulose containing methoxyl groups and hydroxypropyl groups (FDA GRAS Notification No. 213). HPMC is a gum that has multiple technical effects, including use as a film former, stabilizer, and thickener.

Blood Cholesterol Levels

Beneficial health effects, such as reduced risk of heart disease, are associated with the reduction of blood total and low-density lipoprotein (LDL) cholesterol levels. Therefore, these biomarkers were used for evaluating the beneficial physiological effects of attenuation of blood cholesterol levels.

Six studies were identified that evaluated the relationship between HPMC consumption and blood cholesterol levels. Scientific conclusions could not be drawn from three studies (Dressman et al., 1993; Maki et al., 2000; Swidan et al., 1996) because 1) an appropriate control was not provided and therefore it was not possible to ascertain whether changes in blood cholesterol levels were due to HPMC or due to unrelated and uncontrolled extraneous factors, or 2) the study was not conducted for a sufficient duration for measuring fasting blood cholesterol levels.[5]

Maki et al. (1999)

Hypercholesterolemic men and women ($n = 36$ to 41 per treatment) participated in a randomized, double-blind, placebo-controlled parallel study in the United States. The subjects were provided either a placebo (microcrystalline cellulose) or 2.5, 5.0 or 7.5 g/day high-viscosity HPMC in an orange drink, along with their diet, for 6 weeks. After the 6 week period, a significant reduction in total and LDL cholesterol was observed with consumption of 5 or 7.5 g/day HPMC ($P < 0.05$)

Maki et al. (2009)

In a randomized, double-blind crossover study, 13 hypercholesterolemic US men and women on statin therapy received 5 g/day (2.5 g twice daily) HPMC in lemonade or a control, along with their diets, for 4 weeks each. After the 4 week intervention, total and LDL cholesterol levels were significantly reduced when compared to the control ($P =$ 0.003 and 0.009, respectively).

Reppas et al. (2009)

In a randomized, double-blind, placebo-controlled parallel study, hypercholesterolemic US men and women ($n = 10$ to 20 per group) consumed a placebo, 5 or 15 g/day ultra-

[5] Three weeks is considered to be the minimum duration for evaluating the effect of a dietary intervention on fasting blood cholesterol concentration (Kris-Etherton et al. (1997).

high viscosity HPMC in a hot chocolate drink with breakfast and in sugar-molasses cookies with lunch and dinner for 8 weeks. Total and LDL cholesterol levels were significantly lower when consuming 5 or 15 g/day ultra-high HPMC. Furthermore, total ($P = 0.01$) and LDL (P=0.002) cholesterol levels were significantly lower after consuming 15 g/day HPMC compared to 5 g/day HPMC.

Strength of the Evidence

The strength of the total body of publicly available evidence was evaluated by considering the number of studies and number of subjects per group, whether the body of scientific evidence supports a beneficial physiological effect to human health for the U.S. population, whether study results supporting the beneficial physiological effect have been replicated (Wilson, 1990), and the overall consistency of the findings (Hill, 1965; AHRQ, 2002) of the evidence from which scientific conclusions could be drawn. Based on this evidence, FDA determined whether the findings concluded that there is a beneficial physiological effect of a non-digestible carbohydrate to human health and therefore meets the agency's definition of dietary fiber.

The strength of the evidence supports HPMC in reducing blood cholesterol levels with the 3 available studies showing a reduction in total and LDL cholesterol levels. Based on the above studies from which scientific conclusions could be drawn, HPMC meets the definition for dietary fiber.

References

1. AHRQ (Agency for Healthcare Research and Quality) "Systems to rate the scientific evidence" (March 2002) [http://archive.ahrq.gov/clinic/epcsums/strengthsum.pdf], defining "consistency" as "the extent to which similar findings are reported using similar and different study designs."

2. Agency for Healthcare Research and Quality (AHRQ). Methods Guide for Medical Test Reviews. 2014. http://www.ahrq.gov/research/findings/evidence-based-reports/technical/methodology/index.html

3. Aro A, Uusitupa M, Voutilainen E, Korhonen T. Effects of guar gum in male subjects with hypercholesterolemia. *American Journal of Clinical Nutrition* 1984;39:911-916.

4. Aro A, Uusitupa M, Voutilainen E et al. Improved diabetes control and hypocholesterolemic effect induced by long-term dietary supplementation with guar gum in type 2 (insulin-independent) diabetes. *Diabetologia* 1981;21:29-33.

5. Behall KM, Scholfield DJ, Lee K. Mineral balance in adult men: effect of four refined fibers. *American Journal of Clinical Nutrition* 1987; 46:307-314.

6. Behall, KM, Lee KH, Moser PB. Blood lipids and lipoproteins in adult men fed four refined fibers. *American Journal of Clinical Nutrition* 1984;39:209-214.

7. Bell LP, Hectorn KJ, Reynolds H, Hunnighake DB. Cholesterol-lowering effects of soluble-fiber cereals as part of a prudent diet for patients with mild to moderate hypercholesterolemia. *American Journal of Clinical Nutrition* 1990;52:1020-1026.

8. Blake DE, Hamblett CJ, Frost PG et al. Wheat bread supplemented with depolymerized guar gum reduces the plasma cholesterol concentration in hypercholesterolemic human subjects. *American Journal of Clinical Nutrition* 1997;65:107-113.

9. Bosello O, Cominacini L, Zocca I et al. Effects of guar gum on plasma lipoproteins and apolipoproteins C-II and C-III in patients affected by familial combined hyperlipoproteinemia. *American Journal of Clinical Nutrition* 1984;40:1165-1174.

10. Botha AP, Steyn AF, Esterhuysen AJ, Slabbert M. Glycosylated haemoglobin, blood glucose and serum cholesterol levels in diabetics treated with guar gum. *South African Medical Journal* 1981;59:333-334.

11. Brouns F, Theuwissen E, Adam A et al. Cholesterol-lowering properties of different pectin types in mildly hyper-cholesterolemic men and women. *European Journal of Clinical Nutrition* 2012;66:591-599.

12. Castro AI, Monteiro VCB, Marroso LP, Bertolami MC. Effect of eicosapentaenoic/docosahexaenic fatty acids and soluble fibers on blood lipids of individuals classified into different levels of lipidemia. *Nutrition* 2007;23:127-137.

13. Cerda JJ, Robbins FL, Burgin CW et al. The effects of grapefruit pectin on patients at risk of coronary heart disease without altering diet or lifestyle. *Clinical Cardiology* 1988;11:589-594.

14. Challen AD, Branch WJ, Cummings JH. The effect of pectin and wheat bran on platelet function and haemeostasis in man. *Human Nutrition: Clinical Nutrition* 1983;37C:209-217.

15. Chuang LM, Jou TS, Yang WS et al. Therapeutic effect of guar gum in patients with non-insulin-dependent diabetes mellitus. *Journal Formosan Medical Association* 1992;91:15-19.

16. Dakia PA, Wathelet B, Paqut M. Isolation and chemical evaluation of carob (Ceratonia silique L.) seed germ. *Food Chemistry* 2007;102:1368-1374.

17. Danjo K, Sakamoto J, Iwane S. et al. Effects of cellulose supplementation on fecal consistency and fecal weight. *Digestive Disease Science* 2008;53:712-718.

18. Davidson MH, Dugan LD, Stocki J et al. A low-viscosity soluble-fiber fruit juice supplement fails to lower cholesterol in hypercholesterolemic men and women. *Journal of Nutrition.* 1998;128:1927-1932.

19. Dressman JB, Adair CH, Barnett JL et al. High-molecular-weight hydroxypropylmethylcellulose. A cholesterol-lowering agent. *Archives of Internal Medicine* 1993; 153:1345-1353.

20. Durrington PN, Bolton CH, Manning AP, Hartog M. Effect of pectin on serum lipids and lipoproteins, whole-gut transit-time, and stool weight. *The Lancet* 1976; 308:394-396.

21. Eastwood MA, Kirkpatrick JR, Mitchell WD et al. Effects of dietary supplements of what bran and cellulose on faeces and bowel function. *British Medical Journal*. 1973;4:392-394.

22. Ebeling P, Yki-Jarvinen H, Aro A et al. Glucose and lipid metabolism and insulin sensitivity in type 1 diabetes: the effect of guar gum. *American Journal of Clinical Nutrition* 1988;48:98-103.

23. FDA. Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims. 2009. http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm073332.htm

24. FDA. Gras Notification for hydroxypropyl methylcellulose. No.213. 2006. http://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices&id=213&sort=GRN_No&order=DESC&startrow=1&type=basic&search=hydroxypropyl%20methylcellulose

25. Fleming SE, Marthinsen D, Kuhnlein H. Colonic function and fermentation in men consuming high fiber diets. *Journal of Nutrition* 1983; 113:2535-2544.

26. Fuessl HS, Williams G, Adrian TE, Bloom SR. Guar sprinkled on food: effect of glycaemic control, plasma lipids and gut hormones in non-insulin dependent diabetic patients. *Diabetic Medicine* 1987;4:463-468.

27. Gatti E, Catenazzo G, Camisasca E et al. Effects of guar-enriched pasta in the treatment of diabetes and hyperlipidemia. *Annals of Nutrition and Metabolism* 1984;28:1-10.

28. Haskell WL, Spiller GA, Jensen CD et al. Role of water-soluble dietary fiber in the management of elevated plasma cholesterol in healthy subjects. *Preventive Cardiology* 1992;69:433-439.

29. Hill AB. The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine* 1965;58:295-300.

30. Hillman L, Peters S, Fisher A, Pomare W. Differing effects of pectin, cellulose and lignin on stool pH, transit time and weight. *British Journal of Nutrition.* 1983;50:189-195.

31. Hillman LC, Peters SG, Fisher CA, Pomare EW. The effects of fiber components pectin, cellulose and lignin on serum cholesterol levels. *American Journal of Clinical Nutrition* 1985;42:207-213.

32. Hunnighake DB, Miller VT, LaRosa JC et al. Long-term treatment of hypercholesterolemia with dietary fiber. *American Journal of Medicine* 1994;97:504-508.

33. Institute of Medicine. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein and Amino Acids. National Academies Press. Washington DC. 2002.

34. Institute of Medicine. Dietary Reference Intakes: Proposed Definition of Dietary Fiber. National Academies Press. Washington DC. 2001.

35. Jenkins DJA, Leeds AR, Newton C, Cumming JH. Effect of pectin, guar gum and wheat fibre on serum-cholesterol. *The Lancet* 1975;305;1116-1117.

36. Jenkins DJA, Leeds AR, Slavin B et al. Dietary fiber and blood lipids: reduction of serum cholesterol in type II hyperlipidemia by guar gum. *American Journal of Clinical Nutrition* 1979;32:16018.

37. Jenkins DJA, Reynolds D, Slavin B et al. Dietary fiber and blood lipids: treatment of hypercholesterolemia with guar crisp bread. *American Journal of Clinical Nutrition* 1980;33:575-581.

38. Jensen CD, Haskell W, Whittam JH. Long-term effects of water-soluble dietary fiber in the management of hypercholesterolemia in healthy men and women. *American Journal of Cardiology* 1997; 79:34-37.

39. Jensen CD, Spiller GA, Gates JE, Miller AF. The effect of acacia gum and a water-soluble dietary fiber mixture on blood lipids in humans. *Journal of the American College of Nutrition* 1993;12:147-154.

40. Johansen K. Decreased urinary glucose excretion and plasma cholesterol level in non-insulin dependent diabetic patients with guar. *Diabete and Metabolisme* 1981;7:87-90.

41. Judd PA, Truswell AS. Comparison of the effects of high- and low-methoxyl pectins on blood and faecal lipids in man. *British Journal of Nutrition* 1982; 48;451-458.

42. Kay RM, Truswell A. Effect of citrus pectin on blood lipids and fecal steroid excretion in man. *American Journal of Clinical Nutrition* 1977;30:171-175.

43. Khan AR, Khan GY, Mitchel A, Qadeer MA. Effect of guar gum on blood lipids. *American Journal of Clinical Nutrition* 1981;34:2446-2449.

44. Knopp RH, Superko HR, Davidson M et al. Long-term blood cholesterol-lowering effects of dietary fiber supplement. *American Journal of Preventive Medicine* 1999;17:18-23.

45. Kondo S, Xiao JZ, Takahashi N, Miyaji K. Suppressive effects of dietary fiber in yogurt on the postprandial serum lipid levels in healthy adult male volunteers. *Biosciences Biotechnology and Biochemistry*. 2004;1135-1138.

46. Kris-Etherton PM, Dietschy J. Design criteria for studies examining individual fatty acid effects on cardiovascular disease risk factors: human and animal studies. *American Journal of Clinical Nutrition* 1997; 65:1590S-1596S.

47. Landin K, Holm G, Tengborn L, Smith U. Guar gum improves insulin sensitivity, blood lipids, blood pressure, and fibrinolysis in healthy men. *American Journal of Clinical Nutrition* 1992;56:1061-1065.

48. Maki KC, Davidson MH, Malik KC et al. Cholesterol lowering with high-viscosity hydroxypropylmethylcellulose. *American Journal of Cardiology* 1999; 84: 1198-1203.

49. Maki KC, Davidson MH, Torri S et al. High-molecular-weight hydroxypropylmethylcellulose taken with or between meals is hypocholesterolemic in adult men. *Journal of Nutrition* 2000; 130:1705-1710.

50. Maki KC, Carson ML, Miller MP et al. Hydroxypropylmethylcellulose lowers cholesterol in statin-treated men and women with primary hypercholesterolemia. *European Journal of Clinical Nutrition* 2009;63:1001-1007.

51. Makkonen M, Simpanen AL, Saarikoski S et al. Endocrine and metabolic effects of guar gum in menopausal women. *Gynecology Endocrinology* 1993;7:135-141.

52. McIvor ME, Cummings CC, Van Duyn MA et al. Long-term effects of guar gum on blood lipids. *Atherosclerosis* 1986;7-13.

53. Miettinen TA, Tarpila S. Effect of pectin on serum cholesterol, fecal bile acids and biliary lipids in normolipidemic and hyperlipidemic individuals. *Clinica Chimica Acta*. 1977;79:471-477.

54. Niemi MK, Keinanen-Kiukaanniemi SM, Salmela PI. Long-term effects of guar gum and microcrystalline cellulose on glycemic control and serum lipids in type 2 diabetes. *European Journal of Clinical Pharmacology* 1988;34:427-429.

55. Palmer GH, Dixon DG. Effect of pectin on serum cholesterol levels. *American Journal of Clinical Nutrition.* 1966;18:437-442.

56. Park EJ, Jhon DY. Effects of bamboo shoot consumption on lipid profiles and bowel function in healthy young women. *Nutrition* 2009; 25:723–728.

57. Pasman WJ, Westerterp-Plantenga MS, Muls E et al. The effectiveness of long-term fibre supplementation on weight maintenance in weight-reduced women. *International Journal of Obesity* 1997;21:548-555.

58. Penagini R, Velio P, Vigorelli R et al. The effect of dietary guar on serum cholesterol, intestinal transit, and fecal output in man. *American Journal of Gastroenterology* 1986;81:123-125.

59. Raymond TL, Connor WE, Lin DS et al. The interaction of dietary fibers and cholesterol upon the plasma lipids and lipoproteins, sterol balance, and bowel function in human subjects. *Journal of Clinical Investigation* 1977;60:142901437.

60. Reppas C, Swidan SZ, Tobey SW et al. Hydroxypropylmethylcellulose significantly lowers blood cholesterol in mildly hypercholesterolemic human subjects. *European Journal of Clinical Nutrition* 2009; 63:71-77.

61. Ruiz-Roso B, Quintela JC, de la Fuente et al. Insoluble carob fiber rich in polyphenols lowers total and LDL cholesterol in hypercholesterolemic subjects. *Plant Foods Human Nutrition* 2010; 65:50-56.

62. Salenius JP, Harju E, Jokela H et al. Long term effects of guar gum on lipid metabolism after carotid endarterectomy. *British Medical Journal* 1995;310:95-96.

63. Schwab U, Louheranta A, Torronen A, Uusitupa M. Impact of sugar beet pectin and polydextrose on fasting and postprandial glycemia and fasting concentrations of serum total and lipoprotein lipids in middle-aged subjects with abnormal glucose metabolism. *European Journal of Clinical Nutrition* 2006;60:1073-1080.

64. Simons LA, Gayst S, Balasubramaniam, Ruys J. Long-term treatment of hypercholesterolemia with a new palatable formulation of guar gum. *Atherosclerosis* 1982;45:101-108.

65. Sitori CR, Triolo M, Bosisio R et al. Hypercholesterolemic effects of lupin protein and pea protein/fibre combinations in moderately hypercholesterolemic individuals. *British Journal of Nutrition* 2012; 107:1176-1183.

66. Slavin JL, Marlett JA. Influence of refined cellulose on human bowel function and calcium and magnesium balance. *American Journal of Clinical Nutrition* 1980;33:1932-1939.

67. Smith U, Holm G. Effect of modified guar gum preparation on glucose and lipid levels in diabetics and healthy volunteers. *Atherosclerosis* 1982;45:1-10.

68. Spiller GA, Farquhar JW, Gates JE, Nichols SF. Effect of guar gum and an oat fiber source on plasma lipoprotein and cholesterol in hypercholesterolemic adults. *Arteriosclerosis and Thrombosis* 1991;11:1204-1208.

69. Spiller GA, Chernoff MC, Hill RA et al. Effect of purified cellulose, pectin, and a low reside diet on fecal volatile fatty acids, transit time, and fecal weight in humans. *American Journal of Clinical Nutrition* 1980;33:754-759.

70. Stasse-Wolthuis M, Hugo F, Albers F et al. Influence of dietary fiber from vegetables and fruits, bran or citrus pectin on serum lipids, fecal lipids and colonic function. *American Journal of Clinical Nutrition* 1980;33:1745-1756.

71. Stephen AM, Wiggins HS, Englyst HN et al. The effect of age, sex and level of intake of dietary fibre from wheat on large-bowel function in thirty healthy subjects. *British Journal of Nutrition* 1986;56:349-361.

72. Superko HR, Haskell WL, Sawrey-Kubicek L, Farquhar JW. Effects of solid and liquid guar gum on plasma cholesterol and triglyceride concentrations in moderate hypercholesterolemia. *American Journal of Cardiology* 1988; 62:51-55.

73. Swidan SZ, Reppas C, Barnett JL et al. Ability of two comestible formulations of hydroxypropylmethylcellulose to lower serum cholesterol concentrations. *European Journal of Pharmaceutical Sciences* 1996; 4:239-245.

74. Tsai ES, Fok AC, Chu R, Tan CE. A study to assess the effect of dietary supplementation with soluble fibre (Minolest) on lipid levels in normal subjects with hypercholesterolemia. *Annals Academy of Medicine Singapore* 1999;28:209-213.

75. Turner PR, Tuomilehto J, Happonen P et al. Metabolic studies on the hypolipidaemic effect of guar gum. *Atherosclerosis* 1990;81:145-150.

76. Uusitupa M, Siitonen O, Savolainen K et al. Metabolic and nutrition effects of long-term use of guar gum in the treatment of noninsulin-dependent diabetes of poor metabolic control. *American Journal of Clinical Nutrition* 1989;49:345-351.

77. Uusitupa M, Sodervik H, Silvasti M, Karttunen P. Effects of gel forming dietary fiber, guar gum, on the absorption of glibebcalmide and metabolic control and serum lipids in patients with non-insulin-dependent (Type 2) diabetes. *International Journal of Clinical Pharmacology Therapy and Toxicology* 1990;28:153-157.

78. Vargo D, Doyle R, Floch MH. Colonic bacterial flora and serum cholesterol: Alterations induced by dietary citrus pectin. *American Journal of Gastroenterology* 1985;80:361-364.

79. Veldman FJ, Chenicheri HN, Vorster HH et al. Dietary pectin influences fibrin network structure in hyerpcholesterolaemic subjects. *Thrombosis Research* 1997;86:183-186.

80. Vuorinen-Markkola H, Sinisalo M, Koivisto VA. Guar gum in insulin-dependent diabetes: effects on glycemic control and serum lipoproteins. *American Journal of Clinical Nutrition* 1992;56:1056-1060.

81. Wilson EB. An Introduction to Scientific Research, pages 46-48, Dover Publications, 1990.

82. Wrick KL, Robertson JB, Van Soest PJ et al. The influence of dietary fiber source in human intestinal transit and stool output. *Journal of Nutrition* 1983;113:1464-1479.

83. Zavoral JH, Hannan P, Fields DJ et al. The hypolipidemic effect of locust bean gum food products in familial hypercholesterolemia and hypercholesterolemic adults and children. *American Journal of Clinical Nutrition* 1983;38:285-294.

84. Zunft HJF, Luder W, Harde A et al. Carob pulp preparation for treatment of hypercholesterolemia. *Advances in Therapy* 2001; 18:230-236

85. Zunft HJF, Luder W, Harde A et al. Carob pulp preparation rich in insoluble fibre lowers total and LDL cholesterol in hypercholesterolemic patients. *European Journal of Nutrition* 2003;42:235-242.