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September 4, 2019

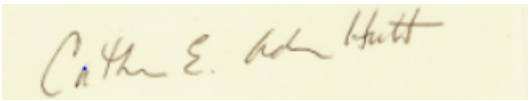
Submission of Citizen Petition

To: Docket No. FDA-2016-D-3401 for "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).

I submit this Citizen Petition on behalf of Fiber Research International. We petition under 21 CFR 10.30 of the Food, Drug and Cosmetic Act and request the Commissioner of Food and Drugs amend 21 CFR 101.9 Nutrition Labeling of Food to include a highly purified form of glucomannan with not less than 95% purity by HPLC, including that sold under the trade names Propol and Propolmannan, as a dietary fiber in the Nutrition Facts label on foods, beverages, and dietary supplements.

This request provides information demonstrating a highly purified glucomannan with not less than 95% purity by HPLC, consistent with the purity and quality standards of Propol and Propolmannan, meets the 21 CFR 101.9 definition of dietary fiber and provides physiological benefits to human health, including reduced blood cholesterol levels, improved laxation, and reduced energy intake.

Signed,



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Citizen Petition Requesting 21 CFR 101.9(c)(6)(i) Listing of Be Amended To Include a Highly Purified Form of Glucomannan as a Dietary Fiber

Dear Commissioner Sharpless:

Fiber Research International (FRI) submits this petition under 21 CFR 10.30 and 21 CFR 10.21 to request that a highly purified form of glucomannan with not less than 95% purity as determined by high performance liquid chromatography (HPLC), including that sold under the trade name Propol or PropolMannan, a polysaccharide isolated from the roots of *Amorphophallus konjac*, be included as Dietary Fiber in the Nutrition Facts label on foods, beverages, and dietary supplements. The basis for this request is provided below. Propol and PropolMannan are manufactured by Shimizu Chemical Company of Japan.

A. Action Requested

Fiber Research International petitions under 21 CFR 10.30 of the Food, Drug and Cosmetic Act requesting the Commissioner of Food and Drugs amend 21 CFR 101.9 Nutrition Labeling of Food to include a highly purified form of glucomannan, including that sold under the trade names Propol and Propolmannan, as a dietary fiber in the Nutrition Facts label on foods, beverages, and dietary supplements. This request provides information demonstrating a highly purified glucomannan with not less than 95% purity by HPLC, consistent with the purity and quality standards of Propol and Propolmannan, meets the 21 CFR 101.9 definition of dietary fiber and provides physiological benefits to human health, including reduced blood cholesterol levels, improved laxation, and reduced energy intake.

B. Statement of Grounds

1. Regulatory Requirements Regarding Dietary Fiber

21 CFR 101.9(c)(6)(i) defines dietary fiber as; "… isolated… non-digestible carbohydrates (with 3 or more monomeric units) determined by FDA to have physiological effects that are beneficial to human health."

2. Manufacture of Propol and PropolMannan Glucomannan

Manufacturing Process for Highly Purified Glucomannan, consistent with Propol and PropolMannan

► The 1st Step Processing:

Raw-Material(Konjac Tuber) → Sorting → Washing (Water) → Crushing → Extraction(1) (Ethanol,Water) → Separation(1)

→ Extraction(2) (Ethanol,Water) → Separation(2) → Drying → Sieving → (Product of the 1st Step Processing)

► The 2nd Step Processing:

(Product of 1st Process) → Stirring (Ethanol,Water) → Polishing → Extraction (Ethanol,Water) → Separation → Drying

→ Sieving → Metal Detection / Magnetic Sorting → Propol, PropolMannan

3. Chemical Structure and Nondigestibility of Glucomannan

Glucomannan, unlike a crude vegetable material, is a specific water-soluble, long-chain polysaccharide molecule. It is a constituent of *Amorphophallus konjac*, as well as other plants, and can be isolated and purified using several complex and sophisticated extraction methods [1]. Glucomannan is a nearly linear chain (1.2 – 1.6% of units are branch points) of randomly distributed β-D-mannose and β-D-glucose units with a ratio of 1.5-2.0:1, respectively, a range of molecular weights from 500,000 to 2,000,000 AMU, and a purity of 95% or greater as measured by HPLC [1]. These physical properties allow glucomannan to be formed into heat stable gels that maintain their viscosity for over 72 hours (Figure 1C), expand in aqueous solutions, and exhibit distinct physical properties in the gut, which allows them to function as dietary fibers.

Notably, UV/Vis spectrophotometric analysis is not appropriate for quantification or purity determination of glucomannan, as this method is unable to separate individual constituents and is only appropriate for identification purposes, not purity analysis. HPLC analysis, on the other hand, is a sensitive and selective analytical procedure that is appropriate for separation, identification, and quantification purposes in the characterization of glucomannan materials.

The chemical and physical distinctions between konjac flour and glucomannan, as defined by the Joint FAO/WHO Expert Committee on Food Additives (JEFCA; INS 425 konjac flour) and European Food Safety Authority (E425 (ii) konjac glucomannan) on the basis of expert consensus, are summarized in Table 1 [2, 3]. Most notably, glucomannan is of higher purity than konjac flour, which results in a tighter mannose:glucose ratio and solubility, a higher molecular weight, more linear polysaccharide chain, and reduced protein and ash impurities. Collectively, these properties allow glucomannans to form gels with higher viscosity at both room temperature and physiologic temperature for prolonged periods of time when compared to konjac flours, konjac powder gums, and lower purity glucomannans (Figure 1).

Table 1
Chemical and Physical Properties of Konjac Flour and Glucomannan [3]

	Glucomannan
Definition	A water-soluble hydrocolloid obtained from konjac flour by washing with water-containing ethanol. The main component is a water-soluble high-molecular-weight polysaccharide glucomannan, which consists of d-mannose and d-glucose units at a molar ratio of 1.6:1 connected by β(1-4)-glycosidic bonds with a branch at about each 50^{th} or 60^{th} unit. About each 19^{th} sugar residue is acetylated.
Purity	Not less than 95% as determined by HPLC
Molecular Weight	500,000 – 2,000,000 AMU
Solubility	Dispersible in hot or cold water forming a highly viscous solution with a pH between 5.0 and 7.0
Viscosity (1% Solution)	Not less than 20 kg/m·s @ 25 °C
Stability (1% Solution)	Not less than 40 kPA at 37 °C for 72 h
Loss on Drying	Not more than 8.0% (105 °C, 3 h)
Starch	Not more than 1.0%
Protein	Not more than 1.5% as determined by the Kjeldahl method
Total Ash	Not more than 2.0% (800 °C, 3 – 4 h)
Sulfite	Not more than 4 mg/kg

The majority of human clinical studies evaluating glucomannan's physiological benefits utilize an ultrapure glucomannan (greater than 95% by HPLC) marketed under the name Propol and PropolMannan (including

subcategory forms “A” and “KW”), produced by the Shimizu Chemical Corporation of Japan (referred to hereafter as “Shimizu”). Shimizu maintains distribution records that allow the form of glucomannan that was used in each clinical study to be identified, which have been listed in the attached declaration [see Attachment 1, Declaration of Rieu Shimizu].

Glucomannan with not less than 95% purity validated by HPLC, such as Propol glucomannan, forms high viscosity glucomannan gels that are stable at room temperature (Figure 1A) and physiologic temperature (37 °C) for periods beyond 72 hours (Figure 1B, C), distinguishing them outright in physical and mechanical characteristics from simple konjac flours. Indeed, konjac flour, konjac gums, and glucomannans of purity less than 95% are unable to form hydrocolloids that maintain comparable viscosity for more than 24 h (Figure 1). Because konjac flour gels are unable to maintain viscosity at physiologic temperature over time, their capacity to function as a dietary fiber is likely inconsistent and inferior to glucomannan of 95% purity or greater, *i.e.*, Propol glucomannan.

Figure 1

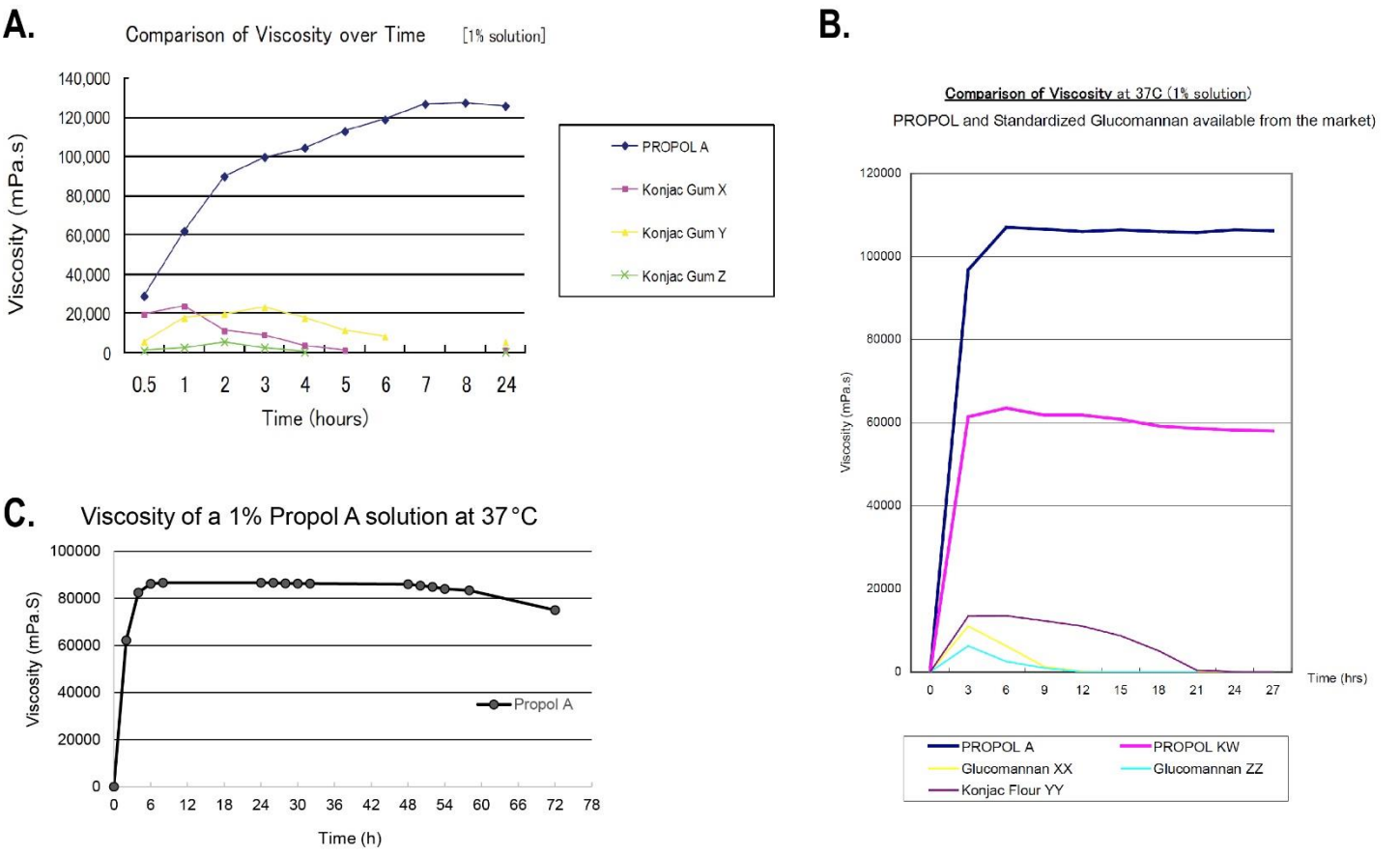

Figure 1 – **Glucomannans (Shimizu Propols) create gels that are thermally stable at physiological temperature.** Glucomannan gel viscosity was compared to konjac flour, konjac gums, and low purity products sold as “glucomannans” at different temperatures over time using a type B viscometer. **A)** A 1% Shimizu Propol A (black diamond line) gel maintains high viscosity for over 24 h at 25 °C in comparison to 1% konjac gum gels. **B)** 1% Shimizu Propol A and Propol KW gels maintain high viscosity for over 24 h at physiological temperature of 37 °C in comparison to 1% konjac flour and lower purity glucomannan gels. **C)** A 1% Shimizu Propol A gel maintains high viscosity for over 72 h at physiological temperature of 37 °C.

4. Physiologic Benefits Consistent with Dietary Fibers

Human clinical studies support claims that oral consumption of Propol glucomannan (at least 95% purity by HPLC) can provide physiological benefits consistent with a soluble dietary fiber, including reduced blood lipids in the form of low-density lipoprotein (LDL) cholesterol, improved laxation, and reduced energy intake. A summary of study findings is presented in Sections 4.1, 4.2, and 4.3 below.

While standards for the physical and chemical properties have been defined (Table 1) by international regulatory bodies, products cited as glucomannan within the pre-clinical and clinical literature do not necessarily adhere to these standards. As noted above, the majority of human clinical trials evaluating the impacts of glucomannan on physiological parameters used Propol glucomannan of ultrahigh purity (at least 95% by HPLC), and stability, which can be verified by the attached declaration of Rieu Shimizu of Shimizu Chemical Corporation of Japan, who sourced the products for many of these trials. However, a number of human clinical studies do not list the physical properties of glucomannan use or cite a source. Where possible, the purity of glucomannan has been provided in the tables found within each subsection. High purity and viscosity glucomannans are listed by name (*e.g.*, Propol with subcategories "A" or "KW" where applicable) and highlighted green, indeterminate forms of glucomannan materials in grey, and low purity glucomannan (*e.g.*, konjac flour) in red. If a study supports the dietary physiologic claim being made it is highlighted in green, and if not, it is highlighted in red.

Three sets of human clinical studies were not included in this petition. First, clinical studies using konjac flour and/or konjac gum were not considered as they are discrete dietary entities with different chemical and physical properties. Second, studies on juveniles and adolescents were not considered. Though a number of studies demonstrate glucomannan to improve laxation in children and adolescents, because sufficient dosing has not been clearly defined in juvenile populations in a manner equivalent to adults (*e.g.*, EFSA), studies in juveniles were not considered. Third, studies in which glucomannan was a component of an enriched food or blend of other factors were not considered because glucomannan was not studied in isolation, as requested by as the FDA in *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): Guidance for Industry*, and dosing consistent with EFSA guidelines were not adhered to.

The quality of each clinical trial reviewed was graded "high", "moderate" or "low" on the basis of criteria presented in the FDA's *Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims* (Table 2).

Table 2
Quality Ratings for Human Intervention Studies

High Quality	Moderate Quality	Low Quality
- Randomized, controlled - Placebo if appropriate - Double-blind - Description of subjects - Similar subject baseline characteristics - Adequate sample size - No significant difference in food intake between groups - Good compliance - Less than 20% drop out rate - Appropriate statistical analysis	- Randomized, controlled, and blinded but with some deficiencies or bias, but not enough to invalidate results	- Not randomized or unclear statement of randomization - No proper control - Insufficient blinding - Fewer than 10 subjects per treatment - Environmental, behavioral, or health factors are inconsistent between groups - Subjects have health issues or take medication that may alter study outcome independent of treatment

- Proper wash out period for crossover studies - Sufficient treatment period per FDA industry guidance - No reporting errors or obvious bias		- Poor compliance - High drop-out rate (more than 20%) - Study duration too short for effect to be properly observed - Missing information and/or reporting discrepancies - Inappropriate claims on the basis of outcome measures - Any factor that could introduce significant result bias

4.1. Reduced Blood Lipids in the Form of LDL Cholesterol

Justification of Blood Cholesterol as a Physiologic Measure of Health

Reduction in fasting blood total cholesterol and LDL cholesterol levels are indicated in the FDA's *Final Rule on Nutrition Labeling* (81 FR 33855-6) and *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): Guidance for Industry* as beneficial physiological endpoints of dietary fiber consumption, and function as surrogates for risk of cardiovascular disease.

Summary of Studies

Known studies evaluating the effect of glucomannan on total and LDL blood cholesterol have been identified, reviewed for quality and appropriateness, and are summarized in Table 3 and described in detail thereafter.

Table 3
Claim: Blood Lipids

Study	Glucomannan	Supports Claim	Findings
Arvill et. al. 1995 [4]	Propol (A)	Yes	Glucomannan significantly reduced total cholesterol, LDL, and triglycerides in healthy males after two weeks of treatment
Cairella et. al. 1995 [18]	Propol (KW)	Yes	Glucomannan resulted in greater cholesterol normalization compared to placebo conditions
Chearskul et. al. 2007 [5]	Indeterminate	Yes	Glucomannan significantly reduced LDL cholesterol and blood glucose rise in type 2 diabetic adults when consumed before an oral glucose tolerance test, as compared to control
Doi et. al. 1979 [6]	Propol	Yes	Glucomannan significantly decreased serum cholesterol and fasting blood glucose in type 2 diabetic adults, and reduced blood glucose and serum insulin in healthy individuals taking a glucose tolerance test

Keithley et. al. 2013 [7]	Purity consistent with konjac flour	No	No difference in any lipid measure was observed between overweight adults taking konjac flour and those taking placebo
Kraemer et. al. 2007 [8]	Propol	Yes	Glucomannan alone significantly decreased LDL and total cholesterol in overweight adults, and the addition of exercise further improved these parameters
Reffo et. al. 1988 [9]	Propol	Yes	Glucomannan alone or with a concurrent restricted calorie diet significantly reduced total cholesterol and triglycerides in hypertensive patients as compared to placebo control after four weeks of treatment
Reffo et. al. 1990 [10]	Propol	Yes	Glucomannan significantly reduced total cholesterol and increased HDL after eight weeks in post-infarcted patients undergoing cardiac rehabilitation as compared to placebo control
Terasawa et. al. 1979 [11]	Propol	Yes	Glucomannan significantly decreased serum cholesterol and triglycerides in elderly, constipated females
Vita et. al. 1992	Propol (A)	Yes	Glucomannan significantly reduced total cholesterol while preserving HDL compared to a hypocaloric diet alone
Walsh et. al. 1984 [12]	Propol (A)	Yes	Glucomannan significantly reduced body weight, serum total cholesterol, and LDL as compared to controls
Wood et. al. 2007 [13]	Indeterminate	Yes	Glucomannan significantly reduced LDL to a significantly greater degree within a 6-week time period than a carbohydrate-restricted diet alone in overweight and obese men
Yoshida et. al. 2006 [14]	Indeterminate	Yes	Glucomannan significantly reduced LDL in type 2 diabetic and nondiabetic controls as compared to control (untreated) group

4.1.1 Arvill et. al. 1995 *Effect of short-term ingestion of konjac glucomannan on serum cholesterol in healthy men*. Am J Clin Nutr 61(3): 585-589

- High quality
- Double-blind, placebo-controlled, randomized, parallel study
- 63 healthy males received 3.9 g/d glucomannan or placebo for two weeks
- Propol A glucomannan
- Pubmed ID 7872224

Findings: High purity glucomannan significantly reduced total cholesterol, LDL, and triglycerides as compared to placebo control

4.1.2 Cairella et. al. 1995 *Evaluation of the action of glucomannan on metabolic parameters and on the sensation of satiation in overweight and obese patients.* Clin Ter 146(4): 269-74

- High Quality
- Double-blind, placebo-controlled, randomized study
- 30 adult females, BMI 25-30 all consumed a calorie-restricted diet of 1200 kcal/day + placebo capsules for 30 days. The diet was then continued for an additional 30 days, wherein subjects

according to the randomization consumed either 3.86g/day glucomannan or matching placebo 30-60 minutes before the two main meals with 1-2 glasses of water
- High purity glucomannan (Dietoman is prepared with PropolMannan glucomannan)
- Pubmed ID 7796558

Findings: High purity glucomannan supplementation resulted in significantly improved frequency distributions for cholesterol normalization compared to the placebo conditions during the treatment period.

4.1.3 Chearskul et. al. 2007 *Glycemic and lipid responses to glucomannan in Thais with type 2 diabetes mellitus*. J Med Assoc Thai 90(10): 2150-2157

- Medium quality
  (i) Single-blind
  (ii) Not representative of a US population
- Single-blind, placebo-controlled, cross-over study
- 20 type 2 diabetic adults received 3 g/d glucomannan or placebo for 4 weeks with a 2-week washout period in between
- Indeterminate glucomannan sourcing
- Pubmed ID 18041436

Findings: Glucomannan prevented a significant rise in LDL as compared to a placebo control group.

4.1.4 Doi et. al. 1979 *Treatment of Diabetes with Glucomannan (Konjac Mannan)*. Lancet 1(8123): 987-988

- Low quality
  (i) Unblinded
  (ii) Non-randomized
  (iii) Not representative of a US population
- Unblinded, non-randomized, uncontrolled two-part study
- 18 adults (13 type II diabetic and 5 healthy) were involved in a two-part study:
  (i) Diabetics received 3.6 g/d or 7.2 g/d glucomannan for 90 d
  (ii) Healthy subjects received 2.6 g glucomannan or nothing prior to a glucose tolerance test
- Propol glucomannan
- Pubmed ID 87668

Findings: Type 2 diabetics taking 3.6 g/d or 7.2 g/d experienced a significant reduction in LDL cholesterol and fasting blood glucose 90 d after supplementation with high purity glucomannan. Healthy individuals given 2.6 g/d high purity glucomannan prior to a glucose tolerance test experienced a reduction in post-prandial blood glucose and serum insulin rise.

4.1.5 Keithley et. al. 2013 *Safety and efficacy of glucomannan for weight loss in overweight and moderately obese adults*. J Obes 2013:610908

- High Quality
- Double-blind, placebo-controlled, randomized, parallel study
- 53 adults with BMI 23-35 consumed 3.99 g/d glucomannan for 8 weeks
- Glucomannan source not reported; correspondence with the author revealed purity to be consistent with konjac flour and not glucomannan

- Pubmed ID 24490058

Findings: No difference in any measure was observed between the glucomannan and placebo groups. Though glucomannan was cited within the manuscript, correspondence with the principal investigator (see Attachment 2) indicate the source material used was of low purity and consistent with konjac flour.

4.1.6 Kraemer et. al. 2007 *Effect of adding exercise to a diet containing glucomannan*. Metabolism 56(8): 1149-1158

- Low quality
  (i) Open-label
- Open-label, exercise-controlled, parallel study
- 42 solitary and overweight adults received 3 g/d glucomannan with or without additional exercise for 8 weeks
- Propol glucomannan
- Pubmed ID 17618964

Findings: High purity glucomannan alone significantly decreased LDL, total cholesterol, BMI, and body fat percentage, and the addition of exercise further improved these parameters.

4.1.7 Reffo et. al. 1988 *Glucomannan in hypertensive outpatients: pilot clinical trial*. Curr Ther Res 44(1): 22-27

- Medium quality
  (i) Single-blind
- Single-blind, placebo-controlled, randomized, parallel trial
- 31 hypertensive patients received 3 g/d glucommannan, 3 g/d glucomannan on a restricted calorie diet, or a placebo for four weeks
- Propol glucomannan

Findings: High purity glucomannan alone or with a concurrent restricted calorie diet significantly reduced total cholesterol and triglycerides in hypertensive patients as compared to placebo control after four weeks of treatment.

4.1.8 Reffo et. al. 1990 *Double-blind evaluation of glucomannan versus placebo in post-infarcted patients after cardiac rehabilitation*. Curr Ther Res 47: 753-758

- Medium quality
  (i) Potentially confounding health issues
- Double-blind, placebo-controlled, randomized, parallel study
- 28 post-infarcted patients were given 3 g/d glucomannan or placebo for eight weeks
- Propol glucomannan

Findings: High purity glucomannan significantly reduced total cholesterol and increased HDL after eight weeks in post-infarcted patients undergoing cardiac rehabilitation as compared to placebo control.

4.1.9 Terasawa et. al. 1979 *The effects of Konjac Flour on the Blood Lipids of Elderly Subjects*.

- Low quality

(i) Open label
(ii) Single group
(iii) Small sample size

- Open label, single group study
- 12 elderly, constipated women were given 3 g/d glucomannan for 4 weeks
- Propol glucomannan; ultrapure glucomannan used despite being termed konjac flour in the manuscript.

Findings: High purity glucomannan significantly decreased serum cholesterol and triglycerides

4.1.10 Vita et. al. 1992 *Chronic use of glucomannan in the dietary treatment of severe obesity*. Minerva Med 83(3): 135-139

- Medium quality
  (i) Single-blind
  (ii) Control group, no placebo
- Single-blind, randomized, controlled trial
- 50 severely obese patients received 3.87 g/d glucomannan supplement 30min before main meals on a restricted calorie diet (1000 kcal for women and 1300 kcal men) or underwent the same restricted calorie diet alone (control) for 3 months
- Propol (A) glucomannan (Dimanel – Tipomark)
- Pubmed ID 1313163

Findings: High purity glucomannan supplementation resulted in significantly decreased total cholesterol while preserving HDL compared to dietary modifications alone.

4.1.11 Walsh et. al. 1984 *Effect of Glucomannan on Obese Patients: A Clinical Study*. Int J Obes 8(4): 289-293

- High quality
- Double-blind, placebo-controlled, randomized, parallel study
- 20 obese females were given 3 g/d glucomannan or placebo for 8 weeks
- Propol A glucomannan
- Pubmed ID 6096282

Findings: High purity glucomannan significantly reduced body weight, serum total cholesterol, and LDL as compared to controls.

4.1.12 Wood et. al. 2007 *Effects of a carbohydrate-restricted diet with and without supplemental soluble fiber on plasma low-density lipoprotein cholesterol and other clinical markers of cardiovascular risk.* Metabolism 56(1): 58-67

- High quality
- Double-blind, placebo-controlled, randomized, diet-controlled, parallel study
- 30 males with BMI 25 – 35 received 3 g/d glucomannan or placebo for 12 weeks
- Indeterminate glucomannan source
- Pubmed ID 17161227

Findings: Glucomannan significantly reduced LDL to a significantly greater degree within a 6-week time period than a carbohydrate-restricted diet alone in overweight and obese men.

4.1.13 Yoshida et. al. 2006 *Effect of plant sterols and glucomannan on lipids in individuals with and without type II diabetes*. Eur J Clin Nutr 60(4): 529-537

- High quality
- Double-blind, randomized, cross-over study of four 21 d phases with a 28 d washout between each phase
- 34 adults (18 healthy, 16 type II diabetics) were given either 10 g/d glucomannan, 1.8 g/d plant sterols, 10 g/d glucomannan and 1.8 g/d plant sterols, or placebo for 21 d
- Indeterminate glucomannan source
- Pubmed ID 1631591

Findings: Glucomannan significantly reduced plasma LDL in type 2 diabetic and nondiabetic controls as compared to control (untreated) group

Totality of the Evidence

In summary, 13 studies evaluating the impact of glucomannan on LDL blood cholesterol were identified and included a wide range of patient populations, including healthy and overweight and/or diseased populations. Of these, 12 studies showed a decrease in total and/or fasting blood cholesterol; whereas one study, Keithley et. al. 2013, showed no change in any cholesterol measure using low purity glucomannan.

High purity Propol glucomannan, determined by HPLC, which maintains high viscosity at high temperature for at least 72 h, was specifically identified in 12 studies, each of which demonstrated a reduction in LDL cholesterol. Across all studies, high purity glucomannan was provided in a dose range of 3 – 10 g/d for at least 3 weeks, was well-tolerated, and side-effects were minimal and limited to gastrointestinal discomfort. Because the mean transit time through the human gut averages 2-3 days (48 – 72 h) with an *ad libitum* diet, high purity (*e.g*., Propol) glucomannan's stability for 72h likely plays a key role in its ability to pass through the gut undigested and its effect as a dietary fiber. Indeed, the low purity glucomannan used in Keithley et. al. 2013, which is comparable in purity to konjac flour, showed no effect on LDL cholesterol --likely due to a low mannose: glucose ratio and impurities that resulted in a lack of stability during gut transit and failure to function as a dietary fiber.

Taken together, the totality of evidence demonstrates oral consumption of 3 g/d high purity glucomannan as characterized by HPLC reduces fasting LDL blood cholesterol within a broad spectrum of the adult population.

4.2. Improved Laxation

Justification of Laxation as a Physiologic Measure of Health

Improved laxation is indicated in the FDA's *Final Rule on Nutrition Labeling* (81 FR 33855-6) and S*cientific 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): Guidance for Industry* as a beneficial physiological endpoint of dietary fiber consumption. Studies that measured transit time, defecation rate, and subjective measures of laxation such as reported ease of defecation were included.

Summary of Studies

Known studies evaluating the effect of glucomannan on laxation (both using Propol) have been identified, reviewed for quality and appropriateness, and are summarized in Table 4.

Table 4
Claim: Laxation

Study	Glucomannan	Supports Claim	Findings
Marzio et. al. 1989 [15]	Propol (KW)	Yes	Glucomannan significantly reduced mouth-to-cecum time compared with the range of healthy controls, and in constipated patients compared with placebo and control groups
Passaretti et. al. 1991 [16]	Propol (KW)	Yes	Glucomannan significantly decreased the number of enemas and increased bowel movement frequency in chronically constipated adults

4.2.1 Marzio et. al. 1989 *Mouth-to-cecum time in patients affected by chronic constipation: effect of glucomannan.* Am J Gastroenterol 84(8): 888-891

- Medium quality
  (i) No clear washout period defined
- Double-blind, placebo-controlled, randomized cross-over study with a 10 d treatment period
- 31 adults (18 healthy, 13 with chronic idiopathic constipation) were given 2 g/d glucomannan or placebo for 10 d
- Propol (KW) glucomannan
- Pubmed ID 2547312

Findings: High purity glucomannan significantly reduced mouth-to-cecum time compared with the range of healthy controls, and in constipated patients compared with placebo and control groups.

4.2.2 Passaretti et. al. 1991 *Action of glucomannans on complaints in patients affected with chronic constipation: a multicentric clinical evaluation.* Ital J Gastroenterol 23(7): 421-425

- Low quality
  (i) Open and non-controlled study
- Open and non-controlled
- 93 chronically constipated adults were given 3 g/d glucomannan during an initial 30 d phase followed by 2 g/d glucomannan during a maintenance phase.
- Propol (KW) glucomannan
- Pubmed ID 1742540

Findings: High purity glucomannan significantly decreased the number of enemas and increased bowel movement frequency.

Totality of the Evidence

In summary, two studies that evaluated the impact of glucomannan on laxation were identified, both of which used a high purity glucomannan as determined by HPLC, Propol. Both studies improved measures of laxation, with Marzio et. al. (1989) demonstrating highly purified glucomannan (*i.e.*, Propol) significantly reduced

mouth-to-cecum time in constipated adults as compared to the placebo and healthy control groups. Across both studies, high purity glucomannan was provided in a dose rage of 2 – 3 g/d, was well-tolerated, and side-effects were minimal and limited to gastrointestinal discomfort. The totality of evidence suggests consuming high purity glucomannan, specifically Propol, improves measures of laxation.

4.3. Reduced Energy Intake

Justification of Reduced Energy Intake as a Physiologic Measure of Health

Reduced energy intake is indicated in the FDA's *Final Rule on Nutrition Labeling* (81 FR 33855-6) and *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): Guidance for Industry* as a beneficial physiological endpoint of dietary fiber consumption. Studies evaluating changes in total body weight, body fat percentage, fat mass, and/or BMI following prolonged (*e.g.*, weeks) glucomannan supplementation were considered as measures of reduced energy intake and metabolism over time. In addition, studies showing indicators of carbohydrate metabolism (*e.g.*, breath hydrogen content) immediately following glucomannan consumption as part of a meal were also considered.

Summary of Studies

Known studies evaluating the effect of glucomannan on energy intake have been identified, reviewed for quality and appropriateness, and are summarized in Table 5.

Table 5
Claim: Energy Intake

Study	Glucomannan	Supports Claim	Findings
Birketvedt et. al. 2005 [17]	Propol (A)	Yes	Glucomannan caused significant weight loss in healthy overweight subjects compared to placebo
Cairella et. al. 1995 [18]	Propol (KW)	Yes	Glucomannan caused significant weight loss, BMI reduction, reduced hunger, increased fullness, and cholesterol normalization compared to placebo conditions
Keithley at. al. 2013 [7]	Purity consistent with konjac flour	No	No difference in weight, body composition, or energy intake measures was observed between overweight adults taking konjac flour and those taking placebo
Kraemer et. al. 2007 [8]	Propol	Yes	Glucomannan alone significantly decreased BMI and body fat percentage in overweight adults, and the addition of exercise further improved these parameters
Oku et. al. 2014 [19]	Propol (A)	Yes	Glucomannan significantly reduced breath hydrogen content (AUC) in healthy females over an 8 hour, 14 hour, and 24 hour period compared to a fructooligosaccharide control
Reffo et. al. 1988	Propol	Yes	Glucomannan alone or with a concurrent restricted calorie diet significantly reduced

			total body weight in hypertensive patients compared to placebo control after four weeks of treatment
Reffo et. al. 1990	Propol	Yes	Glucomannan significantly reduced total body weight after eight weeks in post-infarcted patients undergoing cardiac rehabilitation compared to placebo control
Vita et. al. 1992	Propol (A)	Yes	Glucomannan significantly reduced body weight, body fat percent, and total cholesterol while preserving HDL compared to a hypocaloric diet alone
Walsh et. al. 1984	Propol (A)	Yes	Glucomannan significantly reduced body weight, serum total cholesterol, and LDL compared to controls
Wood et. al. 2007	Indeterminate	No	Glucomannan did not provide additional reduction in body weight, body fat percent, blood pressure, waist circumference, or plasma glucose when added to a carbohydrate-restricted diet

4.3.1 Birketvedt et. al. 2005 E*xperiences with three different fiber supplements in weight reduction.* Med Sci Moni 11(1): PI5-8

- High quality
- Double-blind, placebo-controlled, randomized, parallel study
- 176 overweight adults received either 1.24 g/d glucomannan; 4.32 g/d glucomannan, 900 mg/d guar, and 900 mg/d alginat; 420 mg/d glucomannan, 420 mg/d guar; or placebo for 5 weeks
- Propol (A) glucomannan
- Pubmed ID 15614200

Findings: High purity glucomannan caused significant weight loss in healthy overweight subjects compared to placebo control.

4.3.2 Cairella et. al. 1995 *Evaluation of the action of glucomannan on metabolic parameters and on the sensation of satiation in overweight and obese patients.* Clin Ter 146(4): 269-74

- High Quality
- Double-blind, placebo-controlled, randomized study
- 30 adult females, BMI 25-30 all consumed a calorie-restricted diet of 1200 kcal/day + placebo capsules for 30 days. The diet was then continued for an additional 30 days, wherein subjects according to the randomization consumed either 3.86g/day glucomannan or matching placebo 30-60 minutes before the two main meals with 1-2 glasses of water
- Propol glucomannan (Dietoman is prepared with PropolMannan glucomannan)
- Pubmed ID 7796558

Findings: High purity glucomannan supplementation resulted in significantly greater weight loss and BMI reduction as well as a reduction in hunger ratings and an increase in fullness ratings compared to the placebo conditions. Frequency distributions for cholesterol normalization in the glucomannan group was significantly greater compared to the placebo conditions during the treatment period.

4.3.3 Keithley et. al. 2013 *Safety and efficacy of glucomannan for weight loss in overweight and moderately obese adults*. J Obes 2013:610908

- High Quality
- Double-blind, placebo-controlled, randomized, parallel study
- 53 adults with BMI 23-35 consumed 3.99 g/d glucomannan for 8 weeks
- Glucomannan source not reported; correspondence with the author revealed purity to be consistent with konjac flour and not glucomannan
- Pubmed ID 24490058

Findings: No difference in any weight, body composition, or energy intake measure was observed between the glucomannan and placebo groups. As noted above, though glucomannan was cited within the manuscript correspondence with the principal investigator indicate the source material used was of low quality and consistent with konjac flour.

4.3.4 Kraemer et. al. 2007 *Effect of adding exercise to a diet containing glucomannan.* Metabolism 56(8): 1149-1158

- Low quality
  (i) Open label
- Open label, exercise controlled, parallel study
- 42 solitary and overweight adults received 3 g/d glucomannan with or without additional exercise for 8 weeks
- Propol glucomannan
- Pubmed ID 17618964

Findings: High purity glucomannan alone significantly decreased LDL, total cholesterol, BMI, and body fat percentage, and the addition of exercise further improved these parameters.

4.3.5 Oku et. al. 2014 *Evaluation of the relative available energy of several dietary fiber preparations using breath hydrogen evolution in healthy humans.* J Nutr Sci Vitaminol (Tokyo) 60(4): 246-254

- Low quality
  (i) Very small sample size
  (ii) Open label
- Open-label, within-subject, repeated measures study
- 9 healthy females were given 5 g gelated glucomannan in 120 ml soft drink over 24 h, another fiber type, or fructooligosaccharide positive control
- Propol (A) glucomannan
- Pubmed ID 25297613

Findings: Consumption of high purity glucomannan significantly reduced breath hydrogen contant (AUC) over the 8-hour, 14 hour, and 24 hour period compared to a fructooligosaccharide control.

4.3.6 Reffo et. al. 1988 *Glucomannan in hypertensive outpatients: pilot clinical trial*. Curr Ther Res 44(1): 22-27

- Medium quality
  (i) Single-blind
- Single-blind, placebo-controlled, randomized, parallel trial

- 31 hypertensive patients received 3 g/d glucommannan, 3 g/d glucomannan on a restricted calorie diet, or a placebo for four weeks
- Propol glucomannan

Findings: High purity glucomannan alone or with a concurrent restricted calorie diet significantly reduced total body weight in hypertensive patients compared to placebo control after four weeks of treatment.

4.3.7 Reffo et. al. 1990 *Double-blind evaluation of glucomannan versus placebo in post-infarcted patients after cardiac rehabilitation*. Curr Ther Res 47: 753-758

- Medium quality
  (i) Potentially confounding health issues
- Double-blind, placebo-controlled, randomized, parallel study
- 28 post-infarcted patients were given 3 g/d glucomannan or placebo for eight weeks
- Propol glucomannan

Findings: High purity glucomannan significantly reduced total body weight after eight weeks in post-infarcted patients undergoing cardiac rehabilitation as compared to placebo control.

4.3.8 Vita et. al. 1992 *Chronic use of glucomannan in the dietary treatment of severe obesity*. Minerva Med 83(3): 135-139

- Medium quality
  (i) Single-blind
  (ii) Control group, no placebo
- Single-blind, randomized, controlled trial
- 50 severely obese patients received 3.87 g/d glucomannan supplement 30min before main meals on a restricted calorie diet (1000 kcal for women and 1300 kcal men) or underwent the same restricted calorie diet alone (control) for 3 months
- Propol (A) glucomannan (Dimanel – Tipomark)
- Pubmed ID 1313163

Findings: High purity glucomannan supplementation resulted in significantly greater weight loss and body fat percent loss (vs. lean mass) compared to dietary modifications alone and decreased total cholesterol while preserving HDL.

4.3.9 Walsh et. al. 1984 *Effect of Glucomannan on Obese Patients: A Clinical Study*. Int J Obes 8(4): 289-293

- High quality
- Double-blind, placebo-controlled, randomized, parallel study
- 20 obese females were given 3 g/d glucomannan or placebo for 8 weeks
- Propol A glucomannan
- Pubmed ID 6096282

Findings: High purity glucomannan significantly reduced body weight as compared to controls.

4.3.10 Wood et. al. 2007 *Effects of a carbohydrate-restricted diet with and without supplemental soluble fiber on plasma low-density lipoprotein cholesterol and other clinical markers of cardiovascular risk.* Metabolism 56(1): 58-67

- High quality
- Double-blind, placebo-controlled, randomized, diet-controlled, parallel study
- 30 males with BMI 25 – 35 received 3 g/d glucomannan or placebo for 12 weeks
- Indeterminate glucomannan source
- Pubmed ID 17161227

Findings: Glucomannan did not provide additional reduction in body weight, body fat percent, blood pressure, waist circumference, or plasma glucose when added to a carbohydrate-restricted diet.

Totality of the Evidence

In summary, 10 studies evaluating the impact of glucomannans on energy intake were identified and included healthy, overweight, and obese adults who were otherwise healthy, showed premature indicators of type 2 diabetes, or were diagnosed with type 2 diabetes. Of these studies, seven showed that high purity glucomannan as determined by HPLC, including Propol, reduced body weight, BMI, and/or body fat percentage, and one. In contrast, two studies, Keithley et. al. 2013 and Wood et. al. 2007, showed no change in these measures following glucomannan supplementation. However, neither of the studies that showed no change reported the use of a high purity glucomannan, suggesting the glucomannan source used in these studies was of lower purity and have different physical characteristics. Further, Oku et. al. (2014) showed consumption of high purity glucomannan (*i.e*., Propol) in conjunction with a sugary drink reduced breath hydrogen levels within a 24-hour period compared to a fructooligosaccharide control. Across all studies, prolonged consumption (*e.g*., weeks) of 3 – 5 g/day of high purity glucomannan (*e.g*., Propol) can reduce glucose absorption; leading to a reduction of body weight, body fat percentage, and/or BMI as consequence of reduced energy intake. The totality of evidence demonstrates high purity glucomannan, (Propol), can improve clinical measures of energy intake.

5. Conclusions Respecting Requested Agency Action

The foregoing evidence demonstrates that high purity glucomannan of at least 95% purity by HPLC, including Propol, is an "… isolated … non-digestible carbohydrate (with 3 or more monomeric units) determined by FDA to have physiological effects that are beneficial to human health." As such, it should be included in the list of dietary fibers within 21 CFR 101.9(c)(6)(i).

C. Environmental Impact

The undersigned do not believe the actions requested in this Petition would have any environmental impact. Further, the actions requested in this petition are not within any categories requiring environmental assessment pursuant 21 CFR 25.22 and would be exempt pursuant 21 CFR 25.30(k).

D. Economic Impact

The action requested is subject to a categorical exclusion under 21 CFR 25.30(k) and therefore does not require the preparation of an environmental assessment.

E. Action Requested

The petitioner requests the Commissioner of Food and Drug amend 21 CFR 101.9(c)(6)(i) to include high purity glucomannan (at least 95% pure **by HPLC**), as defined within this petition, to be included in the regulation's list of dietary fibers."

F. Certification

The undersigned certifies, that, to the best of their knowledge and belief, this Petition includes all information and views on which the petition relies; and that it includes any and all representative data and information known to the petitioner which are unfavorable to the petition.

Works Cited

1. BeMiller, J.N., *10 - Inulin and Konjac Glucomannan*, in *Carbohydrate Chemistry for Food Scientists (Third Edition)*, J.N. BeMiller, Editor. 2019, AACC International Press. p. 253-259.
2. *Scientific Opinion on the substantiation of health claims related to konjac mannan (glucomannan) and reduction of body weight (ID 854, 1556, 3725), reduction of post-prandial glycaemic responses (ID 1559), maintenance of normal blood glucose concentrations (ID 835, 3724), maintenance of normal (fasting) blood concentrations of triglycerides (ID 3217), maintenance of normal blood cholesterol concentrations (ID 3100, 3217), maintenance of normal bowel function (ID 834, 1557, 3901) and decreasing potentially pathogenic gastro-intestinal microorganisms (ID 1558) pursuant to Article 13(1) of Regulation (EC) No 1924/2006.* EFSA Journal, 2010. **8**(10): p. 1798.
3. Mortensen, A., et al., *Re-evaluation of konjac gum (E 425 i) and konjac glucomannan (E 425 ii) as food additives.* EFSA Journal, 2017. **15**(6): p. e04864.
4. Arvill, A. and L. Bodin, *Effect of short-term ingestion of konjac glucomannan on serum cholesterol in healthy men.* Am J Clin Nutr, 1995. **61**(3): p. 585-9.
5. Chearskul, S., et al., *Glycemic and lipid responses to glucomannan in Thais with type 2 diabetes mellitus.* J Med Assoc Thai, 2007. **90**(10): p. 2150-7.
6. Doi, K., et al., *Treatment of diabetes with glucomannan (konjac mannan).* Lancet, 1979. **1**(8123): p. 987-8.
7. Keithley, J.K., et al., *Safety and efficacy of glucomannan for weight loss in overweight and moderately obese adults.* J Obes, 2013. **2013**: p. 610908.
8. Kraemer, W.J., et al., *Effect of adding exercise to a diet containing glucomannan.* Metabolism, 2007. **56**(8): p. 1149-58.
9. Reffo, G.C., P.E. Ghirardi, and C. Forattini, *Glucomannan in hypertensive outpatients: Pilot clinical trial.* Curr. Ther. Res., 1988. **44**: p. 22-27.
10. Reffo, G.C., P.E. Ghirardi, and C. Forattini, *Double-blind evaluation of glucomannan versus placebo in postinfarcted patients after cardiac rehabilitation.* Current Therapeutic Research - Clinical and Experimental, 1990. **47**: p. 753-758.
11. 寺沢, 富., et al., *老年者血中脂質に及ぼすコンニャク精粉の影響.* 栄養学雑誌, 1979. **37**(1): p. 23-28.
12. Walsh, D.E., V. Yaghoubian, and A. Behforooz, *Effect of glucomannan on obese patients: a clinical study.* Int J Obes, 1984. **8**(4): p. 289-93.
13. Wood, R.J., et al., *Effects of a carbohydrate-restricted diet with and without supplemental soluble fiber on plasma low-density lipoprotein cholesterol and other clinical markers of cardiovascular risk.* Metabolism, 2007. **56**(1): p. 58-67.
14. Yoshida, M., et al., *Effect of plant sterols and glucomannan on lipids in individuals with and without type II diabetes.* Eur J Clin Nutr, 2006. **60**(4): p. 529-37.
15. Marzio, L., et al., *Mouth-to-cecum transit time in patients affected by chronic constipation: effect of glucomannan.* Am J Gastroenterol, 1989. **84**(8): p. 888-91.
16. Passaretti, S., et al., *Action of glucomannans on complaints in patients affected with chronic constipation: a multicentric clinical evaluation.* Ital J Gastroenterol, 1991. **23**(7): p. 421-5.

17. Birketvedt, G.S., et al., *Experiences with three different fiber supplements in weight reduction.* Med Sci Monit, 2005. **11**(1): p. PI5-8.
18. Cairella, M. and G. Marchini, *[Evaluation of the action of glucomannan on metabolic parameters and on the sensation of satiation in overweight and obese patients].* Clin Ter, 1995. **146**(4): p. 269-74.
19. Oku, T. and S. Nakamura, *Evaluation of the relative available energy of several dietary fiber preparations using breath hydrogen evolution in healthy humans.* J Nutr Sci Vitaminol (Tokyo), 2014. **60**(4): p. 246-54.
20. Vita et al., *Chronic use of glucomannan in the dietary treatment of severe obesity*. 1992. Minerva Med 83(3): 135-139